ejpmr, 2023,10(3), 264-267

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

OXIDATIVE STRESS AND ANTIOXIDANTS AMONG WOMEN WITH PREECLAMPSIA AT A TERTIARY HEALTH FACILITY IN NORTH-WESTERN NIGERIA

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Article Received on 16/01/2023 **Article Revised on 06/02/2023** **Article Accepted on 26/02/2023**

ABSTRACT

Background: Preeclampsia is a potentially dangerous complication of pregnancy. The cause remains largely unknown. Oxidative stress, which is a negative balance between oxidants and antioxidants, has been implicated in its pathogenesis. Free radicals released by the ischemic placenta is thought to be responsible for the impaired endothelial cell function. We evaluated the oxidative stress marker (oxidant), malondialdehyde (MDA) and antioxidants (Superoxide dismutase and Zinc) in preeclamptic women, and their correlation with severity of preeclampsia. **Materials and Methods:** It was a cross-sectional study of women diagnosed with preeclampsia matched with normotensive pregnant women. Serum MDA, Superoxide dismutase (SOD) and Zinc of the participants were measured. Severity of preeclampsia was assessed by the blood pressure at presentation. Statistical analysis was done using SPSS version 24. **Results:** There was no difference in the level of MDA between women with preeclampsia and normotensive pregnant women ($p = 0.505$). SOD was significantly higher ($p < 0.001$), with a positive correlation with severity of preeclampsia (Systolic blood pressure ($\rho = 0.289$, $p < 0.001$) diastolic blood pressure $\rho = 0.258$, $p < 0.001$), while zinc was significantly lower ($p < 0.001$), with a negative correlation with severity of preeclampsia (systolic blood pressure $\rho = -0.212$, $p = 0.004$), diastolic blood pressure $\rho = -0.203$, $p = 0.006$). **Conclusion:** In this study, there was a difference in the level of the antioxidants between women with preeclampsia and normotensive pregnant women, which correlated with the severity of preeclampsia.

KEYWORDS: Oxidative stress; Preeclampsia; Malondialdehyde; Antioxidants.

INTRODUCTION

Preeclampsia is a disease specific to humans, that adversely affects pregnant women and the developing fetus.[1] Defective placentation resulting from poor trophoblastic invasion of the myometrium, leads to reduced uteroplacental perfusion.[1] This culminates in placental ischemia. The link between this initial placental trigger, and a maternal systemic reaction that produces the clinical signs and symptoms of this disorder, has been the focus of various research.[2] Oxidative stress which is an imbalance between oxidants (free radicals and reactive species) and anti-oxidants in favour of the oxidants, has been implicated in the pathogenesis of preeclampsia.[3] Free radicals released from the ischemic placenta are capable of cellular damages, including endothelial damages.[3] Reactive oxygen species (ROS) are short-lived and thus difficult to assay.[4] Therefore, products of peroxidation such as malondialdehyde are commonly used as a biomarker to assess oxidative stress.

Preeclampsia complicates 2-8% of all pregnancies worldwide.[3][5] Its incidence in developing countries is between 3% and 10%[1] with an average of 6%.[5]

The aim of this study was to evaluate an oxidative stress marker and antioxidants in women with preeclampsia and assess the correlation of these markers with the severity of preeclampsia.

MATERIALS AND METHODS

This was a comparative cross-sectional study conducted among pregnant women at Federal Medical Centre Birnin Kebbi, in North-Western Nigeria, from November 2020 to May 2021. Ethical approval was obtained from the Human Research and Ethics Committee of the institution. Informed consent was also obtained from each participant while ensuring confidentiality. Consenting pregnant women with a diagnosis of preeclampsia between 20 – 40 weeks of gestation were recruited consecutively as they presented. They were matched for age (± 2 years) and parity (matched at par) with normotensive pregnant women. Women with co-

morbidities like chronic hypertension, diabetes mellitus, thyroid disease, renal disease, and hepatitis; those with multiple pregnancies, those on chronic drug use like antiretroviral and antipsychotic drugs, NSAIDS and chemotherapeutic agents, or had recently used antioxidants were excluded from the study.

The minimum sample size was determined using the formula for a comparative cross-sectional study (quantitative variable)[6] for a mean malondialdehyde (MDA) of 3.44 and 3.024 for women with preeclampsia and normotensive women respectively, by Shehu et al. in Sokoto, North-western Nigeria[7] and a standard deviation of 1.25[7] as follows.

$$n = \frac{SD^2 (Z_\beta + Z\alpha_2)^2}{(\mu_1 - \mu_2)^2}$$ [8]

Thus, 90 patients were recruited for each arm of the study.

Data Collection

A pre-tested structured proforma was used to collect data regarding respondents' socio-demographic characteristics and obstetric variables. The participants were then examined, and their blood pressure measured using the ACCOSON mercury sphygmomanometer[9] (Accoson Irvine, Scotland); the 1st and the 5th Korotkoff sounds were taken as the systolic and diastolic blood pressure respectively.[9] Ultrasound estimated gestational age was used for uniformity. A blood sample was taken from both preeclamptic and normotensive women via a sterile procedure and after observing the basic universal precautions. Immediate separation of serum was done followed by storage in the laboratory at -40 ^{0}C. Malondialdehyde (MDA) was the oxidative stress marker while superoxide dismutase (SOD) and Zinc were the antioxidants assessed in this study.

Measurement of Malondialdehyde (MDA) and superoxide dismutase (SOD) levels were done using competitive (Pars Biochem Elisa kit Cat NO. PRS-00991hu) and non-competitive (Pars Biochem Elisa kit cat NO.PRS-01469hu) ELISA respectively. Zinc was analysed using the fluorometric method. All analyses were controlled using two-level commercial quality control materials and the coefficients of variation were within acceptable ranges provided by the kit manufacturers.

Data Analysis

The data obtained were imputed into an SPSS computer statistical software version 24 for analysis. Mann-Whitney U test was used to test for difference in the levels of oxidative stress marker and antioxidants between women with preeclampsia and normotensive women. Spearman's rank correlation coefficient was used to determine the correlation between oxidative stress marker/antioxidants and severity of preeclampsia (assessed by the systolic and diastolic blood pressure). *p* value of less than 0.05 was considered to be statistically significant.

RESULTS

One hundred and eighty women were recruited for the study, which included 90 preeclamptic women and 90 normotensive pregnant women. The mean age of women with preeclampsia was 25.98±7.04, and this was not statistically different from that of the normotensive pregnant women. The average gestational age at recruitment was 35 weeks while the mean systolic and diastolic blood pressure for women with preeclampsia were 165.44±22.08 and 108.20±20.43 respectively.

Table 1: Malondialdehyde and antioxidant levels in women with preeclampsia and normotensive pregnant women.

	Preeclamptic women Median (Q1-Q3)	Normotensive women Median (Q1-Q3)	Mann-Whitney U test (U)	*p* value
MDA* (nmol/ml)	4.39 (3.91-5.42)	4.39 (3.99-4.99)	3,817.000	0.505
SOD† (ng/ml)	39.38 (33.18-57.37)	32.40 (27.2-41.49)	5,417.000	< 0.001
Zinc (µg/dl)	50.00 (40.00-60.00)	60.00 (50.00-70.00)	2,636.000	< 0.001

***MDA** – Malondialdehyde*
*†**SOD** – superoxide dismutase*

There was no correlation between serum malondialdehyde level and the systolic blood pressure of preeclamptic women (Spearman's rho correlation = 0 .011, p = 0.879) or diastolic blood pressure (Spearman's rho correlation = 0 .042, p = 0.576)

Table 2: Correlation between superoxide dismutase/Zinc and blood pressure levels.

	Superoxide dismutase Spearman's rho correlation (ρ)	*p* value	Zinc Spearman's rho correlation (ρ)	*p* value
Systolic blood pressure	0.289	< 0.001	-0.212	0.004
Diastolic blood pressure	0.258	< 0.001	-0.203	0.006

DISCUSSION

The serum MDA level was not different in women with preeclampsia compared to the normotensive pregnant women ($p = 0.505$). This is similar to findings by Bowen et al[10] in South Africa where they reported no significant difference in the MDA level in women with preeclampsia compared to normotensive pregnant women. The finding is however contrary to findings from some other studies conducted in Nigeria, Adeniji et al in Ogbomoso[11]and Shehu et al in Sokoto[7]; and Bahediya et al in India[12] all reported a significantly higher serum MDA among patients with preeclampsia. The differing findings could be due to differences in the methods of biochemical analysis of MDA used in these studies. Adeniji et al and Shehu et al used the Thiobarbituric acid (TBA) assay which has the tendency to give a higher value than the actual value due to its reaction with other carbonyl group-containing compounds, i.e. it has low specificity when compared to the ELISA method and High-Performance Liquid Chromatography (HPLC) used in our study and by Bowen et al respectively.

Women with preeclampsia had a higher serum SOD than the normotensive pregnant women and this difference was statistically significant ($p < 0.001$). This finding is a bit unusual. Other researchers have suggested that an increased antioxidant level may be a response to a high pro-oxidant level.[8][13] MDA level in this study was not different from the level in normotensive pregnant women, so it cannot explain the difference in the antioxidant level. The higher SOD could however be in response to other pro-oxidants not measured in this study, such as the iso-prostanes, 4 hydroxynonenal, and the oxidation products of proteins and nucleic acid. The body might produce more antioxidants to mop up a high pro-oxidant level. Llubra et al in Spain[14], have also revealed such mixed outcomes.

The antioxidant, zinc was lower in women with preeclampsia compared to normotensive pregnant women and this was statistically significant ($p < 0.001$). This is theoretically what is expected in the presence of oxidative stress, where the antioxidants are not able to mop up the pro-oxidants, and it agrees with findings by Bakacak et al in Turkey[15] and Ugwuja et al in Nigeria.[16]

There was no correlation between serum MDA level and the severity of preeclampsia, assessed by the systolic and diastolic blood pressure (systolic blood pressure, $\rho = 0.011$, $p = 0.879$; diastolic blood pressure, $\rho = 0.042$, $p = 0.576$). This finding was expected since the MDA level was not different between the preeclamptic and the normotensive women; it therefore did not vary with the severity of preeclampsia. Our finding differed from findings from the study by Priyamvada et al[13] and Saxena et. al[17] where there was a significant positive correlation between MDA and the systolic and diastolic blood pressure. This could be because the mean systolic and diastolic blood pressure in the present study were only marginally in the severe range. Perhaps if the blood pressure were severely elevated beyond what was found, a correlation may have been observed.

There was a positive correlation between serum levels of superoxide dismutase and the severity of preeclampsia (systolic blood pressure; $\rho = 0.289$, $p < 0.001$ and diastolic blood pressure; $\rho = 0.258$, $p < 0.001$). This means that the level of SOD increases as the severity of preeclampsia increases. This was consistent with findings by Llubra et. al in Spain[15] and Diedrich et al in Germany[18], but at variance with the findings by Madazli et al in Turkey.[19]

There was a negative correlation between serum level of zinc and the severity of preeclampsia, suggesting that serum levels of zinc would be low the more severe the disease state. The finding could be clinically relevant as a measure of worsening disease severity.

Majority of the women with preeclampsia in this study were between 20-29 years. This was similar to what was found in a study by Shehu et al in Sokoto where majority of the women were between 25-34 years. In contrast, studies by Duckitt et al[20] and Ukah et al[21] in England, concluded that preeclampsia was commoner among teenagers and those greater than 30 years of age. This could be due to differences in the geographical location where these studies were conducted, in relation to cultural differences and age at first pregnancy.

Majority of the women diagnosed with preeclampsia were primigravidae and mostly unbooked. This is not surprising as several studies have reported that preeclampsia was commoner among primigravidae.[8][20][21]

CONCLUSION

Women with preeclampsia had a significantly higher level of SOD and lower level of Zinc than normotensive women in this study and the levels correlated with the severity of PE. However, the level of oxidative stress marker, in this case MDA, between the two groups were similar. It would therefore appear that antioxidant levels, especially for those measured in this study, could be better indicators for preeclampsia assessment than levels of oxidative stress marker, in this case MDA.

We also found that the two antioxidants studied, that is SOD and zinc, demonstrated significant but opposite correlation with the severity of preeclampsia; while SOD had a positive relationship, zinc had a negative correlation with the severity of the disease. This suggests the need for further research.

ACKNOWLEDGEMENT

The authors wish to thank the management of Federal Medical Centre, Birnin Kebbi for approving this research. We also extend our appreciation to all research

assistants and resident doctors of the Department of Obstetrics and Gynecology for their role in the conduct of the study. We thank Adamu Haruna Wara, Ahmad Isa and other laboratory scientists who participated in the study. Above all, we thank all the patients that consented to participate in this study.

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