DOI: 10.7860/JCDR/2023/64581.18606

Original Article

Obstetrics and Gynaecology Section

Inflammatory Marker Levels in Preeclampsia versus Normal Pregnancies and Prediction of Preeclampsia Occurrence: A Prospective Mixed Methods Study

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ABSTRACT

Introduction: Preeclampsia is an important cause of adverse maternal and perinatal outcomes. However, this condition remains poorly understood, and since the only cure is delivery, prediction and prevention are crucial to prevent preterm birth or maternal compromise.

Aim: To determine the levels of acute phase reactants, namely high-sensitivity C-reactive Protein (hsCRP) and fibrinogen, between preeclamptic and non preeclamptic pregnancies. Additionally, the study aims to determine the predictive value of these acute phase reactants for preeclampsia.

Materials and Methods: A prospective mixed methods study was conducted in two tertiary hospitals and two specialist hospitals in the Ijebu/Remo axis of Ogun state, Nigeria. Preeclamptic participants were recruited during pregnancy and postpartum and matched with non preeclamptic controls (case-control arm, n=179, comprised of 87 preeclamptics and 92 controls). Additionally, a cohort of non preeclamptic women (n=71) was recruited and biomarker-assayed before 20 weeks gestation, followed-up for the development of preeclampsia. The biomarker assay was performed using the ELISA technique. The Student's t-test was used to compare the mean levels of markers between the studied groups. Categorical data were compared using the Chi-square test. A p-value <0.05 was considered to be statistically significant.

Results: The levels of hsCRP were significantly higher in pregnant preeclamptic women (12.71±1.99 mg/L) compared to non preeclamptic women (4.39±3.41 mg/L) (p-value=0.001). Similarly, fibrinogen levels were elevated in preeclamptic women (9.45±1.28 g/L) compared to non preeclamptic women (7.19±1.86 g/L) (p-value=0.001). This trend was also observed among postpartum women, with hsCRP levels of 10.39±2.43 mg/L in preeclamptics compared to 2.53±2.06 mg/L in non preeclamptics (p-value=0.001). The mean fibrinogen level was 8.63±1.91 g/L in preeclamptics compared to 4.09±1.66 g/L in non preeclamptics. Fibrinogen demonstrated a higher specificity (88.9%) and Negative Predictive Value (NPV) of 100% compared to hsCRP (specificity=47.1% and NPV=76.1%). The biomarker levels also correlated significantly with the severity of preeclampsia. For hsCRP, there was a correlation with Systolic Blood Pressure (SBP) (r-value=0.385, p-value=0.001), Diastolic Blood Pressure (DBP) (r-value=0.364, p-value=0.001), and proteinuria (r-value=0.314, p-value=0.001). For fibrinogen, there was a correlation with SBP (r-value=0.252, p-value=0.014), DBP (r-value=0.378, p-value=0.001), and proteinuria (r-value=0.356, p-value=0.001).

Conclusion: Although hsCRP and fibrinogen levels were significantly higher and correlated well with the severity of preeclampsia, their use for prediction may be limited. However, fibrinogen appears to have better prospects.

Keywords: Acute phase protein, Biomarker levels, Diastolic blood pressure

INTRODUCTION

Preeclampsia is the most common and least understood hypertensive disorder of pregnancy [1,2]. Arguably, it is the leading cause of maternal mortality globally, as there is now an increasing ability to combat haemorrhage [2,3]. This condition is also responsible for a significant proportion of preterm births before 34 weeks of gestation. It can rapidly progress to eclampsia or life-threatening complications like the Haemolysis Elevated Liver Enzymes and Low Platelet Count (HELLP) syndrome and haemorrhage, all within a short time with minimal or subtle warning signs [4].

Prevention of this condition remains the key, as delivery is the only known cure [5]. However, delivery can be a challenging because early delivery risks prematurity, while delayed delivery exposes the mother to the risk of progressive disease and complications. This aligns with the currently held pathophysiological theory of preeclampsia being a placental disease, with symptoms resolving after delivery of the placenta [6]. Preventive measures are available, including low-dose aspirin, calcium supplementation, and antioxidants. Omega-3 fish oils have also been shown to be useful in preventing or alleviating preeclampsia [7].

Prediction of preeclampsia has been at the forefront, with early pregnancy uterine artery Doppler ultrasound scanning being the most important screening tool today for identifying pregnant women at greater risk of developing preeclampsia later in pregnancy [8]. Despite this breakthrough, the search for other screening tools continues. There is a need for simpler, readily available, less expensive, less specialist-dependent, and easily reproducible methods that can be incorporated into routine antenatal investigations. Some researchers have found variations in levels of serum albumin, creatinine, and uric acid with the severity of preeclampsia; however, they have low negative predictive values for prediction preeclampsia [9-11].

Preeclampsia is also considered a multisystemic inflammatory disorder, injury to the microvasculature is and associated with the production of acute phase reactants and other inflammatory markers. These markers have plasma levels higher than those in non preeclamptic pregnant women and may correspond with the severity of the disease [12].

The acute phase reactants CRP and fibrinogen have been shown to predict the occurrence of cardiovascular events, such as stroke, myocardial infarction, myocardial ischemia, and chronic hypertension, in non pregnant adult populations. Levels of hsCRP in preeclampsia have been found to be higher and predictive of adverse maternal and perinatal outcomes [13]. It has also been demonstrated to be a good predictor of gestational diabetes [14]. The hsCRP assay is now widely used due to its ability to detect very low levels of CRP [15,16]. Their use in preeclampsia holds great promise for grading the severity of the disease, prognostication, prediction of occurrence, and assessing the risk for future cardiovascular events in survivors of preeclampsia.

Therefore, this study aims to compare the levels of inflammatory markers, hsCRP and fibrinogen, between preeclamptic and non preeclamptic women during pregnancy and after delivery. The study also aims to determine their usefulness in predicting preeclampsia by assessing the risk of developing preeclampsia among pregnant women with elevated biomarker levels in early pregnancy in the Remo/Ijebu axis of Ogun State, southwestern Nigeria.

MATERIALS AND METHODS

It was a multicenter prospective cohort study with a mixed-method study design involving the four highest-level referral centres in the Remo/Ijebu axis of Ogun State, comprising two teaching hospitals and two State Specialist Hospitals. Participant recruitment and data collection lasted for a duration of 16 months, from December 2019 to March 2021. The study was registered with clinicaltrials.gov, with protocol number NCT04468763. Ethical clearance was obtained from the health and research ethics committees of Babcock University Teaching Hospital (BUHREC014/19) and Olabisi Onabanjo University Teaching Hospital (OOUTH/HREC/248/2019AP) before commencing the study. Written informed consent, with signature or thumbprints, was obtained from the study participants or their relatives before the start of the interview. Patient confidentiality was maintained by ensuring that the proforma was anonymous.

Inclusion criteria: Pregnant women whose pregnancies were within 20 weeks gestational age and attending antenatal clinics in any of the study sites, women diagnosed with preeclampsia between the gestational ages of 20 and 41 weeks at any of the study sites, and delivered mothers who presented with preeclampsia postpartum. Controls were pregnant or delivered women without preeclampsia matched for age, parity, and gestational age at the same site.

Exclusion criteria: Participants with a history of pre-existing hypertension, cardiac disease, renal disease, diabetes mellitus, or connective tissue disorders were excluded. Women who failed to consent for the study were also excluded from the study.

Sample size determination and sampling technique: The primary outcome variable was the serum level of hsCRP. The mean serum levels of hsCRP obtained by Jannesari R and Kazemi E (2017) in women with preeclampsia (7.71±6.19 mg/L) and in women without preeclampsia (5.44±3.94 mg/L) were applied in the calculation of the sample size using the formula for comparison of means. To attribute variations in hsCRP levels to preeclampsia, a minimum difference of 2.27 mg/L, obtained in the same study, was applied to the formula. Thus:

$$N=(u+v)^2\ (Ó_1^2+Ó_0^2)/(\mu_1-\mu_0)$$

When 10% was added for attrition, a sample size of N=263 participants was obtained.

The participants were recruited into three groups:

1. **Cohort study group:** Comprised of 72 pregnant women without preeclampsia before 20 weeks gestational age (Group A).
2. **Case-control study Group I:** Comprised of 120 pregnant women, with 60 preeclamptic women and 60 women without preeclampsia as controls (Group B).
3. **Case-control study Group II:** Comprised of 72 postpartum women, with 36 preeclamptic women and 36 women without preeclampsia (Group C).

Consecutive preeclamptic pregnant or delivered patients were recruited for the study, and corresponding non preeclamptic women matched for age, parity, and gestational age were recruited as controls. For the cohort arm of the study, systematic random sampling was used to recruit pregnant non preeclamptic women from the antenatal care booking clinics. Participant recruitment stopped when the calculated sample size was attained.

Procedure

Blood pressure measurements were obtained by a trained nurse at each site using a manually operated mercury-powered sphygmomanometer, with the readings taken in the sitting position. The Korotkoff sound V was used as the level for DBP in all cases [6]. After explaining the procedure, obtaining written informed consent, and completing the history segments of the proforma, 10 mL of venous blood samples were obtained from the participants prior to the commencement of any intravenous therapy. This sample was collected from the contralateral upper limb of patients who were already on intravenous infusion. The venous blood was aspirated from the participant's antecubital vein and placed in a lithium heparin vacuum tube (5 mL) and a plain anticoagulant-free bottle (5 mL).

All participants recruited within the first half of pregnancy were followed-up in the antenatal clinic through delivery and in the postnatal clinic until the end of puerperium. During this time, they were observed for the development of preeclampsia. Those admitted with preeclampsia in pregnancy were observed for the correlation of preeclampsia severity with the levels of biomarkers. Together with those recruited postpartum, their levels of inflammatory markers were compared with those of healthy postpartum women.

The blood samples were immediately transported in an ice container to the laboratory for analysis. They were centrifuged at 2,500 rpm for five minutes at all sites before the well-labeled supernatant and packed red cells were transported to Babcock University. Serum aliquots were then stored at 2-8°C until further analysis. The biomarkers hsCRP and fibrinogen were assayed using the ELISA technique. Elevation of inflammatory biomarker levels was considered as a serum level of hsCRP ≥3 mg/L [13,14,17] and fibrinogen ≥5 g/L [18,19].

STATISTICAL ANALYSIS

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) software version 21.0. Numerical data were expressed as mean±Standard Deviation (SD). The Student's t-test was used to compare the mean levels of hsCRP and fibrinogen between the studied groups. Pearson correlation statistics were used to assess the relationship between biomarkers and indices of preeclampsia severity. Categorical data were compared using the Chi-square test to determine risks between groups in the study. The level of statistical significance was set at a p-value <0.05.

RESULTS

A total of 264 patients were recruited for the study, but only the data of 250 were included in the final analysis. Six samples were observed to have lysed preanalytically, including one sample from the cohort group, three samples from the pregnant preeclamptic group, and two from postpartum preeclamptic women. Although the aforementioned samples were not analysed, the samples and data from the corresponding non preeclamptic controls were included in the analysis. Additionally, among the postpartum recruited preeclamptics, two were found to have chronic kidney disease, one was diabetic, and one refused to allow blood sample collection after signing the consent form. However, the clinical data and samples for the non preeclamptic controls for these postpartum preeclamptic women

were not included in the final analysis. Therefore, data from a total of 71 participants in the cohort study group, 117 in the pregnant women group (57 preeclamptics and 60 controls), and 62 in the postpartum group (30 preeclamptics and 32 controls) are presented.

[Table/Fig-1] shows that the participants were similar in socio-demographic characteristics such as age (p-value=0.145), parity (p-value=1.000), educational level attained (p-value=0.461), employment status (p-value=0.711), and BMI (p-value=0.397). However, they differed in booking status (p-value <0.001) and the number of foetuses carried (p-value=0.048).

Characteristics	Study group		p-value
	Preeclamptic (n=95)	Non preeclamptic (n=155)	
Maternal age (years)	31.11±5.97	30.03±5.43	0.145#
Parity	**n (%)**	**n (%)**	
<2 (n=177)	67 (37.9)	110 (62.1)	1.000
≥2 (n=73)	28 (38.4)	45 (61.6)	
Booking status			
Unbooked (n=86)	50 (58.1)	36 (41.9)	<0.001
Booked (n=164)	45 (27.4)	119 (72.6)	
Highest educational level			
Primary (n=11)	4 (36.4)	7 (63.6)	0.461
Secondary (n=135)	56 (41.5)	79 (58.5)	
Tertiary (n=104)	35 (33.7)	69 (66.3)	
Employment status			
Unemployed (n=36)	15 (41.7)	21 (58.3)	0.711
Employed (n=214)	80 (37.4)	134 (62.6)	
Maternal BMI (kg/m²)	31.57±6.65	30.79±6.22	0.397#
No. of foetuses	**n (%)**	**n (%)**	
Singleton (n=236)	86 (36.4)	150 (63.6)	0.048
Twin (n=14)	9 (64.3)	5 (35.7)	

[Table/Fig-1]: Comparing socio-demographic characteristics of the patients.
Chi-square test was used; #=student t-test was used

The preeclamptic patients had significantly poorer outcomes, as depicted in [Table/Fig-2], with a higher risk of delivery at gestational age <34 weeks (OR=3.58, 95% CI=1.64-7.84, p-value=0.001), birth weight <2.5 kg (OR=3.97, 95% CI=2.21-7.11, p-value <0.001), first-minute APGAR score <7 (OR=2.76, 95% CI=1.49-5.09, p-value=0.02), perinatal death (OR=5.75, 95% CI=0.90-35.58, p-value=0.002), and severe maternal outcome (OR=5.13, 95% CI=1.78-14.80, p-value <0.001).

Characteristics	Study group		OR (95% CI)	p-value
	Preeclamptic (n=95)	Non preeclamptic (n=155)		
GA at delivery	**n (%)**	**n (%)**		
<34 weeks (n=32)	21 (65.6)	11 (34.4)	3.58 (1.64-7.84)	0.001
≥34 weeks (n=210)	73 (34.8)	137 (65.2)		
Birth weight				
*<2.5 kg (n=73)	44 (60.3)	29 (39.7)	3.97 (2.21-7.11)	<0.001
≥2.5 kg (n=159)	44 (27.7)	115 (72.3)		
First minute APGAR score				
*<7 (n=60)	33 (55.0)	27 (45.0)	2.76 (1.49-5.09)	0.002
≥7 (n=153)	47 (30.7)	106 (69.3)		
Sex of baby at delivery				
Male (n=136)	57 (41.9)	79 (58.1)	1.24 (0.90-1.73)	0.192
Female (n=113)	38 (33.6)	75 (66.4)		
Mode of delivery				
Operative (n=107)	47 (43.9)	60 (56.1)	1.29 (0.99-1.78)	0.067
SVD (n=142)	48 (33.8)	94 (66.2)		
Foetal outcome				
Alive (n=241)	87 (36.1)	154 (63.9)	5.75 (0.90-35.58)	0.002
*Dead (n=9)	8 (88.9)	1 (11.1)		
Maternal outcome				
Alive (n=227)	75 (33.0)	152 (67.0)	5.13 (1.78-14.80)	<0.001
*Severe maternal outcome (n=23)	20 (87.0)	3 (13.0)		

[Table/Fig-2]: Comparing the outcomes between preeclamptic and non preeclamptic pregnancies.
The calculated odds ratios were for the outcomes with the sign; Chi-square test was used

The mean levels of inflammatory biomarkers observed during pregnancy were significantly higher among the preeclamptic patients, with an hsCRP level of 12.72±1.99 mg/L compared to 4.39±3.41 mg/L in the non preeclamptics (p-value <0.001), and a fibrinogen level of 9.45±1.28 g/L compared to 7.19±1.86 g/L among the non preeclamptics (p-value <0.001), as shown in [Table/Fig-3]. A similar finding of higher mean inflammatory marker levels was noted among the postpartum preeclamptic patients, with an hsCRP level of 10.39±2.43 mg/L compared to 2.53±2.06 mg/L (p-value=0.001), and a fibrinogen level of 8.63±1.91 g/L compared to 4.09±1.66 g/L (p-value=0.001).

Pregnancy state	Study group (n=117)		p-value
Pregnant women (n=117)	Preeclamptic (n=57)	Non preeclamptic (n=60)	
hsCRP (mg/L)	12.72±1.99	4.39±3.41	<0.001
Fibrinogen (g/L)	9.45±1.28	7.19±1.86	<0.001
Postpartum women (n=62)	Preeclamptic (n=30)	Non preeclamptic (n=32)	
hsCRP (mg/L)	10.39±2.43	2.53±2.06	0.001
Fibrinogen (g/L)	8.63±1.91	4.09±1.66	0.001

[Table/Fig-3]: Comparing the mean levels of inflammatory markers between the preeclamptic and non preeclamptic women.
Student t-test was used

[Table/Fig-4] reveals that the preeclamptic patients had a significantly higher risk of having inflammatory marker levels above the upper limits of the normal reference range for pregnancy and the postpartum period: hsCRP (OR=1.71, 95% CI=1.38-2.12, p-value <0.001) and fibrinogen (OR=1.13, 95% CI=1.02-1.26, p-value=0.033). In the postpartum period, the findings were: hsCRP (OR=4.57, 95% CI=2.38-8.80, p-value <0.001) and fibrinogen (OR=5.97, 95% CI=2.66-13.49, p-value <0.001).

Group	Biomarker elevation		OR (95% CI)	p-value
	hsCRP (≥3 mg/L)			
Pregnant women (n=117)	Yes	No	1.71 (1.38-2.12)	<0.001
Preeclamptic (n=57)	57 (100.0%)	0		
Non preeclamptic (n=60)	35 (58.3%)	25 (41.7%)		
Postpartum women (n=62)				
Preeclamptic (n=30)	30 (100.0%)	0 (0%)	4.57 (2.38-8.80)	<0.001
Non preeclamptic (n=32)	7 (21.9%)	25 (78.1%)		
Group	Fibrinogen (≥5 g/L)		OR (95% CI)	p-value
Pregnant women (n=117)	Yes	No	1.13 (1.02-1.260)	0.033
Preeclamptic (n=57)	56 (98.2%)	1 (1.8%)		
Non preeclamptic (n=60)	52 (86.7%)	8 (13.3%)		
Postpartum women (n=62)				
Preeclamptic (n=30)	28 (93.3%)	2 (6.7%)	5.97 (2.66-13.49)	<0.001
Non preeclamptic (n=32)	5 (15.6%)	27 (84.4%)		

[Table/Fig-4]: Comparing the rates of abnormal biomarker elevations between preeclamptic and non preeclamptic women.
Chi-square test was used

[Table/Fig-5] highlights the use of these acute phase reactants for preeclampsia prediction: hsCRP had a sensitivity of 100%, specificity of 85.7%, PPV of 47.1%, and NPV of 76.1%, while

fibrinogen was observed to have a sensitivity of 100%, specificity of 88.9%, PPV of 53.3%, and NPV of 100%.

HSCRP elevation before 20 weeks as screening test for preeclampsia (n=71)			
	Preeclampsia occurrence		
Test result	Yes	No	Total
Positive	8	9	17
Negative	0	54	54
Total	8	63	71
Sensitivity=100.0% Specificity=85.7% PPV=47.1% NPV=76.1%			
Fibrinogen elevation before 20 weeks as screening test for preeclampsia (n=71)			
	Preeclampsia occurrence		
Test result	Yes	No	Total
Positive	8	7	15
Negative	0	56	56
Total	8	63	71
Sensitivity=100.0% Specificity=88.9% PPV=53.3% NPV=100.0%			

[Table/Fig-5]: Prediction of preeclampsia before 20 weeks using inflammatory marker elevation as screening test.

[Table/Fig-6] shows that hsCRP had a statistically significant moderate positive correlation with the severity of preeclampsia indicated by SBP (r-value=0.385, p-value=0.001), DBP (r-value=0.364, p-value=0.001), and proteinuria (r-value=0.314, p-value=0.001). A similar finding was observed for fibrinogen: SBP (r-value=0.252, p-value=0.014), DBP (r-value=0.378, p-value=0.001), and proteinuria (r-value=0.356, p-value=0.001). However, the biomarkers did not show any statistically significant correlation with each other: hsCRP vs fibrinogen (r-value=0.033, p-value=0.747).

Correlation of hsCRP level with severity		
Parameters	Pearson r-coefficient	Significance (2-tailed)
Systolic BP (n=95)	0.385**	<0.001
Diastolic BP (n=95)	0.364**	<0.001
Degree of proteinuria (n=95)	0.314	<0.001
BMI (n=72)	0.002	0.987
Birth weight (n=88)	0.078	0.468
Gestational age at delivery (n=94)	0.054	0.606
1st minute APGAR score (n=80)	0.002	0.984
Fibrinogen (n=95)	0.033	0.747
Correlation of fibrinogen level with severity		
Parameters	Pearson r-coefficient	Significance (2-tailed)
Systolic BP (n=95)	0.252	0.014
Diastolic BP (n=95)	0.378	<0.001
Degree of proteinuria (n=95)	0.356	<0.001
BMI (n=72)	-0.013	0.914
Birth weight (n=88)	-0.223	0.037
Gestational age at delivery (n=94)	-0.240	0.159
1st minute APGAR score (n=80)	-0.005	0.966
hsCRP level (n=95)	0.033	0.747

[Table/Fig-6]: Correlation between inflammatory biomarkers and severity of preeclampsia.

DISCUSSION

The participants in the two different study groups were comparable with respect to baseline socio-demographic data; thus, any differences in outcome variables (hsCRP, fibrinogen, and clinical parameters) may be due to preeclampsia.

Skilled care in pregnancy and delivery has been shown to be useful in the prevention of obstetric complications and reduction of morbidity from them [20]. Therefore, it is not surprising to observe significantly higher rates of "unbooked" mothers among the preeclamptic group, as their population was further increased by the number of unbooked women presenting with convulsions. Skilled antenatal care offers opportunities for preventive measures and early detection with appropriate treatment of preeclampsia [21]. Present study finding of a significantly higher proportion of twin pregnancies among preeclamptic women also supports earlier observations that multi-foetal gestation is a recognised risk factor for preeclampsia. This can be explained by the fact that preeclampsia is a disease of the trophoblast, and a larger or increasing number of placentas raises the risk for its development [6]. Preeclampsia is an important cause of preterm birth before 34 weeks of gestational age, and present study findings of a significantly lower gestational age at delivery largely corroborate this [22]. Additionally, significantly higher rates of operative deliveries, lower birth weight, lower first-minute APGAR scores, and higher rates of perinatal mortality and adverse maternal outcomes observed among the preeclamptic pregnancies are in line with widely reported complications of preeclampsia in Nigeria, sub-Saharan Africa, and globally [23-25].

The observed mean levels of the two acute phase reactants, hsCRP and fibrinogen, were significantly higher among preeclamptic women both during pregnancy and after delivery. A study among a similar population in southwestern Nigeria also observed significantly elevated hsCRP levels among preeclamptic pregnant women [26]. These findings align with the consideration of preeclampsia as an inflammatory condition [27]. The finding of elevated mean levels of CRP obtained among the preeclamptic group largely corroborates consistent findings of CRP elevation and its correlation with the severity of preeclampsia from earlier studies in Turkey, Bulgaria, India, South Korea, and Nigeria [28-33]. However, it contrasts with the findings from one study in the United Kingdom, where it was concluded that CRP levels did not suggest maternal inflammatory response as an underlying factor in preeclampsia [34]. It is also important to note that hsCRP levels tend to be higher among pregnant women compared to non pregnant women, and CRP levels demonstrate wide variations as the pregnancy advances [26,31,32]. Furthermore, elevation of serum hsCRP was also found in other hypertensive disorders of pregnancy in general, not just in preeclampsia alone [35].

Fibrinogen levels in pregnancy have been shown to progressively increase, especially close to delivery, due to increased procoagulation activity and a decrease in fibrinolytic activity. This is an adaptive mechanism necessary to limit blood loss at delivery [36,37]. Maintaining fibrinogen within normal levels is critical for a successful pregnancy outcome. Exaggerated levels increase the risk for Venous Thromboembolism (VTE), while very low levels have been associated with an increased risk of massive postpartum hemorrhage [36,38,39]. Preeclampsia is a recognised cause of consumption coagulopathy leading to low fibrinogen levels when complicated by HELLP syndrome. The finding of elevated fibrinogen levels among preeclamptic women in present study study also supports earlier reports of preeclampsia as an important cause of elevated fibrinogen levels [40,41]. Fibrinogen levels have consistently been shown to rise as pregnancy advances from the first trimester to delivery and then begin to decline in the postpartum period [36,38,40,41]. The level of fibrinogen obtained in non preeclamptic pregnancies after 20 weeks gestational age in this study is notably >5 g/L, which contrasts findings from Sokoto, northwestern Nigeria, where values were consistently lower than 5 g/L throughout pregnancy [38].

Although both hsCRP and fibrinogen had very high sensitivity, the low positive predictive value for hsCRP suggests that it is limited in accurately predicting which pregnant women will develop

preeclampsia. Thus, preeclampsia may not be the sole reason for the elevation of hsCRP. While some earlier studies suggest CRP as a reliable predictor of preeclampsia [28,32,42], it has been reported that hsCRP elevation could be due to various factors, including pregnancy itself, labor (considered an inflammatory condition), bacterial airway infections, and seasonal variation. These factors may be responsible for wide variations in hsCRP levels in a particular individual [43]. This biomarker is not specific for predicting preeclampsia because a normal serum level does not necessarily exclude preeclampsia, as shown by our observed low negative predictive value. Another study from India reported that hsCRP elevation was associated with general adverse maternal and fetal outcomes, not specifically preeclampsia [13]. The findings from a prospective study by Mishra et al., also raise questions about the use of hsCRP alone as a predictor of outcome in women with preeclampsia, suggesting the use of hsCRP in combination with other biomarkers such as uric acid for preeclampsia prediction [31].

Fibrinogen, however, demonstrates better prospects as a predictor of preeclampsia due to the following observations: it has a high sensitivity, a high specificity, and a very high negative predictive value. Therefore, normal levels of fibrinogen in pregnancy largely exclude preeclampsia. The anticipated advantage of these biomarkers over uterine artery Doppler ultrasound scanning is that they do not require the expertise of specialists, extra cost of specialised ultrasound scanning, referral to a specialist, or an extra appointment. The sample for the biomarkers can be obtained alongside other blood samples at the time of the antenatal booking visit.

However, these two biomarkers may be useful for grading the severity of preeclampsia as they demonstrate a significant moderate correlation with blood pressure and the degree of proteinuria, which are important indicators of the severity of preeclampsia [44]. This finding supports earlier studies that demonstrated significantly elevated levels of these biomarkers among preeclamptic women, suggesting that preeclampsia may be responsible for the observed higher levels. Similar findings have been reported in similar sub-Saharan African, European, and Asian populations [28-30,32,33,38,41,42]. However, these biomarkers did not demonstrate a statistically significant correlation with the complications of preeclampsia. This finding may be explained by the fact that outcomes of medical disorders in pregnancy depend on a number of other factors, including health system delays, reproductive health factors, and socioeconomic factors. These factors can modify and determine the timing and quality of access to skilled care and the severity on of individuals with other baseline pre-morbid states. Survival in preeclampsia depends on presentation, the quality, and timeliness of care, and to a lesser extent, the severity of the preeclampsia. Timeliness and quality of care were major determinants of survival in an earlier nationwide study on maternal near miss and mortality in Nigeria [45]. There was no significant relationship between the level of hsCRP and the BMI of the preeclamptic women, which is similar to findings from a study assaying hsCRP levels among women with gestational diabetes mellitus [14].

It is surprising, however, that the levels of hsCRP do not have a significant correlation with fibrinogen levels, contrasting an earlier report from Turkey [29]. This may explain why they have different predictability indices in present study. Another reason could be their difference in origin: while hsCRP is solely a product of inflammatory response, which could occur from other inflammatory conditions common in Lower Middle-Income Countries (LMIC), fibrinogen elevation can additionally be contributed to by a different pathway: coagulation. This could be a consequence of the widespread vascular endothelial affectation and haematological changes that preeclampsia largely mediates, and this may explain why fibrinogen elevation in the abnormal range may be a better predictor of preeclampsia occurrence [39,46,47]. Preeclampsia is associated with an increased risk of coagulopathy [48]. Fibrinogen levels were also observed to show no significant correlation with BMI, present study observed fibrinogen levels can be safely explained as being a consequence of the changes associated with preeclampsia.

Limitation(s)

The outbreak of COVID-19, which occurred soon after the commencement of data collection, created the potential for confusing the diagnosis of preeclampsia with complications of COVID-19 and the loss of preeclampsia cases due to adjustments made by emergency units for patient care at a national level. To mitigate this, a strict case definition for preeclampsia was instituted, protocols for safe patient handling were included, and the duration of patient recruitment was extended from 12 to 16 months at all study sites.

CONCLUSION(S)

There was a significant elevation in acute phase reactant levels due to preeclampsia, which supports the widely held concept of preeclampsia as an inflammatory condition. Although hsCRP and fibrinogen levels were significantly higher and correlated well with the severity of preeclampsia, their use for prediction may be limited, possibly because the condition is in a latent stage at this point in pregnancy and the expression of inflammatory markers is dormant. However, fibrinogen appears to have better prospects as a predictor. Further studies are required to determine the triggers of inflammation and the clinical manifestations of the disease.

REFERENCES

[1] Onyiriuka A, Okolo A. Perinatal outcome in patients with pre-eclampsia in Benin City, Nigeria. Trop J Obstet Gynaecol. 2004;21:148-52.
[2] Sibai BM. Diagnosis, prevention, and management of eclampsia. Obstet Gynecol. 2005;105(2):402-10.
[3] Ghulmiyyah L, Sibai B. Maternal mortality from preeclampsia/eclampsia. Semin Perinatol. 2012;36(1):56-59.
[4] Khan K, Wojdyla D, Say L, Gulmezoglu A, Van Look P. WHO analysis of causes of maternal death: A systematic review. Lancet. 2006;367(9516):1066-74.
[5] National High Blood Pressure Education Program Working Group. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol. 2000;183:S1-22.
[6] Villar J, Say L, Shennan A, Lindheimer M, Dulley L, Conde-Agudelo A. Methodological and technical issue related to the diagnosis, screening, prevention and treatment of pre-eclampsia and eclampsia. Int J Gynecol Obstet. 2004;89(Suppl):528-41.
[7] Atallah A, Hofmeyr G, Duley L. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Database Syst Rev. 2004;2:CD0001059.
[8] Meads CA, Cnossen JS, Meher S, Juarez-Garcia A, ter Riet G, Duley L, et al. Methods of prediction and prevention of pre-eclampsia: Systematic reviews of accuracy and effectiveness literature with economic modeling. Health Technol Assess. 2008;12(1):iii-iv.
[9] Salako B, Odukogbe A, Olayemi O, Adedapo K, Aimakhu C. Prevalence of hypertension at antenatal booking and delivery in Ibadan. Trop J Obstet Gynaecol. 2003;20:49-51.
[10] Thangaratinam S, Ismail K, Sharp S, Coomarasmy A, Khan K. Accuracy of serum uric acid in predicting complications of pre-eclampsia: A systematic review tests in prediction of pre-eclampsia severity review group. BJOG. 2006;113:369-78.
[11] Bellomo G, Venazi S, Saronio P, Verdura C, Narducci P. Prognostic significance of serum uric acid in women with gestational hypertension. Hypertension. 2011;58:704-08.
[12] Redman C, Sacks G, Sargent I. Pre-eclampsia an excessive maternal inflammatory response to pregnancy. Am J Obstet Gynecol. 1999;180(2):499-506.
[13] Dhok A, Daf S, Mohod K, Kumar S. Role of early second trimester high sensitivity C-reactive protein for prediction of adverse pregnancy outcome. JK Sci. 2011;13(3):141-44.
[14] Kumari R, Singh H. The prevalence of elevated high-sensitivity C-reactive protein in normal pregnancy and gestational diabetes mellitus. J Fam Med Prim Care. 2017;6:259-64.
[15] Yu H, Rifai N. High-sensitivity C-reactive protein and atherosclerosis: From theory to therapy. Clin Biochem. 2000;33:601-10.
[16] Yucel D. C-Reactive protein vs. high-sensitivity C-reactive protein: What is the difference? Türk Biyokim Derg. 2014;39:43-44.
[17] Roberts W. CDC/AHA Workshop on Markers of Inflammation and Cardiovascular Disease: Application to clinical and public health practice: Laboratory tests available to assess inflammation--performance and standardization: A background paper. Circulation. 2004;110:572-76.
[18] Szecsi P, Jorgensen M, Klajnbard A, Andersen M, Colov N, Stender S. Haemostatic reference intervals in pregnancy. Thromb Haemostat. 2010;103:718-27.

[19] Karlsson O, Jeppsson A, Thornemo M, Lafrenz H, Radstrom M, Hellgren M. Fibrinogen plasma concentration before delivery is not associated with postpartum haemorrhage: A prospective observational study. Br J Anaesth. 2015;115:99-104.
[20] Hogan M, Foreman K, Naghavi M, Ahn S, Wang M, Makela S, et al. Maternal mortality for 181 countries, 1980-2008: A systematic analysis of progress towards Millennium Development Goal 5. Lancet. 2010;8(375):1609-23.
[21] Owolabi A, Fatusi A, Kuti O, Adeyemi A, Faturoti S, Obiajunwa P. Maternal complications and outcomes in booked and unbkooked Nigerian mothers. Singap Med J. 2008;49(7):526-31.
[22] Ngoc N, Merialdi M, Abdel-Aleem H, Carroli G, Purwar M, Zavaleta N, et al. Causes of stillbirths and early neonatal deaths: Data from 7993 pregnancies in six developing countries. Bull World Health Organ. 2006;84(9):699-705.
[23] Walker J. Preeclampsia. Lancet. 2000;7(356 (9237)):1260-65.
[24] Anorlu R, Iwuala N, Odun C. Risk factors for pre-eclampsia in Lagos Nigeria. Aust N Z J Obstet Gynaecol. 2005;45(4):278-82.
[25] Makinde O, Adegoke O, Adeniran I, Ndububa D, Adeyemi A, Owolabi A, et al. HELLP syndrome: The experience at Ile-Ife, Nigeria. J Obstet Gynaecol. 2009;29(3):195-99.
[26] Akiibinu M, Kolawole T, Ekun O, Akiibinu S. Metabolic dysfunctions in Nigerian pre-eclamptics. Arch Gynecol Obstet. 2013;288:1021-26.
[27] Teran E, Escudero C, Moya W, Flores-Manzur M, Lopez-jaramillo P. Elevated C-reactive protein and pro-inflammatory cytokines in Andean women with pre-eclampsia. Int J Gynaecol Obstet. 2001;75:243-49.
[28] Ustun Y, Engin-Ustun Y, Kamaci M. Association of fibrinogen and C-reactive protein with severity of preeclampsia. Obstet Gynecol Reprod Biol. 2005;121:154-58.
[29] Kumru S, Godekmerdan A, Kutlu S, Ozcan Z. Correlation of maternal serum high-sensitive C-reactive protein levels with biochemical and clinical parameters in preeclampsia. Eur J Obstet Gynecol Reprod Biol. 2006;124:164-67.
[30] Batashki I, Milchev N, Topalovska D, Uchikova E, Mateva N. C-reactive protein in women with pre-eclampsia. Akush Ginekol Sofiia. 2006;45((Suppl 1)):47-50.
[31] Mishra N, Pradhan K, Sahoo G, Rohilla M, Meena M. Can hsCRP be the sole investigation for predicting the severity and outcome in women with pre-eclampsia presenting late in pregnancy? Trop J Obstet Gynaecol. 2019;36:54-60.
[32] Hwang H, Kwon J, Kim M, Park Y, Kim Y. Maternal serum highly sensitive C-reactive protein in normal pregnancy and pre-eclampsia. Int J Gynaecol Obstet. 2007;98:105-09.
[33] Udenze I, Amadi C, Awolola N, Makwe C. The role of cytokines as inflammatory mediators in preeclampsia. Pan Afr Med J. 2015;20:219.
[34] Savvidou M, Lees C, Parra M, Hingorani A, Nicolaides K. Levels of C-reactive protein in pregnant women who subsequently develop pre-eclampsia. BJOG. 2002;109:297-301.
[35] Joshi K, Acharya N, Acharya S, Joshi S. Maternal serum High-Sensitivity C-Reactive Protein (hsCRP) as a prognostic marker of fetomaternal outcome in hypertensive disorders of pregnancy: A novel study. Cureus. 2022;14(4):e24327.
[36] Siennicka A, Kłysz M, Chełstowski K, Tabaczniuk A, Marcinowska Z, Tarnowska P, et al. Reference values of D-dimers and fibrinogen in the course of physiological pregnancy: The potential impact of selected risk factors-A pilot study. BioMed Res Int. 2020;2020:3192350.
[37] Hellgren M. Hemostasis during normal pregnancy and puerperium. Semin Thromb Hemost. 2003;29(2):125-30.
[38] Okwesili A, Ibrahim K, Nnadi D, Barnabas B, Abdulrahaman Y, Udomah F, et al. Fibrinogen levels among pregnant women of African Descent in Sokoto North Western Nigeria. Front Biomed Sci. 2016;1(2):07-11.
[39] Matsunaga S, Takai Y, Seki H. Fibrinogen for the management of critical obstetric hemorrhage. J Obstet Gynaecol Res. 2019;45(1):13-21.
[40] Amilo G, Anokwute M, Ifeanyichukwu M, Chukwuanukwu O, Ifediata F, Ezeah S. Fibrinogen concentration and thrombin levels in pregnant women in Nnewi, Anambra State, South, Eastern Nigeria. J Biol Agric Health. 2013;3:14.
[41] Romero R, Rosner B, Willett W. Inflammation in pregnancy: Its roles in reproductive physiology, obstetrical complications, and foetal injury. Nutr Rev. 2007;2:194-202.
[42] Gandevani S, Banaem L, Mohamadi B, Moghadam N, Asghari M. Association of high-sensitivity C-reactive protein serum levels in early pregnancy with the severity of preeclampsia and foetal birth weight. J Perinat Med. 2012;40:601-05.
[43] Fink N, Chawes B, Bønnelykke K, Thorsen J, Stokholm J, Rasmussen M, et al. Levels of systemic low-grade inflammation in pregnant mothers and their offspring are correlated. Sci Rep. 2019;9:3043.
[44] Waugh J, Clark T, Divakaran T, Khan K, Kilby M. Accuracy of urinalysis dipstick technique in predicting significant proteinuria in pregnancy. Obstet Gynaecol. 2004;103:769-77.
[45] Oladapo O, Adetoro O, Ekele B, Chama C, Etuk S, Aboyeji A, et al. When getting there is not enough: A nationwide cross-sectional study of 998 maternal deaths and 1451 near-misses in public tertiary hospitals in a low-income country. BJOG. 2016;123(6):928-38.
[46] Ridker P, Bassuk S, Toth P. C-reactive protein and risk of cardiovascular disease: Evidence and clinical application. Curr Atheroscler Rep. 2003;5(5):341-49.
[47] Cerneca F, Ricci G, Simeone R, Malisano M, Alberico S, Guaschino S. Coagulation and fibrinolysis changes in normal pregnancy. Increased levels of procoagulants and reduced levels of inhibitors during pregnancy induce a hypercoagulable state, combined with a reactive fibrinolysis. Eur J Obstet Gynecol Reprod Biol. 1997;73:31-36.
[48] Metz J, Cincotta R, Francis M, Derosa L, Balloch A. Screening for consumptive coagulopathy in preeclampsia. Int J Gynecol Obstet. 1994;46(1):03-09.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Apr 13, 2023
- Manual Googling: Jul 15, 2023
- iThenticate Software: Jul 28, 2023 (7%)

ETYMOLOGY: Author Origin

EMENDATIONS: 5

AUTHOR DECLARATION:
- Financial or Other Competing Interests: The study was funded with support from the Research Innovation and International Cooperation Committee (RIIC) of the Babcock University, Ilishan-Remo, Nigeria, seed grant, No: BU/ RIIC/2018/010.
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Apr 08, 2023**
Date of Peer Review: **Jul 14, 2023**
Date of Acceptance: **Jul 31, 2023**
Date of Publishing: **Oct 01, 2023**