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Serum Catestatin and Severity of Preeclampsia at a Tertiary Hospital in Southern Nigeria

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Abstract

Background*:** Preeclampsia is one of the most common causes of maternal morbidity and mortality. Extensive research into biomarkers that can help us understand the disease is vital to alleviating its burden. Catestatin, an endogenously produced regulator of cardiac function and blood pressure, may be associated with the severity of the disease. ***Methods*:** This was a cross-sectional study involving 56 pregnant women with varying forms of preeclampsia. Blood samples were obtained at diagnosis, centrifuged and the sera were stored at -20^{0}C until analysis. The catestatin levels of the sera were then measured by enzyme-linked immunosorbent assays. ***Results: The mean serum catestatin among patients with mild preeclampsia and severe preeclampsia were 3.3 ±1.2ng/ml and 4.5±2.5ng/ml, respectively (p=0.011). ***Conclusion*:** The serum catestatin level significantly relates to the increasing severity of preeclampsia. There might be a potential value for using serum catestatin to assess the severity of the disease.

Keywords: Catestatin, Pregnancy, Preeclampsia, Severity, Hypertension, Nigeria.

INTRODUCTION

Preeclampsia is a devastating pregnancy-specific disorder that is one of the leading causes of maternal morbidity and mortality worldwide. It also accounts for iatrogenic preterm delivery, leading to many neonatal morbidity and mortality. There are about 70,000 reported preeclampsia-related deaths worldwide [1]. In the Caribbean and Latin America, hypertensive disorder accounts for about 26% of maternal mortality while contributing 9% to maternal deaths in Africa and Asia [2]. In a nationwide cross-sectional study of 998 maternal deaths and 1451 near-misses in Nigeria, more than 50% of maternal deaths are due to hypertensive disorders of pregnancy and obstetric haemorrhage [3].

Significant advances have been made in the understanding of the disease. Placenta growth factor (PIGF), vascular endothelial growth factor (VEGF) and transforming growth factor-beta (TGF-β1) are soluble angiogenic factors that aid the growth of blood vessels as well as maintaining a healthy endothelium in normal pregnancy. In preeclampsia, the ischaemic placenta releases anti-angiogenic factors like soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng), which bind and block the angiogenic growth factors. Several studies have shown that the actions of the upregulated sFlt-1 and sEng on maternal endothelium result in hypertension, proteinuria and other systemic manifestations of preeclampsia [4, 5].

Catestatin is an endogenous peptide that has been shown to have diverse functions in cardiovascular and neuroendocrine systems [6]. It acts by inhibiting catecholamine release and stimulating histamine release from mast cells. Thus, the hypotensive effect of catestatin is by direct inhibition of this sympathoadrenal system and indirectly by the potent vasodilatory effects of the released histamines [7]. Several studies have shown a significant reduction of plasma catestatin levels in individuals with essential hypertension [8, 9]. This reduction is also noted in their still-normotensive offspring, indicating its role in the pathogenesis of hypertension [10]. Aside from its role in essential hypertension, catestatin has antioxidant activity and can induce angiogenesis [11]. Its favourable role is also seen in diabetes, coronary heart diseases and atherosclerosis, as it has an obesity-reducing effect and an increase in

insulin sensitivity [8-12]. Chromogranin (CgA), a prohormone of catestatin is confirmed to be expressed by decidual and trophoblasts and may be useful in predicting the disease owing to the central role placenta plays in the pathogenesis of preeclampsia [13]. It has been observed that the level of CgA gene expression was higher in the placenta of preeclamptics [14].

Though the diagnosis of preeclampsia seems not cumbersome, the ideal time for delivery to avert adverse outcomes like eclampsia, acute kidney injury, and foetal death is still challenging. Routine urinalysis being used for diagnosis is unreliable in predicting the severity. The American College of Obstetricians and Gynaecologists (ACOG) concluded that there is a poor correlation between clinical outcomes and severe proteinuria [15].

It is documented that Catestatin is elevated in preeclampsia [14-16], but the implication of its level on severity, fetal and maternal outcomes has not been documented sufficiently. The aim of this study was to compare serum catestatin levels to the severity of preeclampsia.

METHODS

This was an analytical cross-sectional study at the Department of Obstetrics and Gynaecology, University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria.

The study population included all consenting women with singleton pregnancies with preeclampsia, who received care at our hospital during the data collection period. These women with preeclampsia were divided into mild and severe cases. Preeclampsia was defined as blood pressure greater than or equal to 140/90mmHg after 20 weeks of gestation, measured on at least two occasions with an interval of at least 4 hours apart and proteinuria ≥ 1+ on dipstick. Severe preeclampsia were cases of preeclampsia with a systolic blood pressure of ≥160mmHg, a diastolic blood pressure of ≥110mmHg, features of end-organ damage, or uteroplacental dysfunction [15]. The gestational age was determined from the last menstrual period or the earliest ultrasound scan done, preferably in the first trimester, for patients who were unsure of their last menstrual period.

Women were excluded if they smoked or had coexisting medical conditions like chronic hypertension, renal disease, diabetes mellitus, sickle cell disease, peripheral vascular disease or thrombophilia. The consecutive sampling method was utilized by recruiting consecutive consenting participants who met the eligibility criteria until the desired sample size was reached.

Sample Size Determination

The sample size was determined using the formula for calculating minimum sample size involving comparison of 2 means, using a significance level of 0.05 and a power of 80%. Based on the result of our pilot study, the mean serum catestatin of the two groups were 3.5±1.2ng/ml and 4.4 ±1.8ng/ml for mild and severe preeclampsia, respectively. Thus, 28 women were needed in each group to detect a statistical difference.

Data Collection

Using a structured proforma, information was collected by direct questioning. This included the socio-demographic characteristics, parity, last menstrual period, estimated gestational age, and expected delivery date. The medical history, previous obstetric history, systolic and diastolic blood pressures and treatment regimens received were noted. Pregnancy outcomes were obtained by extracting information from the antenatal, labour, delivery and neonatal records after delivery. Fetal outcomes such as birth weight, the existence of intrauterine growth restriction and intrauterine demise were also noted.

Assay for Serum Catestatin

The serum samples obtained from participants were stored at -20^{0}C until analysis. Catestatin level was measured using Human Catestatin enzyme-linked immunosorbent assay kits by Bioassay Technology Laboratory, Jiaxing, China.

A standard solution (50µl) was added to the standard well and 40µl of the sample was added to sample wells. After that, 10µl of biotinylated human anti-catestatin antibody was added to the sample wells and this bound to catestatin in the sample. Then, 50µl of streptavidin-HRP was added to the sample wells and standard wells. They were mixed and the plate was covered with a sealer. After 60 minutes of incubation at 37^{0}C, the plate was washed five times with wash buffer, ensuring the wells were soaked with at least 300µl wash buffer for 30 seconds to 1 minute for each wash. Then, 50µl of solution A and 50µl of solution B were added to each well. The plate was covered with a new sealer and incubated for 10 minutes at room temperature. The reaction was terminated by adding 50µl acidic stop solution, and colour developed according to the amount of human catestatin. The optical density (OD value) of each well was determined immediately using a microplate reader set to 450 nm within 10 minutes of adding the stop solution.

Data Analysis

The data was imputed in IBM Statistical Package for Social Sciences (SPSS) version 27.0 software. Descriptive statistics were computed for all relevant data and shown as frequency tables and charts. The association between serum catestatin level and severity of preeclampsia was tested using student's t-test. A p-value of less than 0.05 was accepted to be statistically significant.

Ethical Approval

Approval was obtained from the ethical and research committee of the hospital (UPTH/ADM/90/S.I1/VOL.XI/1287).

RESULT

A total of 56 pregnant women with preeclampsia were recruited for the study period; 28 mild preeclampsia and 28 severe preeclampsia. The participants' characteristics and neonatal outcomes are presented in Table 1.

The participants in both groups had similar age, parity and body mass index. The majority (75%) of women with mild preeclampsia booked for antenatal care at our facility, whereas 82% of those with severe form were either unbooked or booked elsewhere (referred to our facility). There was a statistically significant difference in the diastolic blood pressure, systolic blood pressure, and fetal status between mild preeclampsia and severe preeclampsia. (p-value < 0.05).

The mean gestational age at delivery was 36.3±3.2 weeks for women with mild preeclampsia, and 32.1±3.4 weeks for women with severe preeclampsia. Additionally, the mean birth weights of neonates born to participants with mild and severe preeclampsia were 2.6±0.9kg and 1.6±0.6kg, respectively (Table 1).

Table 1: Patient characteristics and neonatal outcomes

Characteristics	Mild Preeclampsia n=28	Severe Preeclampsia n=28	P-value
	n (%)	n(%)	
Age (years) mean ± SD	33.4±5.9	34.3±5.3	0.647 #
Parity			
0	11 (39.3)	5 (17.9)	0.76 ^
≥1	17 (60.7)	23 (82.1)	
Booking status			
Booked	21 (75)	5 (17.9)	<0.001 ^*
Booked elsewhere	6 (21.4)	10 (35.7)	
Unbooked	(3.6)	13 (46.4)	
BMI (kg/m^2)	27.9±3.6	30.6±5.1	0.324 #
Systolic BP (mmHg)	146.9±4.8	177.5±16.2	<0.001 #*
Diastolic BP (mmHg)	94.6±5.8	113.93.8±12.9	0.001 #*
GA at delivery	36.3±3.2	32.1±3.4	0.545 #
Birthweight	2.6±0.9	1.6±0.6	0.095
Fetal status			
Alive	27 (96.4)	17 (60.7)	
Stillbirth	0	8 (28.6)	0.001$*
Early neonatal death	1 (3.6)	3 (10.7)	
SCBU			
Yes	9 (32.1)	13 (46.4)	0.274 ^
No	19 (67.9)	15 (53.6)	

*Statistically Significant, # Student's t-test; ^ Pearson's Chi-square; $ Fischer's test; BMI- Body Mass Index, GA- Gestational Age, SCBU- Special Care Baby Unit.

The mean serum catestatin among women with mild preeclampsia and severe preeclampsia were 3.3 ±1.2ng/ml and 4.5±2.5ng/ml respectively (Table 2). The levels were significantly higher in women with severe preeclampsia than those with mild preeclampsia (p=0.011). The median catestatin levels among participants with mild preeclampsia were 3.3ng/ml and 3.7ng/ml, respectively (Figure 1).

Table 2: Serum catestatin (ng/ml) and severity of preeclampsia

Characteristics	Mild Preeclampsia n=28	Severe Preeclampsia n=28	(P-value)
Serum Catestatin (ng/ml) (mean ±SD)	3.3 ±1.2	4.5±2.5	0.011#
# Student's t-test;			

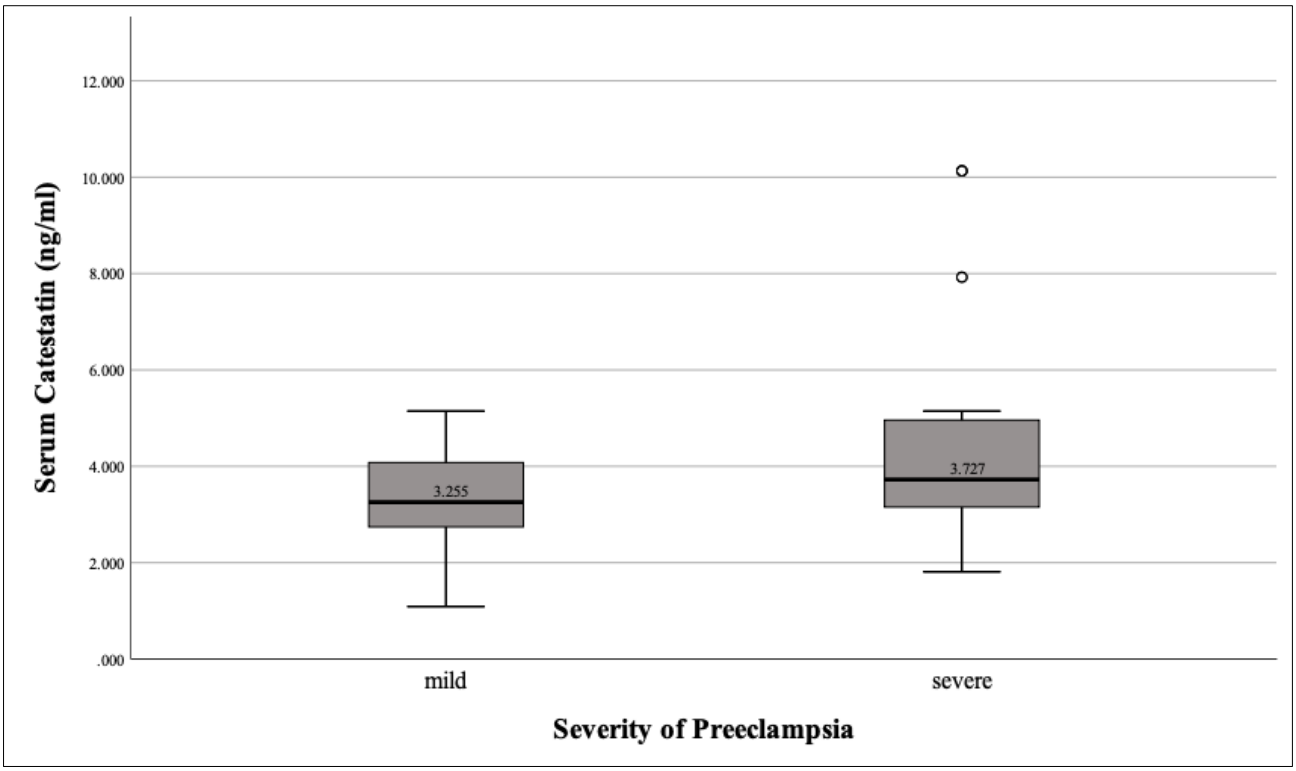

Figure 1: Serum catestatin for mild preeclampsia and severe preeclampsia

DISCUSSION

The current study demonstrated a significant association of serum catestatin levels with the severity of preeclampsia in women. Serum catestatin levels were significantly higher in participants with severe preeclampsia compared with those with mild preeclampsia (4.5 ± 2.5 ng/ml vs 3.3 ± 1.2 ng/ml; p=0.011). These results are in line with the potential involvement of catestatin in the pathophysiology of preeclampsia.

Preeclampsia is a multisystemic disorder with an incompletely understood etiology. Altered placental perfusion and increased levels of anti-angiogenic factors, including sFlt-1 and sEng, are well described in the pathogenesis of preeclampsia; however, the contribution of the sympathoadrenal system is being newly appreciated. Catestatin is an endogenously produced peptide that inhibits the release of catecholamine and causes vasodilation through histamine release, suggesting a role for catestatin in blood pressure.

The elevated serum levels of catestatin observed in this study may reflect a compensatory increase in response to augmented sympathetic outflow characteristic of preeclampsia. Our findings differ from studies by Tuten *et al*., [16], and Ozalp *et al*., [17], which were unable to show any association of catestatin levels with severity of preeclampsia. This variation could have been accounted for by genetic, geographic, or environmental differences in the study populations. The significantly higher serum catestatin in severe preeclampsia observed in our study raises interesting questions regarding its potential clinical significance.

Although catestatin has known hypotensive actions, we speculate that the catestatin levels found in our study in severe preeclampsia go beyond a beneficial effect and reflect an overwhelmed compensatory mechanism. Meng *et al*., [18], observed elevated serum catestatin levels in patients with essential hypertension. This suggests that catestatin may not act in isolation, but rather in the context of a series of regulatory systems that can become dysregulated in advanced disease states.

The perinatal outcomes from the current study reflect the substantial morbidity associated with severe preeclampsia. Women with severe disease were delivered at a significantly earlier gestational age (32.1 ± 3.4 weeks vs. 36.3 ± 3.2 weeks; p<0.05), and neonates had lower mean birth weights (1.6 ± 0.6 kg vs. 2.6 ± 0.9 kg; p<0.05). Neonates born to mothers with severe preeclampsia also had a significantly higher incidence of special care baby unit admission (46.4% vs. 32.1%), and stillbirth rate (28.6% vs. 0%). These findings are consistent with prior studies showing the profound impact of uteroplacental insufficiency and preterm delivery on neonatal outcomes.

The link between catestatin levels and the degree of severity of preeclampsia further indicates that catestatin may provide a biomarker for disease severity. Currently, diagnostic tests like platelet counts, renal function tests, and blood pressure measurements provide some predictive information about the severity of

disease. Serum catestatin, therefore, may offer an additional tool for the identification of women at risk for severe disease, enabling early intervention and enhanced outcomes.

Additional research is required to determine its utility clinically and in predicting maternal and neonatal outcomes. The limitations of this study was our modest sample size which limits the generalization of our findings. Besides, potential confounders like dietary habits, genetic susceptibilities, as well as differences in health-seeking behaviours were not sufficiently covered.

CONCLUSION

This study indicates that serum catestatin levels in women with preeclampsia were directly proportional to the severity of the disease, suggesting that catestatin may either function as a novel biomarker for the severity of the disease or may exert functional contributions to the pathophysiology of preeclampsia. Future studies with a large sample size and multiple populations are needed to confirm and explore the clinical significance of catestatin in the management of preeclampsia.

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