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Interrelationship Between Markers of Oxidative Stress, Inflammation and Hematological Parameters Among Preeclamptic Nigerian Women

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Background: Preeclampsia is a multifaceted pregnancy-related disorder affecting women and fetuses. A link between preeclampsia, oxidative stress, and inflammation has been suggested. This study evaluated the interrelationship between biomarkers of oxidative stress, inflammation, and hematological parameters among preeclamptic Nigerian women.

Material/Methods: A cross-sectional study was conducted among 49 preeclamptic and 50 normotensive healthy pregnant women. Blood samples were obtained after 20-week gestation in all participants. Levels of superoxide dismutase (SOD), catalase, glutathione (GSH), malonaldehyde (MDA), total protein, high-sensitivity C-reactive protein (hs-CRP), and cardiac-specific troponin I (cTnI) were determined by spectrophotometric and ELISA techniques. FBC, prothrombin time, and activated partial thromboplastin time were determined using an auto-analyzer, Quick's one-stage, and Proctor's and Rappaport's modification methods, respectively.

Results: The mean SOD (0.051±0.050 *vs.* 0.073±0.047, p 0.029), catalase (2.62±1.93 *vs.* 8.48±4.40, p<0.001), GSH (49.05±17.57 *vs.* 187.10±56.07 p<0.001), platelet (127.63±89.75 *vs.* 267.16±212.82, p<0.001 were lower in preeclampsia. MDA (7.16±5.00 *vs.* 2.91±2.66, p<0.001), cTnI (0.46±0.31 *vs.* 0.13±0.14 p<0.001), PT (19.36±4.06 *vs.* 13.45±1.97 p<0.001), APTT (45.53±2.92 *vs.* 37.49±4.99; p<0.001) were higher in preeclampsia. Negative associations between SOD and MDA (r –0.527 p<0.001), CAT and MDA (r –0.469, p 0.001) and positive associations between catalase and hs-CRP (r 0.844, p 0.029), RBC and HB (r 0.442, p 0.001), platelet, and SOD (r 0.353, p 0.013) were observed among preeclamptic volunteers.

Conclusions: Preeclampsia is associated with oxidative stress, derangement of hematological and coagulation homeostasis, as well as deleterious effects on the cardiovascular system.

MeSH Keywords: Blood Coagulation Tests • Oxidative Stress • Pre-Eclampsia • Troponin I

Abbreviations: **PE** – preeclampsia; **SOD** – superoxide dismutase; **GSH** – glutathione (reduced); **CAT** – catalase; **MDA** – malondialdehyde; **PT** – prothrombin time; **APTT** – activated partial thromboplastin; **cTnI** – cardiac troponin-I; **hs-CRP** – high-sensitivity C-reactive protein; **LV** – left ventricle

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Background

Preeclampsia is a human pregnancy-specific disorder that adversely affects the mother and the fetus. It is a common condition of pregnancy, marked by the onset of hypertension and proteinuria [1]. It has been suggested that the pathogenesis of pre-eclampsia is complex, since it is thought to involve interactions between numerous genetic, immunologic, and environmental factors [2]. In fetuses and newborns, the most frequent complications of preeclampsia are reduced amniotic fluid, fetal distress, intrauterine growth restriction (10–25%), prematurity (15–67%), low birth weight, with possibility of future cardiovascular complications [3–5].

The incidence of preeclampsia is 3–10% of pregnancies [6,7], with a recent study suggesting 2–8% [8]. It has been reported that the incidence of preeclampsia in developing countries is 7 times higher than in developed countries [9]. The syndrome associated with preeclampsia is polymorphic and is characterized by generalized endothelial damage, which can result in organ system damage [10].

A previous study has hypothesized that preeclampsia results from a reduction in uteroplacental perfusion, which leads to uteroplacental ischemia [10]. In preeclampsia, placenta trophoblasts do not develop normally and are unable to invade the myometrium effectively [11]. The only intervention that effectively reverses the syndrome is delivery. A large portion of perinatal mortality is consequently due to iatrogenic prematurity. Up to 15% of preterm births are a result of preeclampsia [12]. The combination of hypertension and proteinuria markedly increases the risk of perinatal morbidity and mortality over that of hypertension alone [13]. It has been suggested that maternal endothelial cell dysfunction may be the key event resulting in the diverse clinical manifestations of preeclampsia [14]. Evidence has since accumulated to support a major role of the endothelium in preeclampsia [14,15]. The mechanisms involved in induction of endothelial cell dysfunction are poorly understood. Abnormal placentation is clearly involved in the genesis of both preeclampsia and fetal intrauterine growth restriction (IUGR) [16,17].

It has been proposed that product(s) of the fetal-placental unit enter the circulation and then initiate the maternal pathophysiologic changes of preeclampsia [18]. However, there is increasing evidence that both feto-placental and maternal factors interact in manifesting endothelial cell dysfunction and its clinical manifestations [15,19–21]. Other previous studies have also hypothesized that placental and maternal free radical reactions may promote a cycle of events that compromise the defensive functioning of the vascular endothelium in preeclampsia [14,22]. Thus, in preeclampsia, evidence of oxidative stress (a consequence of free radical generation) may be seen both in the maternal circulation and in the placenta, as the contents of placental micro-particles released into the maternal circulation during preeclampsia contributes to the elevated level of systemic oxidative stress [23–26]. It has also been reported that the pattern of left ventricular dysfunction and remodeling seen among preeclamptic individual is similar to that seen in early essential hypertension in non-pregnant women [27]. Thus, there is a need to evaluate some cardiac biomarkers among Nigerian preeclamptic patients in order to assess their status, since it has been suggested in a previous study that women with preeclampsia have a significantly higher risk of major adverse cardiovascular events (MACEs), especially myocardial infarction and stroke [28]. It has also been reported that preeclampsia can have deleterious effects on markers of hemostatic activities [29]. This study therefore evaluated the interrelationship between oxidative stress, inflammatory markers, cardiac specific troponin I, and hematological parameters among Nigerian preeclamptic women.

Material and Methods

Participants selection and study design

This was a cross-sectional study conducted on female preeclamptic patients and apparently healthy normotensive pregnant women attending Lagos University Teaching Hospital (LUTH), Ifako General Hospital, Isolo General Hospital, Lagos Island Maternity Hospital, and the Mother and Child Center Amuwo Odofin. A total of 99 volunteers participated in this study: 49 were preeclamptic volunteers while the remaining 50 were apparently healthy normotensive volunteers without urinary protein abnormality. The normotensive participants served as control. This study was conducted from July to November 2017. Blood samples were collected into dipotassium Ethylenediaminetetraacetic acid, trisodiumcitrate and serum separator tube (SST) gel vacutainer bottles in the morning from all consenting participants.

Ethical consideration

Approval was obtained from the Research and Ethics Committee College of Medicine of University of Lagos (CMUL) and the Lagos State Health Service Commission (HSC) prior to the commencement of the study. Informed consent was sought and obtained from all participants who volunteered to participate in this study.

Inclusion criteria

The following were included in this study: pregnant volunteers with gestational age greater than 20 weeks and preeclamptic women with no previous history of hypertension or proteinuria before gestational age of 20 weeks and above.

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Table 1. Comparative analysis of markers of oxidative stress in preeclampsia and control women.

Variables	Preeclampsia Mean ±SD (n=49)	Control Mean ±SD (n=50)	t Value	p Value
SOD (µmol/ml/min/mg protein)	0.051±0.055	0.073±0.047	2.211	0.029*
CAT (µmol/ml/min/mg protein)	2.623±1.933	8.483±4.427	8.503	<0.001*
MDA (µmol/ml)	7.158±5.005	2.913±2.662	–5.284	<0.001*
GSH (µmol/ml)	49.05±17.57	187.10±56.07	16.459	<0.001*
Cardiac-specific troponin-I (ng/ml)	0.46±0.31	0.13±0.14	–6.635	<0.001*
High-sensitivity CRP (µg/ml)	7.70±1.70	5.46±0.95	–1.240	0.218

* Significant probability (probability <0.05 is significant).

Table 2. Comparative analysis hematological and coagulation variables in preeclampsia and control women.

Variables	Preeclampsia Mean ±SD (n=49)	Control Mean ±SD (n=50)	t Value	p Value
WBC ($\times 10^9$/L)	7.35±5.54	5.09±2.07	–2.69	0.008*
RBC ($\times 10^{12}$/L)	3.87±0.44	3.73±0.45	–1.47	0.144
HGB (g/L)	115.92±11.33	109.22±11.85	–2.87	0.005*
PLT ($\times 10^9$/L)	127.63±89.75	267.16±212.82	4.24	<0.001*
PT (s)	19.36±4.06	13.45±1.97	–9.25	<0.001*
APTT (s)	45.53±2.92	37.49±4.99	–9.74	<0.001*

* Significant probability (probability <0.05 is significant).

Exclusion criteria

The following were excluded from this study: pregnant women who were recently treated for *Plasmodium* infestation (malaria) and pregnant women with other medical conditions such as anemia, viral hepatitis, diabetes mellitus renal failure, tuberculosis, and auto-immune diseases.

Methodology

Malondialdehyde (MDA) level was determined using the method of Buege and Aust [30], while superoxide dismutase (SOD) level was determined based on the method described by Sun and Zigma [31]. Catalase level was determined according to the method of Sinha et al. [32]. Glutathione (GSH) level was estimated according to the method described by Sedlak and Lindsay [33]. Total protein level was determined using the Biuret method as described by Gonall et al. [34] and bovine serum albumin (BSA) was used as the standard. High-sensitivity C-reactive protein and cardiac-specific troponin I levels were determined by ELISA [35,36]. Full blood count was determined using a Mindray 5-part auto-analyzer. The prothrombin time test and activated partial thromboplastin test were performed using Quick's one-stage method [37] and Proctor and Rapaport's [38] Modification Method, respectively.

Data analysis

The data from the study were analyzed using IBM SPSS Statistics for Windows, version 21.0 (Armonk, NY). Quantitative data were expressed as mean, standard deviation, and standard error of the mean. The independent-samples *t* test was used to compare differences between groups. Pearson correlation coefficient was used to evaluate the degree of association. The level of significance for all the inferential statistics was set at $p<0.05$.

Results

Table 1 presents the mean SOD, CAT, MDA, and GSH values of preeclamptic volunteers and normotensive control group. The SOD, CAT, and GSH levels were 0.051 µmol/ml/min/mg protein *vs.* 0.073 µmol/ml/min/mg protein, 2.623 µmol/ml/min/mg protein *vs.* 8.48 µmol/ml/min/mg protein, and 49.05 µmol/ml *vs.* 187.10 µmol/ml for preeclamptic volunteers and normotensive control

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Table 3. Degree of association between markers of oxidative stress and inflammation measured.

Variable correlation	Coefficient (r)	p Value
GSH-MDA	–0.277	0.054
SOD-MDA	–0.527	<0.001*
CAT-SOD	0.270	0.061
CAT-MDA	–0.469	0.001*
CAT-hs-CRP	0.844	0.029*
GSH-Troponin I	0.484	0.102
SOD-hs-CRP	–0.128	0.383

* Significant probability (probability <0.05 is significant).

Table 4. Pearson correlation studies on hematological and coagulation variables.

Variables	Correlation coefficient (r)	p Value
WBC *vs.* RBC	–0.075	0.610
WBC *vs.* HGB	0.001	0.993
RBC *vs.* HB	0.442	0.001*
PLT *vs.* PT	–0.033	0.823
PLT *vs.* APTT	0.175	0.229
PT *vs.* RBC	0.282	0.050

* Significant probability (probability <0.05 is significant).

group, respectively. The MDA acid level was 7.158 µmol/ml *vs.* 2.913 µmol/ml for preeclamptic and normotensive pregnant volunteers, respectively. Table 2 presented the mean hematological and coagulation profile results of preeclamptic volunteers and control as follow: the mean total white blood cell count (×10^9/L) was 7.35±5.54 *vs.* 5.09±2.07, while Hb (g/l) was 115.92±11.33 *vs.* 109.22±11.85, platelet count (×10^9/L) was 127.63±89.75 *vs.* 267.16±212.87, PT (s); 19.36±4.06 *vs.* 13.45±1.97, APTT (s); 45.53±2.92 *vs.* 37.49±4.99.

Table 3 shows the degree of association among biochemical variables studied. There was an inverse association between superoxide dismutase (SOD) and malondialdhyde (MDA) (r=–0.527 p<0.001), as well as between catalase and malondialdehyde (MDA) (r –0.469, p 0.001). Catalase correlated positively with high-sensitivity C-reactive protein (r 0.844 p 0.029). Table 4 shows correlation between hematological variables while Table 5 shows association between hematological variables and markers of oxidative stress. RBC correlated positively

Table 5. Pearson correlation studies on hematological, coagulation, and oxidative stress markers variables.

Variables	Correlation coefficient (r)	p Value
PLT *vs.* SOD	0.353	0.013*
PLT *vs.* MDA	–0.052	0.724
PT *vs.* SOD	0.156	0.284
PT *vs.* MDA	–0.151	0.299
APTT-SOD	0.272	0.059
APTT-MDA	0.129	0.375

* Significant probability (probability <0.05 is significant).

with Hb (r 0.442, p 0.001), while platelet correlated positively with SOD (r 0.353, p 0.013).

Discussion

Preeclampsia as a disorder of pregnancy has long affected humans [39]. It is a complex pregnancy disorder that occurs almost solely in humans [40]. The exact cause or etiology of preeclampsia is still unknown [39]. A previous study has suggested that preeclampsia is associated with oxidative stress [41], but another study has suggested that oxidative stress may be a cause rather than effect of preeclampsia [42].

In the present study, markers of oxidative stress were evaluated among preeclamptic volunteers. We observed a significantly higher MDA level (p<0.05) among preeclamptic women (Table 1), our observation is in agreement with previous studies by Madazli et al. [43], Chamy et al. [44], Patil et al. [45], Krishna et al. [46], Akiibinu et al. [47], and Ćebović et al. [48]. MDA is a marker of lipid peroxidation, suggesting that preeclamptic Nigerian women possibly experienced increased lipid peroxidation. Thus, an increase in MDA among preeclamptic women may be a key pathological factor importantly contributing to endothelial dysfunction and hypertension [48–50]. It has been suggested that lipid peroxidation causes oxidative stress in preeclampsia. However, a previous study has found that free radicals initiate lipid peroxidation by attacking polyunsaturated fatty acids in cell membranes [43]. Uncontrolled peroxidation of fatty acids and cholesterol alter membrane fluidity and permeability, as lipid peroxides are toxic compounds that damage endothelial cells, increase peripheral vasoconstriction, and increase thromboxane synthesis, as well as decreasing prostacyclin synthesis [51]. It has been suggested that a steady increase in blood lipid peroxide sets the stage for a self-perpetuating chain-reaction processes to take place. Thus, endothelial contact with lipid peroxides would allow peroxidative damage of

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endothelial cell membrane lipids, leading to a compromise of endothelium permeability to plasma components [52]. Exposure of the vascular endothelium to lipid peroxides possibly shuts off production of prostacyclin, increasing the propensity for vasoconstriction and platelet aggregation [52]. This might have contributed to the significantly ($p<0.05$) lower platelet count observed among preeclamptic women (Table 2). It has been demonstrated that the presence of free radicals promotes platelet aggregation in stored samples [53]. Moreover, a previous study has shown that platelet count is usually elevated in the first trimester and significantly reduced in the third trimester in normal pregnancy [54]. However, in preeclamptic patients, thrombocytopenia has been shown to exist in about half of the cases, and the degree of thrombocytopenia has been demonstrated to correlate with the severity of the disorder and may precede clinical manifestations of the disorder [55]. Available data suggest that thrombocytes plays a significant role in the pathogenesis of preeclampsia because it is associated with the release of thromboxane A2, leading to an increased thromboxane/prostacyclin ratio [56]. It has also been shown that thromboxane A2 promotes vasospasm, leading to platelet aggregation and endothelial damage [57].

Furthermore, in the present study we observed a significantly ($p<0.05$) reduced level of the studied antioxidants (SOD, CAT and GSH). Our observation agrees with some previous studies [49,50,58–60]. A significant decrease ($p<0.05$) in the level of (SOD) enzymatic antioxidant has been suggested to be one of the hallmarks of preeclampsia [48], as this enzyme is one of the most important antioxidant defense mechanisms, and its lower activity has been used previously in predicting future development of preeclampsia as well as screening for low antioxidant status [61]. Available data have shown that placentas from women with preeclampsia have reduced antioxidant capacity compared to normal placentas [58,62,], and other studies have also shown that the levels of antioxidants in blood from women with preeclampsia are reduced [63,64]. A possible explanation for this could be the deleterious effects of the free radicals released as an effect of preeclampsia [65] on these antioxidants.

Moreover, the mean hs-CRP value and cardiac-specific Troponin-I were determined among preeclamptic volunteers. Troponin-I was significantly ($p<0.05$) higher among preeclamptic volunteers, whereas hs-CRP did not show any significant increase ($p>0.05$). An increase in troponin I among preeclamptic volunteers, as observed in this study, suggests the possibility of preeclampsia impacting deleterious effects on cardiac cells in the affected women. It appears that this observation supports a previous study, which reported that preeclampsia is associated with subtle impairments of the vascular reactivity, hemodynamic indices, and left ventricular (LV) functions [66]. Thus, the abnormal LV remodeling as seen in some preeclamptic individuals may result in hypertrophy. Left ventricular involvement among preeclamptic individuals has been suggested to lead to cardiac ischemia, which may result in changes in some biomarkers of heart function [67].

An evaluation of prothrombin time test (PT) and activated partial thromboplastin time (APTT) among preeclamptic patients showed a significant increase ($p<0.05$) in these coagulation parameters when compared with the control group (Table 2). Our finding regarding PT and APTT agree with a study by Ducloy-Bouthors [68], which reported that clotting disorders are associated with the severe early and complicated forms of preeclampsia. The changes in the mean PT and APTT might also be secondary to thrombocytopenia that resulted from exaggerated platelet activation and consumption, associated with preeclampsia [55]. Thus, the significant increase in (PT) and (APTT) observed in our study corroborates the previous observation of Pinheiro et al. [69]. In preeclampsia, maternal inflammatory reaction and immunological activities are suggested to damage the coagulation-fibrinolytic system [69]. In the present study, elevated prothrombin time test and activated partial thromboplastin time values among preeclamptic women suggest a deleterious effect of preeclampsia on hemostatic physiology. It has been shown that in preeclamptic pregnancies, the coagulation cascade is generally activated [70], suggesting that preeclampsia itself is associated with platelet activation and consumption, promotion of thrombin formation, and promotion of fibrin formation and destruction. In spite of these changes, in most cases of preeclampsia, the coagulation anomalies do not have major clinical significance [55]. A balance between coagulation and anticoagulation has been shown to be vital to the regulation of utero-placenta circulation and organ perfusion in pregnancy. This balance is essential to prevent postpartum hemorrhage and its associated complications [71]. This balance is probably disrupted in preeclampsia, which may expose such group of pregnant women to further complications.

Also, an association between markers of oxidative stress, hematological and coagulation profile as well as marker of inflammation were evaluated among preeclamptic volunteers. There was an inverse and significant ($p<0.05$) relationship between SOD and MDA, as well as between CAT and MDA ($p<0.05$) (Table 3) among preeclamptic women. These observations suggest the presence of oxidative stress in preeclampsia. There was a positive and significant association between hemoglobin (Hb) and red blood cell (RBC) count (Table 4), whereas all other hematological and coagulation profiles did not show any significant association with one another. Platelet count correlated positively with SOD ($p<0.05$) among preeclamptic women (Table 5). A significantly lower SOD value, as seen in this study, is suggestive of oxidative stress. The low SOD value in the present study was associated with low platelet count. This suggests that oxidative stress promotes platelet aggregation [53,55],

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which invariably leads to platelet consumption with attendant thrombocytopenia [55] observed in some of the patients with preeclampsia. These observations show an imbalance between the biomarkers of oxidative stress markers among preeclamptic volunteers, suggesting that oxidative stress occurs among this group of individuals.

Conclusion

Our results show that preeclampsia is associated with oxidative stress, disturbance of hemostasis homeostasis as well as deleterious effects on cardiac cells.

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Conflict of interest

None.

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