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■ Original Research Article

The Association of Serum Neutrophil Gelatinase and Lipocalin Levels With Preeclampsia And Its Severity at A Tertiary Hospital in Northeastern Nigeria.

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ABSTRACT

Background: Hypertensive disorders in pregnancy are among the leading causes of maternal and neonatal morbidity and mortality worldwide particularly in developing countries. The pathogenesis of hypertensive disorders in pregnancy involves complex mechanisms including incomplete invasion and remodeling of the maternal spiral arteries, cytokines, and generalized endothelial dysfunction. Neutrophil gelatinase-associated lipocalin (NGAL) is an acute phase protein which appeared to be a biomaker for acute kidney injury. It has been found to be upregulated in pathological conditions following endothelial cell injury and it is also released from the maternal-fetal interface. However, its role and relationships in preeclampsia has not been fully evaluated especially in our environment. Therefore, the aim of this study was to determine the association between Serum Neutrophil gelatinase-associated lipocalin and preeclampsia and its severity. **Methods**: This was a cross-sectional study of fifty-eight (58) women with preeclampsia recruited as the study group while same number of normotensive pregnant women, served as the control. Serum NGAL levels in both groups were determined using ELISA. Data was analyzed using SPSS IBM version 26.0. Appropriate tests were used to compare continuous and categorical variables in normotensive and preeclamptic women. **Results**: The mean age of normotensive and preeclamptic patients were 28.17±5.57 and 27.98±6.34 (p= 0.573). Mean Serum NGAL Level in normotensive (77.36±40.15ng/ml) was significantly lower than the mean serum NGAL level (120.66±40.26ng/ml) among preeclamptic women (p<0.001). There is difference in the serum NGAL between mild preeclampsia (118.48±31.52ng/ml) and severe preeclampsia (122.43±46.60ng/ml) but was not statistically significant (p=0.714). **Conclusion**: There is an association between serum NGAL levels and preeclampsia but not with severity of preeclampsia in the studied population.

Keywords: Preeclampsia, Severity, NGAL, Lipocalin-2

INTRODUCTION

Hypertensive disorders in pregnancy are among the leading causes of maternal and neonatal morbidity and mortality worldwide particularly in developing countries and affect up to 8% of pregnancies.[1] Hypertensive disorders in pregnancy (HDP) are also a major threat to global health.[2,3] They are associated with an increased risk of adverse fetal, neonatal, and maternal outcomes including premature delivery, fetal growth restriction,

intrauterine fetal death, kidney or liver failure, hemorrhage, and stroke.[2,4] Worldwide about 2–10% of pregnancies are complicated by preeclampsia and its incidence is estimated to be seven times higher in developing countries (2.8% of live births) compared to developed countries where it constitutes 0.4% of live births.[5,6] Over 63,000 maternal deaths annually are due to preeclampsia with about 98% of such deaths occurring in developing countries.[3,5,7,8]

In Nigeria, it is estimated that 5-10% of pregnancies are complicated by hypertensive disorders in pregnancy (HDP) and it results in more admissions in the antenatal period than any other disorder.[9]

The pathogenesis of HDP is still debatable. It is a multifactorial disease and its pathogenesis include a series of complex mechanisms including generalized endothelial dysfunction, high circulating level of antiangiogenic factors and proinflammatory cytokines and incomplete invasion and remodeling of the maternal spiral arterioles.[10,11] It is associated with placental hypoxia and/or ischemia and excessive oxidative stress.[11] Studies have demonstrated that many proteins are dysregulated in preeclampsia including human placenta growth factor (PlGF), plasminogen activator inhibitor-1 (PAI-1), human free vascular endothelial growth factor (VEGF), human pentraxin 3 (PTX3), human endoglin (Endoglin), epidermal growth factor receptor (EGFR), and vascular endothelial growth factor receptor 1 (Flt-1).

Other studies showed that neutrophil gelatinase-associated lipocalin (NGAL), cyclooxygenase-2 (COX-2), human prolactin and human interleukin 27 (IL-27) are also altered in preeclampsia.[12,13,14] Neutrophil gelatinase-associated lipocalin (NGAL) is also known as lipocalin-2, 24p3, siderocalin, or uterocalin. It is a small secreted glycoprotein of 25 kDa and a novel adipokine[15,16,17] initially identified in mature neutrophil granules, but has since been described in many other cell types. NGAL is expressed in renal, endothelial, liver, and smooth muscle cells, as well as cardiomyocytes, neurons, and various populations of immune cells, such as macrophages and dendritic cells.[18]

It is an acute-phase protein which is produced during ischaemia and inflammatory conditions and it has been proven as a sensitive biomarker for predicting renal injury[15,19,20] because it is shown to be highly accumulated in blood after nephrotoxic and ischemic renal insult.[10] Also, NGAL levels in kidney tissue rise by 10-fold within 3 hours after ischaemic injury and this rise appears to be sustained, being evident for several days following the initial insult.[10] As preeclampsia is also recognized to induce renal injury, this suggests a potential role for this novel marker in linkage with maternal outcomes.[19] The kidney has a principal role in the pathogenesis of preeclampsia and NGAL has been observed to be produced at the maternal–fetal interface however only few studies showed the systemic role of NGAL in preeclampsia. In some studies, serum NGAL concentrations was found to be significantly increased in women who subsequently developed preeclampsia.[20,21] Some studies have also shown that NGAL could be used to predict preeclampsia before the clinical diagnosis of the disease. In Nigeria like most countries in the subregion, preeclampsia is a significant cause of morbidity and mortality with consequences on the fragile health systems of the countries. Having a tool to predict the conditions or their severity has been an area of research with potentials to have remarkable impact on the management of the conditions. There is paucity of studies on this biomaker in our subregion.

Neutrophil gelatinase-associated lipocalin which is produced at the maternal-fetal interface is one of the factors which appear to be dysregulated in preeclampsia however only few studies showed its systemic role in preeclampsia hence the need to study the association between preeclampsia and the biomaker especially in this subregion.

This aim of the study was to examine maternal serum levels of Neutrophil Gelatinase associated lipocalin in preeclamptic women and normal pregnant women as well as its association with the severity of the disease.

MATERIAL AND METHODS

The study was a cross-sectional study conducted between 15th July 2021 and 31st December 2021 in Abubakar Tafawa Balewa University Teaching Hospital, Bauchi in North Eastern Nigeria. A total of 116 pregnant women between 15 to 45 years of age with singleton pregnancies after 20 weeks of gestation were consecutively recruited into the study group using convenience sampling method until the required sample size was achieved. They comprised of 26 women diagnosed with mild preeclampsia and 32 women with severe preeclampsia seen in the antenatal clinics, the pregnancy induced hypertension ward or labour ward of the hospital. The control group consisted of normotensive pregnant women recruited from the antenatal clinic and labour ward. For each patient with preeclampsia enrolled in the study, a normotensive pregnant woman that was matched for gestational age (± 2 weeks) and maternal age (±2 years) was enrolled.

Sample Size Determination

The sample size was calculated using this formula.[22]

$$\text{Sample Size} = \frac{r+1}{r}\frac{\sigma^2\left(Z_\beta + Z_{\frac{\alpha}{2}}\right)^2}{d^2}$$

r = Ratio of normal pregnant women to women with preeclampsia, 1 for equal number of case and control

σ= Standard deviation of the variable (serum NGAL) from previous studies.
Z_{β}= Standard normal variate for power. Using a power of 80% it is 0.84
$Z_{\frac{\alpha}{2}}$= Standard normal variate for level of significance. At 5% type 1 error (P<0.05) it is 1.96
d= Expected mean difference between women with preeclampsia (mild 20ng/ml or severe 10ng/ml) and normotensive pregnant women

According to Arikan et al,[16] the mean ±standard deviation of serum NGAL among mild and severe preeclampsia patients in Turkey were 60.33±24.49ng/ml and 56.73±13.54ng/ml respectively. The sample size was calculated as follows:
Sample size for mild PE= $2 \times (24.49)^2 (0.84+1.96)^2 \div (20)^2 = 23.5 \approx 24$
Sample size for severe PE= $2 \times (13.54)^2 (0.84+1.96)^2 \div (10)^2 = 28.7 \approx 29$

Adding a 10% non-response rate to both groups gave 26 and 32 patients for mild and severe preeclampsia respectively. Therefore, total number of 58 patients with preeclampsia was recruited as well as equal number of normal pregnant women matched for maternal age and gestational age. Therefore, total sample size for this study was 116.

Diagnosis of Preeclampsia

The diagnosis of preeclampsia was made when a patient had a blood pressure of at least 140/90 mmHg after 20 weeks gestation on 2 occasions 4 hours apart or a single measurement of at least 160/110mmHg and proteinuria defined as ≥1+ during each blood pressure measurement. Systolic blood pressure of 140-158mmHg and diastolic 90-108mmHg was taken as mild preeclampsia, while severe preeclampsia was taken as systolic blood pressure of ≥160mmHg and diastolic of ≥110mmHg. The severity of pre-eclampsia was based on blood pressure level only for the purpose of this study. Proteinuria was determined using dipstick urinalysis (at least 1+ on dipstick). Participants considered as controls had no proteinuria and were normotensive.

Exclusion Criteria

Pregnant women with Multiple gestation, premature rupture of membranes, Obesity, Sepsis, and medical conditions like Chronic Hypertension, diabetes mellitus, autoimmune diseases, Chronic Kidney disease, Sickle cell Disease were excluded from this study. In addition, women with Assisted Conception and patients who do not give consent were also excluded.

Data Collection

Samples were collected by trained research assistants. Consenting eligible pregnant women who presented to the antenatal clinic, PIH ward or labour ward with mild or severe preeclampsia were recruited into the case group, while the control group comprised of women with normal pregnancy matched for gestational age and maternal age presenting to the antenatal clinic, antenatal ward and labour ward. The gestational age was determined from the last menstrual period and/ or from ultrasound scan done at or before 20 weeks gestation. Informed consent was obtained and using a semi-structured proforma, information on the socio-demographic characteristics, parity, estimated gestational age (EGA) were asked and recorded. Systolic and diastolic blood pressures as well as urinalysis result were also recorded.

Blood Pressure Measurement

The blood pressure was measured with Littman's © stethoscope and Mercury Sphygmomanometer (Accuson, UK) which measures blood pressure to the nearest 2 mmHg. The measurement was taken in sitting position after 10 minutes of resting on the upper arm using an appropriate size cuff. The first and fifth Korotkoff sounds were used for systolic and diastolic blood pressures respectively. In cases where the fifth Korotkoff sound was absent, the fourth was used for diastolic blood pressure.

Sample Collection

About 5ml of venous blood was collected from a peripheral vein on the antecubital fossa under aseptic condition from the subjects which was transferred to a plain bottle and thereafter it was centrifuged to get the serum which was immediately stored in a cryovial at -20^0C in the molecular genetics and infectious disease laboratory of the hospital until analyzed. In addition, 5ml of midstream urine was collected for urinalysis using dipstick method. All samples were collected at recruitment.

Assay Methodology

Serum NGAL level was measured using enzyme-linked immunosorbent assay kit (elabscience, catalog No. E-TSEL-H0003) by the manufacturer's instructions. The reagent kit was stored at 2-8^0C, until utilized but not later than the expiration date. The assay system utilizes high affinity and specificity monoclonal antibodies directed against a distinct antigenic determinant on the NGAL molecule. The test sample reacted simultaneously with the two antibodies, resulting in the NGAL molecule being sandwiched between the solid and enzyme linked

antibodies. The solution resulted in colour change to blue following incubation. The colour development was then stopped with the addition of stopping reagent, changing the colour to yellow. The concentration of NGAL is directly proportional to the colour intensity of the test sample. Absorbance was measured using spectrophotometry at 450nm.

Statistical Analysis

Data was analysed using SPSS version 26. Frequency and percentages were used to present categorical variables while continuous variables were presented as means and standard deviation. Chi-square test or Fisher's exact test was used to compare categorical variables as appropriate while independent sample t-test was used to compare mean of NGAL among two groups. In all cases involving data analysis, $p< 0.05$ was considered statistically significant and $p>0.05$ non-significant.

Ethical Consideration

Approval for the study was obtained from the Health Research Ethics committee of the Hospital (0025/2021). Written informed consent was also obtained from each participant. Ethical considerations in this study were based on the general ethical principles as applicable to human subjects. These are respect for persons, beneficence, non-maleficence and justice.

RESULTS

A total of 116 pregnant women were included in this study. This consisted of 58 normal pregnant women (control group) and 58 women with preeclampsia (26 mild preeclampsia and 32 severe preeclampsia). There was no statistically significant difference between age of normotensive and preeclamptic patients (p= 0.573). However, there was a statistically significant difference between the parity of both cases and controls (p= 0.045) but the marital status, educational levels, ethnic group and gestational ages of both groups showed no difference.

It is observed that the serum NGAL levels of majority of women in both groups was within the reference range, however the preeclampsia group had higher levels than the normotensive women. 36.2% of Normotensive women had serum NGAL levels lower than the reference range, this is higher than preeclampsia of 5.2%. None of the normotensive women had NGAL level above the reference range. 3.4% of women with preeclampsia had serum NGAL levels above the reference range.

Table 1. Socio Demographic Characteristics of Participants.

Variables	Normotensive n(%)=58	Preeclampsia n (%)=58	p-value
Age (years)			
<20	1.7	6.9	
20-29	58.6	51.7	0.573†
30-39	37.9	39.7	
≥40	1.7	1.7	
Mean±SD	**28.17±5.57**	**27.98±6.34**	
Parity			
0	27.6	37.9	
1-4	63.8	41.4	0.045** †
5-9	6.9	19.0	
≥10	1.7	1.7	
Marital Status			
Married	98.3	98.3	
Single	0	0	> 0.999†
Divorced	1.7	0	
Widowed	0	1.7	
Educational level			
None	3.5	3.4	
Primary	3.4	8.6	0.722†
Secondary	44.8	41.4	
Tertiary	44.3	44.8	
Quranic	0	1.7	
Ethnic group			
Hausa	41.4	36.2	
Fulani	17.2	20.7	0.892†
Jarawa	5.2	8.6	
Sayawa	13.8	10.3	
Others	22.4	24.1	
Gestational age (weeks)			
≤28	8.6	12.1	
29-32	19.0	15.5	
33-36	27.6	19.0	0.615*
37-42	44.8	53.4	
Mean±SD	**35.09±4.23**	**35.43±4.66**	

*† Fisher's Exact * Chi-squared ** Statistically Significant*

Reference range= 68.47 to 210.56ng/ml

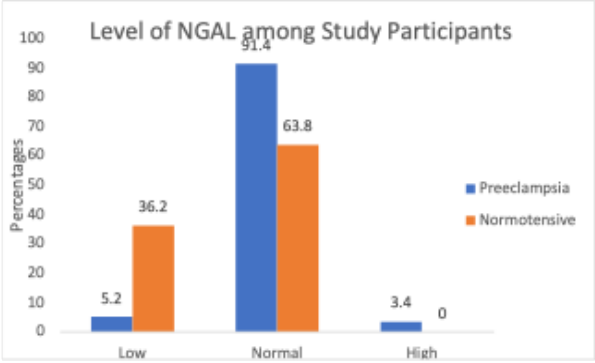

Figure 1: Serum Level of NGAL in Preeclampsia and Normotensive women
Normotensive= 12 to 165ng/ml
Preeclampsia= 37 to 230ng/ml

Table 2. Comparison of Mean Serum NGAL levels in preeclampsia and normal pregnant women using independent t-test.

Variable	Normotensive n=58	Preeclampsia n=58	p- value
Mean Serum NGAL Level	77.36±40.15	120.66±40.26	<0.001*

**Statistically significant*

There was significant difference (p= <0.001) in the mean levels of serum NGAL between normotensive (77.36±40.15ng/ml) and women with preeclampsia (120.66±40.26ng/ml).

Table 3. Association between serum level of NGAL in preeclampsia and normotensive participants.

Variable	Abnormal NGAL	Normal NGAL	p-value
Preeclampsia (%)	5(8.6)	53(91.4)	
Normotensive (%)	21(36.2)	37(63.8)	<0.001*

** Chi-squared*

There was a significant association between NGAL and preeclampsia with a p value <0.001.

Table 4 Comparison of Mean Serum NGAL levels in mild preeclampsia and severe preeclampsia using independent t-test.

Variable	Mild n=26	Severe n=32	p- value
Mean Serum NGAL Level	118.48±31.52	122.43±46.60	0.714

There was no significant difference (p= 0.714) in the mean levels of NGAL in participants with mild preeclampsia (118.48±31.52ng/ml) and those with severe preeclampsia (122.43±46.60ng/ml).

Table 5 Association Between Serum Level of NGAL and Severity of Preeclampsia

Variable	Abnormal NGAL	Normal NGAL	p- value
Mild Preeclampsia (%)	0(0)	26(100)	
Severe Preeclampsia (%)	5(15.6)	27(84.4)	0.058†

† Fisher's Exact

There was no association (p= 0.058) between serum level of NGAL and severity of preeclampsia.

DISCUSSION

This study examined the association between Serum Neutrophil gelatinase associated lipocalin (NGAL) with preeclampsia and its severity among pregnant women at Abubakar Tafawa Balewa University Teaching Hospital, Bauchi.

In this study the mean age of women with preeclampsia was 27.98±6.34 years and that of normotensive women was 28.17±5.57 years. There was no statistically significant difference in the age of both groups and the findings were comparable with the findings of Onoh et al in Abakaliki, Southeast Nigeria who reported a mean of women with preeclampsia as 27.3 ± 5.2 years[7] and that of D'Anna et al and Arikan et al in Italy and Turkey respectively who reported mean age of women with preeclampsia as 28.4±2.1 years and 27.73±7.04 years respectively.[16,23] Guralp et al equally reported mean age of women with preeclampsia to be 30±5.4 years.[24]

In this study, the serum NGAL level in 58 normotensive and 58 preeclamptic patients were compared, there was statistically significant difference in the mean serum level of NGAL in the pregnant women with preeclampsia when compared with the controls (120.66±40.26 Vs. 77.36±40.15 ng/ml) and further analysis showed that there is an association between abnormal NGAL levels and preeclampsia, which was in agreement with a study done by Ulkumen and colleagues in forty women, twenty of whom had preeclampsia and twenty with normal pregnancies.[25] A mean serum NGAL level of 83.38±34.06ng/ml and 123.27±40.96ng/ml in normotensive and preeclamptic women respectively and this was statistically significant.[25]

Similarly, Stepan et al did a case-controlled study of twenty-two women with pre-eclampsia and 22 healthy controls. They reported median serum level of NGAL in preeclamptic and normotensive women were 121.3ng/ml and 99.8ng/ml respectively,[26] this was found

to be statistically significant. On the contrary, the study conducted by Ahmad et al showed mean serum NGAL levels that were not statistically significantly different between patients with preeclampsia and normotensive patients although higher levels were seen in women with preeclampsia.[27] This difference could probably be as a result of the smaller sample size in their study and the socio-demographic differences in the studied populations. The findings in the studies are consistent with the hypothesis that Serum NGAL may play a role in the pathogenesis of the maternal response in preeclampsia.

In this study there was an association between serum NGAL levels and preeclampsia. Most patients with preeclampsia still had serum NGAL level within the normal reference range yet a statistically significant difference between serum NGAL level in preeclamptics and normotensive pregnant women was found probably because the reference range used for the study might not be consistent with the study population since there were no studies that showed the normal reference range of serum NGAL for our population. Therefore, there may be need for further exploration of NGAL in our setting.

Kim and colleagues in a subgroup analysis showed that patients with severe preeclampsia had significantly higher NGAL concentrations than those with mild preeclampsia which showed a statistically significant difference and concentrations appear to be associated with the severity of the disease.[20] In our study, there was also higher NGAL levels in patients with severe preeclampsia than mild preeclampsia however it was not significant and concentrations were not associated with the severity of the disease. Kim et al considered maternal age, gestational age and body mass index while recruiting their samples, and classified severity of preeclampsia based on other features of severity such as pulmonary oedema, impaired liver function etc while we only considered gestational age and maternal age and classified severity based on blood pressure. In addition, the temperature at which blood samples were stored by Kim et al differs from that of our study. This could probably explain the differences between the two studies.

In this study, the mean difference of serum NGAL in mild preeclampsia and severe preeclampsia was not statistically significant ($p = 0.714$), this is in agreement with what was found by Simonazzi et al in Italy.[28] Further analysis also showed no association between serum NGAL levels and severity of preeclampsia.

A limitation of our study is that it is a tertiary hospital-based cross-sectional study so may not be able to definitely show association between preeclampsia and serum NGAL and findings may not be representative of the general population. A Cohort study is required useful in establishing an association between exposure and outcome in an observational study. The serum NGAL level in healthy non-pregnant women in our environment has also not been assessed in order to establish the normal reference range for the population.

CONCLUSION

This study revealed an association between serum NGAL levels and preeclampsia. However, the findings also suggested that NGAL was not a useful adjunct for the classification of preeclampsia.

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