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Assessment of Antioxidant Status and Lipid Peroxidation in Pre-Eclampsia

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Authors' contributions

This work was carried out in collaboration among all authors. Authors POM, CCO, NAM and ACI designed the study, performed the statistical analysis, Authors POM, CCO, NAM and ACI wrote the protocol and wrote the first draft of the manuscript. Authors POM, CCO, NAM and ACI managed the analyses of the study. Authors POM, CCO, NAM, GOC, RCC and ACI managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aim: To assess the role of antioxidants and lipid peroxidation in the pathogenesis of pre-eclampsia.
Study Design: This is a case-control study designed to evaluate the levels of malondialdehyde and total antioxidant capacity with glutathione peroxidase and superoxide dismutase activities in pre-eclamptic. One hundred (100) participants were randomly selected to include fifty pre-eclamptic

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(test), twenty-five (25) healthy pregnant normotensive women (control A) and twenty-five healthy non-pregnant normotensive women (control B).

Place and Duration of Study: This study was carried out at the Holy Rosary Hospital waterside, Onitsha, Anambra state. Nigeria. The study lasted for 13 months.

Methodology: One hundred women (50 pre-eclamptic, 25 pregnant normotensives and 25 non-pregnant normotensives) aged 25-40 years were recruited for this study. Blood samples were collected from the participants for the estimation of total antioxidant capacity (TAC), malondialdehyde (MDA), superoxide dismutase (SOD) and glutathione peroxidase (GPx) activities using spectrophotometric methods. Blood pressures were measured using accosson sphygmomanometer. Data were analysed using analysis of variance and Pearson's correlation coefficient at $p < 0.05$.

Results: The TAC was significantly higher in the pregnant normotensives ($p< 0.05$) compared with the pre-eclamptic and non-pregnant normotensives. There was no significant difference in the MDA in pre-eclamptic compared with pregnant normotensives and non-pregnant normotensives ($p>0.05$). A significant difference was observed in the SOD and GPx activities in the pregnant normotensive and non-pregnant normotensives compared with pre-eclamptic. A positive correlation was observed between the blood pressures (systolic and diastolic) and the activities of TAC, SOD and GPx in pre-eclamptic. Furthermore, a positive correlation was observed between MDA levels and SBP ($r = 0.019$) while a negative correlation ($r = -0.225$) existed between MDA and DBP.

Conclusion: Diminished ability of antioxidants to scavenge free radicals may affect the onset of pre-eclampsia and therefore possible prognostic tool in its management.

Keywords: Antioxidants; pre-eclampsia; glutathione peroxidase; superoxide dismutase; lipid peroxidation.

1. INTRODUCTION

Pre-eclampsia (PE) is defined as the presence of a systolic blood pressure greater than or equal to 140 mmHg or a diastolic blood pressure greater than or equal to 90 mmHg or higher, on two occasions at least four hours apart in a previously normotensive patient [1], with urine protein of at least 30 mg/dl. It is a serious complication of pregnancy in which free radical damage has been implicated. Pre-eclampsia usually begins after 20weeks of a human pregnancy, which can have harmful effects on the immediate and long-term health of the mother and the child [2]. This disease is characterized by multiple maternal disturbances leading to hypertension and proteinuria [3] which occurs due to renal glomerular endothelins, a manifestation of widespread endothelial damage in preeclampsia. The symptoms resolve only after the removal of the placenta, and thus, pre-eclampsia is one of the most common reasons for induced preterm delivery [1].

Human pregnancy imposes huge stress to the maternal body which has to accommodate the increasing energy needs of the developing fetus at the expense of its own needs [4]. Therefore, several physiologic and metabolic changes take place in the maternal body to adapt to such a challenge [4]. The pregnant uterus undergoes important tissue and vascular remodelling, the most remarkable of which is the transformation of the uterine spiral arteries into low-resistance flow vessels that enable large volumes of blood to gain access to the placental intervillous space [5]. Due to metabolic changes and low-grade inflammation, pregnancy increases the susceptibility to oxidative stress [6]. Several organs in pregnancy show increased basal oxygen consumption and changes in substrate energy use resulting in increased mitochondrial mass and production of reactive oxygen species (ROS) [4]. The placenta produces nitric oxide (NO), initiating the pathophysiological events [7] also, being rich with free-radical producing macrophages can contribute to the development of oxidative stress [8].

Globally, pre-eclampsia complicates about 2-10% of pregnancies [9]. According to the World Health Organization (WHO), its incidence is seven times higher in developing countries (2.8% of live births) than in developed countries (0.4%) and 2.3% for eclampsia (as % pre-eclampsia) [10]. In the study on "the prevalence of pre-eclampsia" at Nnamdi Azikiwe University Teaching Hospital Nnewi, the incidence of pre-eclampsia was 3.7% [11].

Abnormal vascular development of the blood vessels in the pre-eclamptic placenta leads to

reduced placental perfusion and induce hypoxia which is by itself a potent stimulus for ROS formation [12]. After initiation of apoptotic pathways, syncytiotrophoblast microvesicles activate maternal neutrophils contributing to oxidative stress and pathophysiology of pre-eclampsia. It has been observed that ROS are increased, and the levels of several detoxifying enzymes are reduced in pre-eclampsia.

Malondialdehyde (MDA) is a byproduct in lipid peroxidation of polyunsaturated fatty acids [13] and a biomarker of oxidative damage and disease severity [14]. Reactive oxygen species degrade polyunsaturated lipids, forming malondialdehyde [15]. This compound is a reactive aldehyde and is one of the many reactive electrophile species that cause toxic stress in cells and form covalent protein adducts referred to as advanced lipo-oxidation end-products (ALE) [15].

Glutathione peroxidase (GPx) is an enzyme family with peroxidase activity whose main biological role is to protect the organism from oxidative damage [16]. The biochemical function of glutathione peroxidase is to reduce lipid hydroperoxides to their corresponding alcohols and to reduce free hydrogen peroxide to water [17]. Superoxide dismutase (SOD) is an enzyme that alternately catalyzes the dismutation (or partitioning) of the superoxide (O_2^-) radical into either ordinary molecular oxygen (O_2) or hydrogen peroxide (H_2O_2) [18].

The measure of total antioxidant capacity (TAC) considers the cumulative action of all the antioxidants present in plasma and body fluids, thus providing an integrated parameter rather than the simple sum of measurable antioxidants [16]. The capacity of known and unknown antioxidants and their synergistic interaction is therefore assessed, thus giving an insight into the delicate balance in vivo between oxidants and antioxidants [16]. Measuring plasma TAC may help in the evaluation of physiological, environmental, and nutritional factors of the oxidative stress status in humans. Multivitamin-mineral supplementation is often recommended for pregnant women. In uncomplicated pregnancies multivitamin- mineral supplementation did not influence the levels of ascorbic acid, lipid peroxidation product MDA and the activities of the antioxidant enzymes GSH-Px and SOD [19].

Pregnancy complications like hypertension induce hypoxia resulting from poor placental perfusion. This leads to increased production of reactive oxygen species, which in turn results in accelerated damage on the placenta and microvessels [20]. Oxidative stress reflects an imbalance between the systemic manifestation of reactive oxygen species and a biological system's ability to readily detoxify the reactive intermediates or to repair the resulting damage [15]. Oxidative stress has been adjudged to be a contributory factor in hypertensive complications such as pre-eclampsia. The absence of reliable laboratory markers for prediction of disease onset and severity in this regard makes these conditions more complicated. It is hoped that the evaluation of the levels of MDA, TAC, SOD and GPx will fill this gap.

The WHO's report (2000) on the 'Global Burden of Disease' stated that pre-eclampsia accounts for 50% of all hypertension in pregnancy. This report further stated that pre-eclampsia accounts for 14% of all maternal deaths rising from 13% in 1990 report [10]. It has become clear that pre-eclampsia contributes largely to the number of deaths recorded among pregnant women. This may be valuable in predicting the onset of pre-eclampsia and a possible prognostic tool in its management.

2. MATERIALS AND METHODS

2.1 Study Site

This case-control study was carried out at the Holy Rosary Hospital waterside, Onitsha, Anambra state. Nigeria.

2.2 Study Population

After clinical diagnosis and laboratory assay, one hundred (100) participants were randomly selected to include fifty pre-eclamptic patients as test subjects A, twenty-five (25) healthy pregnant normotensive women as control B and twenty-five healthy non-pregnant normotensive women as control C. Study participants who were apparently healthy, pregnant and non-pregnant females aged 25–40; pre-eclamptic subjects [BP ≥140/90 and urine protein ≥ + (30 mg/dl)] at ≥20 weeks of pregnancy were included. Excluded were patients with hypertension predating the index pregnancy, subjects with a known history of chronic diseases, heavy alcohol consumers, smokers and those on medication(s) likely to affect antioxidant levels. The subjects were randomly selected after obtaining their consent. Blood pressure was taken on the left arm after 5 min relaxation, in a sitting position, using a

standard mercury sphygmomanometer with appropriate cuff size. Systolic (SBP) and diastolic (DBP) blood pressures corresponded to Korotkoff sounds phase 1 and V respectively. Values above 140 and 90 mmHg for the SBP and DBP respectively were considered abnormal. The average of three readings, taken at first, was used for further analysis. The urinary protein of each participant was quantified using a urine dipstick test as described by [21].

Five (5ml) of venous blood was aseptically collected by venipuncture from the participants following the standard protocol; dispensed into a serum separator tube, allowed to clot, retract and centrifuged at 3000 rpm for 5min. Serum was extracted and used for the estimation of TAC, MDA, SOD and GPx activities using spectrophotometric methods. Blood pressures were measured using accosson sphygmomanometer and stethoscope.

2.3 Estimation of Total Antioxidant Capacity (TAC)

The TAC was estimated by Ferric Reducing Ability of Plasma (FRAP) method as described by Benzie and Strain [22].

2.4 Determination of Malondialdehyde

The MDA concentration was determined by the method as described by Gutteridge and Wilkins [23].

2.5 Determination of Superoxide Dismutase (SOD) Activity

The SOD activity was estimated by the method of Misra and Fridovich [24] as described by Manafa *et al.* [25]

2.6 Determination of Glutathione Peroxidase (GPx) Activity

The GPx activity was determined by the method of Rotruck *et al.* [26] $2GSH + H_2O_2 \xrightarrow{GPx} GSSG + 2\ H_2O$

2.7 Statistical Analysis

Data were analysed and presented as mean ± standard deviation. The statistical software package for Social Sciences (SPSS) version 20.0 computer software (SPSS Inc., Chicago, IL, USA). The analysis of variance (ANOVA) was used to test the significance of variations within and among the group; post-doc was used for comparison of multiple variables. Pearson correlation was used for the comparison of the strength of association among variables. Values were deemed significant at $p < 0.05$.

3. RESULTS AND DISCUSSION

The results for the assay of TAC, MDA, SOD and GPx activities in pre-eclampsia are presented in Table 1. The TAC was significantly higher in the pregnant normotensive ($p < 0.05$) compared with the preeclamptic and non-pregnant normotensive groups.

There was no significant difference in the malondialdehyde levels in pre-eclamptic subjects compared with pregnant normotensive individuals and non-pregnant normotensive. A significant difference was observed in the superoxide dismutase (SOD) and glutathione peroxidase (GPx) activities in the pregnant normotensive individuals and non-pregnant normotensive subjects compared with pre-eclamptic subjects (Table 1). In Table 2, a positive correlation was observed between the blood pressures vs SOD, GPx activities and TAC in pre-eclampsia. A positive and negative correlation was observed between MDA levels vs SBP ($r = 0.019$, $p=0.897$) and MDA vs DBP ($r = -0.225$, $p=0.119$) respectively (Table 2).

Preeclampsia, a disorder of widespread vascular endothelial malfunction and vasospasm occurs after 20 weeks' gestation. It is clinically defined by the presence of hypertension and proteinuria, with or without pathologic oedema and can present as late as 4-6 weeks post-partum [27]. It is strongly related to oxidative stress and leads to a high degree of lipid peroxidation which damages the lipid by-layer of cell membranes resulting in the accumulation of lipid peroxidation end-products such as malondialdehyde (MDA) and 4-hydroxynonenal (HNE). Serum level of MDA gives an insight into the nature of lipid peroxidation and the level of oxidative damage. Detoxification of excess reactive oxygen species is achieved by an efficient antioxidant system comprising of enzymatic and non-enzymatic antioxidants [27].

In this study, the mean serum TAC showed a significant increase in pregnant normotensive individuals compared with pre-eclamptic and non-pregnant normotensive subjects. This observation is probably because, during normal pregnancies, oxidative stress associated with increased basal metabolic rate and increased

oxygen consumption induces an increase in the level of all antioxidants in the system to counteract the reactive oxygen species, ROS released into circulation. However, as the antioxidants are being used up and more and more ROS are generated in complications like preeclampsia, the level of total antioxidants gradually falls as seen in pre-eclamptic subjects. Countering reactive oxygen species released during pre-eclampsia are solely dependent on total endogenous antioxidants present in the system. Mahdiyeh *et al*. [28] observed that serum TAC is positively associated with the risk of pre-eclampsia but no association was found between intake of antioxidant indices and pre-eclampsia risk. The TAC of pregnant women is reduced by high lipid peroxidation, abnormal placentation, oxidative stress, alcoholism, smoking and exposure to radiation and toxic elements. Shaarawy *et al*. [29] reported that radical-scavenging antioxidants are consumed by the increased free-radical activity in pre-eclampsia. Assessment of fatty acids, antioxidants, and oxidative stress in pre-eclampsia showed reduced total omega-3 fatty acids, increased omega-6: omega-3 ratio, higher oxidative stress and lower antioxidant levels [30]. Reduced antioxidants and increased oxidative stress leading to impaired essential polyunsaturated fatty acid levels may be a key factor in the development of pre-eclampsia [30].

Malondialdehyde, a product of lipid peroxidation serves as a marker of cellular injury associated with oxidative stress [31]. The mean serum level of MDA in this study was significantly elevated in pre-eclamptic subjects compared with pregnant normotensive individuals ($p<0.05$), this agrees with the findings of Necip *et al.*[32]. The values in each of these groups showed a gradual increase from non-pregnant normotensive subjects, higher in pregnant normotensive individuals and peaked at the pre-eclamptic group. This is probably because, non-pregnant normotensive subjects have no pregnancy-induced oxidative stress, and as such, the level of lipid peroxidation is minimal, thereby giving low MDA level amongst this group. Normal pregnancy comes with increased levels of lipid peroxidation, as such the level of MDA in circulation is elevated above that seen in the non-pregnant group [33]. However, in cases of pregnancy complications such as pre-eclampsia, the level of lipid peroxidation is greatly increased above normal. This manifests in more elevated values of MDA above that seen in normal groups.

Table 1. Total antioxidant capacity, malondialdehyde levels, superoxide dismutase and glutathione peroxidase activities in pre-eclamptic subjects, pregnant normotensive individuals and non-pregnant normotensive subjects

	N	TAC (µmol/L)	MDA (nmol/L)	SOD (U/mL)	GPx (U/mL)
A	50	887.19± 155.82 [b]	2.30± 0.67 [b]	12.12± 3.26 [b]	0.58± 0.21 [b]
B	25	973.36± 349.04 [a]	2.11± 0.78 [b]	13.47± 3.49 [a]	0.66± 0.30 [a]
C	25	800.89±153.61 [b]	1.69± 0.77 [b]	10.28±4.57 [a]	0.41± 0.16 [a]
F- test		3.622	6.092	7.293	6.674
p-value		0.031	0.003	0.001	0.002

Values are reported as mean ± SD (standard deviation). Mean values are significantly different @ ($p < 0.05$) Pre-eclampsia = A; Pregnant Normotensive = B; Non-Pregnant Normotensive = C; Number of subjects = N Total Antioxidant Capacity (TAC) and Malondialdehyde (MDA) levels; Superoxide dismutase (SOD) and glutathione peroxidase (GPx) activities. Comparism of means along the column followed by 'a' indicate significant difference @ $p < 0.05$, while values followed by letter 'b' are not significantly different @ $p < 0.05$

Table 2. Correlation of the levels of systolic blood pressure and diastolic blood pressure with superoxide dismutase and glutathione peroxidase activities; total antioxidant capacity and malondialdehyde levels in pre-eclamptic subjects

SBP (mmHg)	R - value	P - value	DBP (mmHg)	R – value	P – value
TAC (U/mL)	0.182	0.248	TAC (U/mL)	0.070	0.661
MDA (µmol/L)	0.019	0.897	MDA (µmol/L)	-0.225	0.119
SOD (U/mL)	0.170	0.259	SOD (U/mL)	0.146	0.335
GPx (nmol/L)	0.002	0.987	GPx (nmol/L)	0.119	0.745

Systolic blood pressure (SBP); Diastolic Blood Pressure (DBP); Superoxide dismutase (SOD) and glutathione peroxidase (GPx) activities; Total Antioxidant Capacity (TAC) and Malondialdehyde (MDA) levels; Mean values are significantly different @ ($p < 0.05$); Correlation coefficient (R)

The mean serum activity of superoxide dismutase was significantly elevated in both pre-eclamptic and pregnant normotensive subjects compared with the non-pregnant normotensive individuals ($p<0.05$). Superoxide dismutase is an antioxidant enzyme which plays a crucial role in the dismutation of superoxide radicals generated during metabolic processes or in cellular oxidative damage. In normal pregnancies, metabolic rate and tissue oxygen consumption are increased as such more radicals such as superoxide are generated [34]. In response to this, mRNA expression to produce superoxide dismutase increases to counteract the superoxide activity. This justifies the significant increase in superoxide dismutase activity recorded in pregnant normotensive individuals than that seen in non-pregnant normotensive subjects. Nevertheless, during episodes of preeclampsia, certain factors increase uncontrollably the level of oxidative stress. Such factors include increased metabolic rate, abnormal placentation, and release of placental materials into maternal circulation and induction of inflammation [34]. All these aids the high level of oxygen radicals released in preeclampsia. The body in response produces more antioxidants such as SOD to mop-up these radicals. This goes on until a certain period when the activity of SOD depreciates and gradually falls. This agrees with a related study by Dantas *et al.* [35] who observed that the antioxidant activity of superoxide dismutase was elevated in normal pregnant women than in those with preeclampsia. Superoxide production inactivates two critical antiatherosclerotic enzymes; endothelial nitric oxide synthase (eNOS) and prostacyclin synthase. Through these pathways, increased intracellular ROS cause defective angiogenesis in response to ischemia, activate a number of pro-inflammatory pathways and cause long-lasting epigenetic changes which drive persistent expression of pro-inflammatory genes after proteinuria and glycaemia are normalized [36]. Also in agreement with our findings, Hiten and Paula [37] noted that copper, zinc, and manganese which are all essential cofactors for superoxide dismutases, have reduced activity in pathological pregnancies such as pre-eclampsia. In agreement to this study, Mahadik and Sina [38] observed that the serum levels of superoxide dismutase in preeclampsia and eclampsia were significantly increased when compared with pregnant normotensive individuals.

In this study, the mean serum activity of glutathione peroxidase was significantly elevated in both pre-eclamptic and pregnant normotensive subjects compared with non-pregnant normotensive individuals. GPx activity increases in normal pregnancies. The biochemical function of glutathione peroxidase is to protect the organism from oxidative damage by reducing lipid hydroperoxides to their corresponding alcohols and to reduce free hydrogen peroxide to water. Selenium is a major component of glutathione [19] to prevent oxidative damage [39]. Reduced glutathione peroxidases could be associated with increased generation of toxic lipid peroxides contributing to the endothelial dysfunction and hypertension of pre-eclampsia [40]. Oxidative stress associated with preeclampsia may be a consequence of reduced antioxidant defence pathways specifically involving glutathione peroxidases, perhaps linked to reducing selenium availability [40]. Reactive oxygen species (ROS) are generated as by-products of cellular metabolism, primarily in the mitochondria or in pathological cases which induce high oxidative stress such as in pre-eclampsia [41]. When the cellular production of ROS exceeds the cell's antioxidant capacity, cellular macromolecules such as lipids, proteins and DNA can be damaged, because of this, oxidative stress is thought to contribute to ageing and pathogenesis of a variety of human diseases [41].

The positive correlation observed between the activities of superoxide dismutase, glutathione peroxidase, total antioxidant capacity with systolic and diastolic blood pressures could probably be because, during the onset of pre-eclampsia, systolic and diastolic blood pressures increase above 140 mmHg and 90mmHg respectively. However, as blood pressure increases, the antioxidants rise in order to counteract the high reactive oxygen species released into the system. Nevertheless, as the antioxidants peaks and the level of lipid peroxidation continue unregulated, the antioxidants start to deplete. The negative correlation between MDA levels and diastolic blood pressure as well as a positive correlation between MDA levels and systolic blood pressure could further be explained thus: Oxidative stress in the maternal compartment affects the placenta in such a way as to bring about decreased placental antioxidant enzyme protection. The cause of oxidative stress in the maternal compartment may be preexisting or may be caused by placental secretion of lipid peroxides [42]. The decrease in placental antioxidant enzyme protection leads to a cascade of events

in the placenta of uncontrolled lipid peroxidation with increased thromboxane and tumour necrosis factor (TNF-α) production. Increased placental secretion of lipid peroxides and/or TNF-α result in activation of leukocytes, which serve as circulating mediators that link the increased oxidative stress of the placenta with a widespread increase in oxidative stress and endothelial dysfunction in the mother. In the third trimester, when the placenta is growing rapidly, the mother's antioxidant capacity is no longer able to compensate, and the clinical symptoms of preeclampsia appear [42]. Bullarbo and Rylander [43] observed that systolic and diastolic blood pressures were significantly higher at pregnancy from week 12 among those who developed pre-eclampsia and the increase in blood pressure continues in folds of plus ≥15 mmHg until the onset of pre-eclampsia.

4. CONCLUSION

Pre-eclamptic patients are at greater risk of the dangerous effects of free radical production due to oxidative damage. These effects are most felt when the free radical production exceeds the antioxidant defence in the body, thus leading to oxidative stress. The free radical scavenging SOD is consumed by the increased lipid peroxidation in preeclampsia; this may indicate an involvement of free radicals in the pathophysiology of pre-eclampsia. As a consequence, SOD plays a key antioxidant role and its physiological importance is illustrated by the severe pathologies evident due to lack of these enzymes. Oxidative stress, therefore, may play a major role in the pathogenesis of pre-eclampsia.

CONSENT AND ETHICAL APPROVAL

The ethical approval was obtained from the Ethics committee of Nnamdi Azikiwe University Teaching Hospital. Written informed consent was obtained from all the participants.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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