*Asian Journal of Pregnancy and Childbirth*

*4(4): 127-134, 2021; Article no.AJPCB.78292*

# Levels of Oxidative Stress Marker Malondialdehyde and Some Lipid Fractions in Women Diagnosed with Pre-Eclampsia in a Rural Hospital in South East Nigeria

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***Authors' contributions***

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

***Article Information***

*Editor(s):*
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(3) Rahul Khatri, MGM Medical College and Research Centre, India.
Complete Peer review History, details of the editor(s), Reviewers and additional Reviewers are available here: https://www.sdiarticle5.com/review-history/78292

***Original Research Article***

***Received 09 October 2021***
***Accepted 18 December 2021***
***Published 21 December 2021***

## ABSTRACT

**Background:** In this modern era, the incidence in the prevalence of pre-eclampsia keep increasing globally and Nigeria in particular, even in the face of extensive researches there are still un-collaborating results on the association between lipid peroxidation product (malondialdehyde) and

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the disease of imprecise etiology (pre-eclampsia). The disturbance in the metabolism of antioxidants and excess lipid peroxidation because of stress and other co-factors during pregnancy may be a contributing factor in the development of preeclampsia.

**Aim:** This investigation was carried out to compare the serum MDA status and some lipid fractions in women with preeclampsia and normal pregnancy in a rural hospital of Imo State Nigeria.

**Methods:** A cross sectional study was carried out on 50 pre-eclampsia and 50 normotensive pregnant women attending the Department of Medicine and Antenatal clinic of specialist Hospital Umuguma, Owerri Imo State. The ethics committee and participants gave their consent, (HMB/IM/VOL.30/110/2019/007) after the study protocol was detailed to them and approved.

**Results:** The mean serum MDA TG, VLDL-C, LDL were significantly higher in pre-eclamptic patients when compared to the controls ($P<0.05$). The mean HDL-C was lower in pre-eclamptic subjects when compared with the control ($P<0.05$). There was no significant difference in the level of the mean Total Cholesterols between the groups ($P>0.05$).

**Conclusion:** This current investigation showed significant increase in lipid per oxidation activities and alteration in lipid metabolism in pregnant women with pre-eclampsia and which may be due to the failure of compensatory antioxidant functions in pregnant women with this disorder.

*Keywords: Pre-eclampsia; lipid peroxidation; malondialdehyde.*

## 1. INTRODUCTION

The precise cause of pre-eclampsia, usually ascribed as a disease of theories, remains unknown. But it has been suggested that the placenta play's a major role in the pathophysiology of pre-eclampsia, therefore making some authors to referred it as a placental condition [1], in normal pregnancy major alterations occur in the spiral arteries to allow increased blood supply to the intervillous space in order to meet the needs of the feto-placental unit during the later stages of pregnancy [1,2]. Pre-eclampsia has been suggested to be characterized by failure of spiral artery remodeling [2,3], a phenomenon associated with incomplete endovascular trophoblast invasion in early pregnancy [4]. This impasses results in a reduction in blood flow into the intervillous space [2,3,4]. It has been proven that the placenta is necessary for pre-eclampsia, [5] poor placentation is not the cause of pre-eclampsia, but rather an important predisposing factor [1,5]. This is because in other pregnancies such as those complicated by intrauterine growth restriction and a subgroup of pattern deliveries are also associated with abnormal placentation but do not develop pre-eclampsia [6,7]. This uncanny nature has led to the hypothesis that pre-eclampsia is a two stage disorder, with reduced placental perfusion representing stage one [1,2,8], while stage two refers to the multi-systemic disorder or maternal syndrome produced in response to reduced placental perfusion [9] that is influenced by genetic or environmental maternal constitutional factors. Endothelial activation appears to be central to the pathophysiological changes associated with pre-eclampsia [10,11,12] with circulating markers of endothelial activation increased in pre-eclampsia [13]. But confusions remains as to the nature of the link between poor placentation and endothelial activation for which a number of theories have been put forward [14,11,15]. Some studies suggest that hypoxia resulting from inadequate perfusion upregulates SFT+1, a VEGF and PIGF antagonist, leading to a damaged maternal endothelium and restriction of placental growth [14,16]. It has also been proposed that an unknown factor excreted from the placenta is central to the pathogenesis of pre-eclampsia with candidates for this unknown factor including placental debris, apoptotic fragments, lipid peroxidation products and other reactive oxygen species, all of which are able to induce maternal oxidative stress directly or indirectly [2,17,1,8]. Many of the predisposing factors for pre-eclampsia are also known risk factors for atherosclerosis. Indeed, pre-eclampsia has been suggested to associated with altered athrogenic lipid pattern, with increased plasma Triacylglycerol concentration and decreased HDL-cholesterol concentration evident before clinical manifestations of the disease [18,19,20]. Reactive oxygen species degrade polyunsaturated lipids, forming malondialdehyde [21]. Malondialdehyde is a reactive aldehyde and is one of the many reactive electrophile species that can cause toxic stress in cells and form covalent protein adducts referred to as advanced lipid-oxidation end-product (ALE), in analogy to advanced gylcation end-product (AGE), [22]. Malondialdehyde (MDA), which is a product of lipid peroxidation,

has been reported to be increased in certain disease conditions including pre-eclampsia [12,23] which could lead to oxidative stress. The production of this aldehyde serves as a biomarker to measure the level of oxidative stress in a subject [22]. Malondialdehyde reacts with deoxyadenosine and deoxyguanosine in DNA, forming DNA adducts, the primary one being M1G, which is mutagenic [24]. The guanidine group of arginine residues condenses with malondialdehyde to give 2-amino antipyrine. Malondialdehyde is highly reactive and potentially mutagenic. It has been found in heated edible oils such sunflower and palm oil [25].

In this current investigation, we looked at the level of this oxidative maker malondialdehyde and some lipid fractions in pre-eclampsia and normotensive pregnant women in a rural hospital in Nigeria.

## 2. MATERIALS AND METHODS

### 2.1 Study Design

This was a cross-sectional study designed to investigate the levels of Malondialdehyde and some lipid fractions in pre-eclampsia and normotensive pregnant women.

### 2.2 Study Area

This study was carried out in Department of Chemical Pathology, Nnamdi Azikiwe University Nnewi Campus, located within the South-Eastern part of Nigeria. The climate of the area is tropical with mean daily temperature of 29±50°C for most of the year. The annual rainfall is between 217 and 240cm with distinct wet and dry season.

### 2.3 Study Population

The study population involves pregnant women attending the Department of Medicine and Antenatal care of Specialist Hospital, Umuguma, Owerri Imo State, Nigeria. The sample size for each group (n) was 50 using the formula $n = 2Z2PQ/d^2$ as calculated. A 95% confidence interval with a precision of 0.05 was used. Prevalence of 1.7% of pre-eclampsia in Nnewi as observed by Mbachu et al, [26] was used. A total of 100 pregnant women were therefore recruited into the study who fulfill the inclusion criteria (comprising 50 pre-eclampsia and 50 normotensive group) informed consent was obtained from each of the participants after the study protocol was explained to them.

### 2.4 Exclusion Criteria

Smoking, diabetic and alcoholic women, those with acute or chronic illness, those on lipid lowering drugs, vitamin supplements etc and those with immunological challenges (HIV) were excluded.

### 2.5 Blood Sample Collection

5ml of blood was drawn from the cubital vein using a sterile needle and syringe into an appropriate tube. The samples in plain tubes were allowed to clot undisturbed and serum were separated by centrifugation for 10mins at 4,000rpm and stored at -20°C until time of analysis.

### 2.6 Laboratory Analysis

All reagents used were of analytical grade (AR). Serum MDA was determined using albro et al, [27] methodology. Fasting lipid profile was assessed using commercially available kits (Randox), serum total cholesterol and high density lipoprotein HDLc, was determined by cholesterol oxidase method Allain *et al* [28], serum triglyceride by glycerol kinase method of Tinder [29] and LDLc was calculated using Friedwald formula Friedwald [30]. Quality control was maintained in the analysis of the samples.

### 2.7 Statistical Analysis

Data collected was analyzed using the SPSS software for windows version 20.0. Means were compared using students t-test. Data were presented using tables. Values were set at 95% confidence level, a P-value of <0.05 was considered to be significant.

## 3. RESULTS

The maternal anthropometric parameters were compared in Table 1. The Mean age was 25 years, mean gestational age was 35 weeks, mean BMI was 25kgm$^2$ and mean HBC g/l was 10.0 in pre-eclamptic and controls which were not statistically significant. ($p>0.05$) In pre-eclamptic the mean ±SD systolic blood pressure was 147.04±5.9mmHg while in controls mean ±SD systolic blood pressure was 115.96±4.9mmHg. In pre-eclamptic the mean

±SD diastolic BP was 96.96±6.54mmHg while in controls, the mean±SD diastolic blood pressure was 80.04±9.87mm Hg. Mean Systolic and diastolic blood pressure was statistically significantly higher in pre-eclamptic when compared to controls ($p<0.05$).

In Table 1 the Mean ±SD Total Cholesterol level in pre-eclamptic and controls (4.34 mmol/l±3.62 versus 4.51mmol/l±3.4) were not statistically significant ($p>0.05$). The Mean ±SD HDL-C, levels (0.95mmol/l±3.85 versus 1.32mmol/l±2.7) were statistically significantly lower in pre-eclamptic when compared to normal controls ($p<0.05$). The Mean ±SD LDL-C levels (3.5mmol/l±15.1 versus 2.45mmol/l±8.9) were statistically significantly higher in pre-eclamptic when compared to normal controls ($p<0.05$). The Mean ±SD Triglycerides levels (2.90mmol/l±0.46 versus 1.33±3.8) were statistically significantly higher in preeclamptic when compared to normal controls ($p<0.05$). The mean ±SD VLDL-C levels (1.31mmol/l±0.09 versus 0.60mmol/l±0.98) were statistically significant higher in pre-eclamptic when compared to the normotensive controls. The mean ±SD MDA was elevated in pre-eclamptic subjects when compared to the normotensive controls (3.19nmol±0.25 versus 1.15nmol±0.076) which was statistically significant ($p<0.05$).

### 3.1 Anthropometric Parameters

Table 1 shows the clinical data on the pre-eclamptic women and healthy controls. The mean Age, BMI and HBC, of all pre-eclampsia patients was not statistically significant from those of control subjects ($p>0.05$). There was a statistical significance difference ($p<0.05$) between the Systolic and Diastolic Blood Pressures of the Test and the Control group. The mean maternal years and gestational ages of the subjects and controls were similar. Participants had different gravida distribution and had nearly equal proteinuria.

### 3.2 Biochemical Parameters

Table 2 shows the mean ±SD value of serum MDA and some lipid fraction. Serum MDA were significantly lower ($p<0.05$) in pre eclampsia groups in comparison to the control group. The level of serum Triglyceride, Low Density Lipoprotein, Very Low Density Lipoprotein was significantly lower ($p<0.05$) in normotensive pregnant women when compared to that of pre-eclampsia women. The level of High density cholesterol was significantly lower ($p<0.05$) in pre-eclampsia women when compared to the normotensive pregnant women. There was no statistical difference in the Total Cholesterol of pre-eclampsia and normotensive pregnant women ($p>0.05$).

## 4. DISCUSSION

Lipid per-oxidation can be defined as the oxidative deterioration of lipids containing a number of carbon-carbon bonds [8,31,15]. In pre-eclampsia, oxidative stress has been suggested to result from increased formation of lipid peroxides, reactive oxygen species and superoxide anion radicals, leading to an imbalance in production between per-oxidant and antioxidant defenses, these alteration leads to endothelial dysfunction, platelet and neutrophil activation, with altered lipid synthesis resulting to decreased in prostaglandin and thromboxane $A_2$ ratio [11,32]. The resulting imbalance in prostaglandin cascade, leads to enhanced multi systemic vasospasm phenomenon in the kidneys, brain, uterus and placenta [14,17,32]. The results obtained from this study showed mean systolic blood pressure of 147.04±5.9mmHg and a Diastolic blood pressure of 96.96±6.54mmHg in pre-eclampsia patients in contrast to a systolic blood pressure of 115.96±4.9mmHg and a diastolic blood pressure of 80.04±9.87mmHg in control subjects. This buttress the study of Gifford et al. [33] who reported a systolic blood pressure of 140mmHg and a diastolic blood pressure of 90mmHg, the slight difference in their results and the value obtained in this study may be due to racial differences. The implication of this is that pathogenesis and development of complication may be more sever in pre-eclampsia patients in our environment compared to Caucasians.

Studies has shown that women with greater body mass index (BMI) in pregnancy are more likely to become hypertensive than those with lower BMI [34], but the comparable body mass index (BMI) observed this present study ruled out the influence of the parameter (i.e. body mass index) on the aetiology or severity of pre-eclampsia in pregnant women.

The observation of some lipid fractions of pre-eclamptic subjects in our investigation shows significantly higher serum concentrations of triglycerides, LDL-C, VLDL-C and lower serum concentrations of HDL-C. This indicates a risk factor in the development of pre-eclampsia. It

**Table 1. Comparison of maternal anthropometric characteristics between pre-eclampsia and normotensive pregnant women**

| Parameters | Pre-eclampsia (n=50) | Control (n=50) | t-test | P-value |
|---|---|---|---|---|
| Age(yrs.) | 25.0±1.64 | 25.0±1.70 | -1.497 | P>0.05 |
| Gestational age (week) at sampling | 35.23±1.64 | 35.64±0.95 | 5.289 | p>0.05 |
| Gravida in (%) | | | | |
| primi | 34(52.4) | 28(40) | _ | _ |
| multi | 16(28) | 22(35) | _ | _ |
| BMI(kg/m2) | 25.45±1.66 | 25.94±1.77 | -1.427 | P>0.05 |
| SBP(mmHg) | 147.04±5.9 | 115.96±4.9 | 28.66 | P<0.05 |
| DBP(mmHg) | 96.96±6.54 | 80.04±9.87 | 10.11 | P<0.05 |
| HBC(g/dl) | 10.05±0.58 | 10.33±0.48 | -2.63 | P>0.05 |
| Proteinuria | | | | |
| primi | 2+(34) | 0 | _ | _ |
| multi | 3+(16) | 0 | _ | _ |

*BMI: Body mass index; HBC: Haemoglobin Concentration; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; Values are mean ± standard deviation, P<0.05, n= total number of patients*

**Table 2. Comparison of serum concentration of MDA and some lipid fractions in preeclamptic and normotensive pregnant women**

| Parameters | Pre-eclampsia (n=50) | Control (n=50) | P-value |
|---|---|---|---|
| MDA (nmol/ml) | 3.19±0.25 | 1.15±0.076 | P<0.05 |
| T-CHOL (mmol/l) | 4.34±3.62 | 4.51±3.4 | P>0.05 |
| TG (mmol/l) | 2.90±0.46 | 1.33±3.8 | P<0.05 |
| LDL-C (mmol/l) | 3.5±2.1 | 2.45±3.9 | P<005 |
| VLDL-C (mmol/l) | 1.31±0.09 | 0.60±0.98 | P<0.05 |
| HDL-C (mmol/l) | 0.95±3.85 | 1.32±2.7 | P<0.05 |

has been suggested that hypertriglyceridemia is a risk factor for pre-eclampsia. Increased triglyceride levels seem to elevate the risk of placental vascular disorders, [35] which leads to the development of endothelial dysfunction, atherosclerosis and thrombosis [36]. The development of atherosclerosis in the placental spiral arteries of preeclamptic women indicates that elevated levels of triglycerides are involved in this disorder [37]. From literatures, the principle modulator of this hypertriglyceridemia is estrogen as pregnancy is associated with hyperoestrogenaemia [3,38]. Estrogen induces hepatic biosynthesis of endogenous triglycerides, which is carried by VLDL. This process may be modulated by hyperinsulinism in pregnancy [39]. Hypertriglyceridemia may be associated with hypercoagulability [40]. Furthermore, hypertriglyceridemia has been suggested to be involved in the pathogenesis of hypertensive disorders during pregnancy [18,19,20].

The findings from this study showed increased lipid peroxidation indicating altered levels of antioxidant status in pre-eclamptic women. These are consistent with the conclusions from studies in other population beyond Nigeria [12,21,41]. Although some other studies had reported no significant difference in the levels of lipid peroxidation between gestational age matched cases and controls. Striking patterns noticed in this investigation are relatively higher MDA levels in pre-eclamptic patients and low levels in control groups. The mean MDA in the pre-eclamptic patients and normotensive pregnant control in this study were 3.19±0.25 and 1.15±0.076 respectively. These values are much lower than the reports from other regions of the world, as reported by Howlader et al, [42] and Begun, [43]. However, the findings in this study are similar and in consonant to that of Nnodim et al, [21] and Ilechukwu et al. [10] in south east Nigeria population. Which they reported values of 3.91nmol, 1.68nmol and 2.83±0.9nmol, 1.96±0.63nmol respectively. Also Adetunji et al, [44] reported values of 2.96±0.75 and 1.23±0.12nmol/ml in their patient at Ladoke Akintola University (LAUTECH) Teaching Hospital, Osogbo, Nigeria. Furthermore this result is similar to that of Patil et al, [45] and Gohil et al [12] in India. However, this study was in contrast with the studies of Guptha et al. [46] in which they find no significant difference between pre-eclamptics and normotensive

pregnant controls. This might be due to the sample size, time or geographical variation which might have played a role as factors responsible to the inconsistency of their investigation results.

## 5. CONCLUSION

This investigation demonstrated elevation in lipid membrane damage activities (lipid peroxidation), as evidence by elevated level of serum MDA in pre-eclamptic women. Furthermore it also buttresses the point that Pre-eclamptic women have altered lipid profile courtesy of abnormal lipid metabolism. Elevated triglyceride levels and it delayed clearance coupled with high blood pressure has been shown to play a role in the development of this disorder. The early detection of these abnormalities might help early diagnosis and management of pre-eclampsia. We recommend the assessment of these parameters in both the primi and multi gravida women for early detection of altered lipid metabolism, diagnosis and prevention of this disorder.

## CONSENT AND ETHICAL APPROVAL

The ethics committee and participants gave their consent, (HMB/IM/VOL.30/110/2019/007) after the study protocol was detailed to them and approved.

## ACKNOWLEDGEMENT

The author's wishes to thank the participants for their consent and patience during the course of this study, also the staff of specialist hospital Umuguma for their help and dedication to the success of this research work.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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