JOGM
Journal of Global Medicine

RESEARCH ARTICLE

The metal fingerprint of preeclampsia: evaluating the copper-to-zinc ratio in Nigerian pregnant mothers

Mathias A. Emokpae[1]*, Micheal C. Oyana[1], Irabonosa Asiriuwa[1], Loveth A. Emokpae[1] and Nosakhare O. Enaruna[2]

[1]Department of Medical Laboratory Science, School of Basic Medical Sciences, College of Medical Sciences, University of Benin, Benin City, Nigeria; [2]Department of Obstetrics and Gynaecology, School of Medicine, College of Medical Sciences, University of Benin, Benin City, Nigeria

Abstract

Background: Preeclampsia poses serious medical risks to pregnant women in the world, especially those in developing countries like Nigeria. This study aimed to identify specific levels of zinc, copper, and selenium and to determine the relationship between the copper-to-zinc ratio and preeclampsia in pregnant mothers.
Materials and Methods: Serum levels of zinc, copper, and selenium were analysed using atomic absorption spectrophotometry (AAS). The copper-to-zinc ratio was calculated, and a paired t-test was used to analyse the data; *P*-values less than 0.05 were considered statistically significant.
Results: Serum levels of zinc and selenium in pregnant women with preeclampsia were significantly lower ($P < 0.001$) than those of the normotensive pregnant women. Conversely, the serum copper level and copper-to-zinc ratio of pregnant women with preeclampsia were markedly higher ($P < 0.001$) when compared to those of the normotensive pregnant women. After adjusting for age and body mass index (BMI), the mean Cu/Zn ratio was 2.86 (95% confidence interval of 2.85–2.87, $P < 0.01$) and remained independently associated with pre-eclampsia in a multivariate regression. The Area Under the Receiver Operating Characteristic curve was excellent at 0.9.
Conclusion: The findings provide evidence of an imbalance in essential trace elements, resulting in a significantly elevated Cu/Zn ratio, which could serve as a metal fingerprint linked to preeclampsia in the examined group of Nigerian mothers. The finding is promising as a novel, cost-effective, and easily measurable biomarker for risk evaluation of preeclampsia in resource-limited settings.

Keywords: *preeclampsia*; *micronutrients*; *antioxidants*; *pregnancy*; *hypertension*

Received: 18 January 2026; Revised: 14 February 2026; Accepted: 2 March 2026; Published: 20 March 2026

Preeclampsia (PE) is a significant and high-risk complication during pregnancy, marked by the onset of hypertension and proteinuria after the 20-week gestation period. It continues to be a primary cause of maternal and perinatal morbidity and mortality worldwide [1–3], especially in developing countries. In Nigeria and other West African nations, the impact is particularly severe, highlighting the urgent need for effective early-stage identification and risk-stratification tools to enhance clinical outcomes [4]. In Nigeria, the prevalence of preeclampsia is increasing at a rate of 2–17% among pregnant women, leading to approximately 15% maternal deaths every year [5]. While prevalence varies by region, studies in areas like Benue State have reported a prevalence rate of approximately 18.9%, which is significantly higher than global averages. Present diagnostic approaches frequently depend on the appearance of clinical symptoms such as elevated blood pressure [6], which may manifest too late to implement effective preventive strategies.

The mechanisms underlying preeclampsia are thought to involve placental dysfunction that results in extensive endothelial injury and oxidative stress. Essential trace elements, or micronutrients, including copper (Cu) and zinc (Zn), are crucial in the body's defence against such damage [7–9]. Zinc (Zn) is a vital cofactor for numerous enzymes. Zinc serves as a powerful antioxidant and membrane stabiliser, essential for immune function and the prevention of oxidative damage. Zinc deficiency is prevalent among pregnant populations, which may worsen the underlying pathology of PE [10].

Copper (Cu) is necessary for various metabolic functions; copper levels are often elevated in inflammatory

Citation: Journal of Global Medicine 2026, **6**: 355 - http://dx.doi.org/10.51496/jogm.v6.355

and stressful situations. Although essential, excess of copper can act as a pro-oxidant catalyst, leading to cellular damage if not carefully regulated [11].

The equilibrium between these two metals is physiologically essential [12]. Zinc and copper frequently compete for absorption and binding sites, and their relative concentrations, represented as the copper-to-zinc (Cu/Zn) ratio, have proven to be more sensitive markers of systemic inflammation and oxidative stress than the individual concentrations of either metal alone [13–15].

Elevated Cu/Zn ratios, often resulting from increased copper, decreased zinc, or both, are consistently linked to chronic inflammatory diseases and have been associated with complications during pregnancy. This ratio is proposed to serve as a quantifiable 'metal fingerprint' that indicates the severity of the oxidative stress and inflammatory cascade [16, 17], which are typical of preeclampsia.

Although studies have linked micronutrient status to preeclampsia [18, 19], there is a notable lack of data on the predictive value of the Cu/Zn ratio specifically in Nigerian pregnant women. This study seeks to address this knowledge gap by identifying the specific levels of zinc, copper, and selenium and determining the relationship between the copper-to-zinc ratio and preeclampsia in pregnant mothers.

Materials and methods

Study design and population

This is a cross-sectional study involving pregnant women who booked to receive antenatal care and unbooked pregnant mothers who were admitted into the hospital for treatment, while pregnant women without preeclampsia served as the control group. They comprised of 40 preeclamptic pregnant women with ages ranging from 20 to 45 years (mean 30.9 ± 4.02), and 40 non-preeclamptic pregnant women, ages ranging from 20 to 45 years (mean 29.6 ± 3.9), which served as controls.

Study site

Sample collections were done at the antenatal clinic of the University of Benin Teaching Hospital (UBTH), Benin City. Zinc, copper, and selenium assays were done at the Analytical Laboratory, Faculty of Science Laboratory Technology, University of Benin, Benin City, Edo State.

Ethical consideration

The study protocol was reviewed and approved by the Health Research Ethics Committee of the Edo State Ministry of Health, Benin City (HA/737/25/D/09230937 dated 23rd September 2025), and all participants provided informed consent before the commencement of specimen collection.

Sample size

The minimum sample size was calculated based on a 2.5% prevalence rate of preeclampsia among pregnant women [1].

$$n = \frac{Z^2 Pq}{d^2},$$

where n = sample size, Z = confidence interval of 95%, which is equivalent to confidence of 1.96, P = proportion in the target population estimated to have a particular characteristic, $q = (1-p)$ and D = desired level of size significance (5%)

$$n = \frac{(1.96)^2 \times 0.025 \times (1-0.025)}{0.05 \times 0.05} = 38$$

A total of 40 pregnant women with preeclampsia served as study participants, while 40 pregnant women without preeclampsia served as control participants.

Inclusion and exclusion criteria

The inclusion criteria include pregnant women of ≥ 20 weeks' gestation and between the ages of 18 and 45 years. Pregnant women with preeclampsia served as study participants, while pregnant women with no signs of preeclampsia, diabetes mellitus or renal disease, pregnant women with chronic illness such as chronic hypertension before pregnancy, autoimmune disorder and those on trace minerals or antioxidant supplements; alcohol consumers and smokers were excluded from this study.

Sample collection

Five millilitres (mL) of venous blood samples were collected from each participant using a sterile, disposable syringe and needle. The blood was collected in a sterile leakproof plain container, which was allowed to clot and refract. It was dislodged and spun at 3,000 rpm for 5 min. The serum obtained was stored at −20°C prior to analysis.

Laboratory analysis

Estimation of Zinc, Copper and Selenium using Atomic Absorption Spectrophotometry (Buck Scientific Model 210 VGP)

Principle. Atomic absorption spectrophotometry (AAS) is an analytical technique that is used to determine the concentration of elements in samples. The principle is based on the ability of an atom of an element to absorb light at a specific wavelength. When an atom absorbs light, it becomes excited and moves to a higher energy level. The amount of light absorbed is directly proportional to the concentration of an element in a sample or solution.

Quality control. The equipment (AAS) was first calibrated using Buck-certified atomic absorption standards for the respective metals to obtain a calibration curve. A reagent blank was run at intervals of every 10 samples analysed to eliminate equipment drift. All samples were analysed in triplicate for reproducibility, accuracy checks and precision. The Buck 210VGP is recognised for its stability, often achieving a Relative Standard Deviation (RSD) of < 0.5% for most stable elements. Analytical performance parameters are as follows: copper sensitivity (0.040 ppm), linear range (10–500 μg/dL), zinc sensitivity (0.010 ppm), linear range (0.05–100 μg/dL) and selenium sensitivity (0.500 ppm) and linear range (20–2,000 μg/dL).

Procedure

The sample was diluted with deionised water to form a solution. The solution containing the analyte was aspirated into a flame, usually a flame produced by burning acetylene and air, where the sample was vaporised and the atoms of the analyte were excited to a higher energy level. A beam of light, usually from a hollow cathode lamp that emits light at a specific wavelength corresponding to the element being analysed, was passed through the flame. The atoms of the analyte in the flame absorb some of the light, reducing the intensity of the transmitted light. The amount of light absorbed by the analyte was measured by a detector, and the absorbance was converted to concentration using a calibration curve generated using standard solutions of known concentrations.

Statistical analysis

The data obtained were statistically evaluated using the Statistical Package for Social Sciences (SPSS) version 21 (SPSS Inc., Chicago, IL, U.S.A.). The data were expressed as mean ± SD for both tests and controls, and Student's t-test and ANOVA were used to compare the means. Relationships between values were analysed by the Pearson correlation coefficient. The level of significance was set at $P < 0.05$.

Results

This study involved 80 participants, comprising of 40 pre-eclamptic pregnant women and 40 normotensive pregnant women between the ages of 20 and 45 years.

Table 1. Sociodemographic status of study participants

Variables	Pre-eclamptic Pregnant women (*n* = 40)	Normotensive Pregnant women (*n* = 40)	*P*
Age (years)	30.9 ± 4.02	29.6 ± 3.92	0.09
Body Mass Index (Kg/m^2)	27.9 ± 3.60	24.8 ± 3.67	0.001*
Blood Pressure			
Systolic (mmHg)	147.8 ± 7.80	112.2 ± 7.10	0.001*
Diastolic (mmHg)	93.0 ± 4.20	75.5 ± 5.20	0.001*
Gestational age (weeks)	34.0 ± 4.0	34.0 ± 4.0	1.00
Educational status			
Primary	2 (5%)	4 (10%)	
Secondary	15 (37.5%)	12 (30%)	> 0.05
Tertiary	23 (57.5%)	24 (60%)	
Marital status			
Single	5 (12.5%)	7 (17.5%)	> 0.05
Married	35 (87.5%)	33 (82.5)	> 0.05

*$P < 0.05$ – statistically significant.

Table 1 shows the socio-demographic status of the study participants. The pre-eclamptic pregnant women were slightly older than controls. The pre-eclamptic patients had significantly higher mean body mass index (BMI) and diastolic and systolic blood pressure than controls (Table 1). Gestational age was 34 weeks in both groups.

Table 2 shows the zinc, copper, and selenium levels of the study participants compared with those of the controls. The mean serum levels of zinc and selenium of preeclamptic pregnant women were significantly lower ($P < 0.001$) than those of controls, while the mean serum level of copper of pregnant women with preeclampsia was significantly higher ($P < 0.001$). The Cu/Zn ratio was significantly higher in pre-eclampsia (2.86 ± 0.04, 95% confidence interval [CI]: 2.85, 2.87) than in normotensive pregnant women (1.05 ± 0.02, 95% CI: 1.04, 1.06; $P < 0.001$).

A multivariate linear regression analysis was performed to evaluate the association between Cu/Zn and pre-eclampsia among pregnant women. After adjusting

Table 2. Serum levels of zinc, copper, selenium and copper-to-zinc ratio among pre-eclamptic pregnant women and normotensive pregnant women (Mean ± SD)

Parameters	Pre-eclamptic Pregnant women (*n* = 40)	Normotensive Pregnant women (*n* = 40)	*P*
Zinc (μg/dL) (Ref. Range: 60–120 μg/dL)	35.85 ± 8.89 95% CI: 33.10, 38.60	75.84 ± 14.72 95% CI: 71.28, 80.40	0.001*
Copper (μg/dL) (Ref. Range: 80–140 μg/dL)	103.46 ± 18.70 95% CI: 97.67, 109.25	80.58 ± 14.15 95% CI: 76.20, 84.98	0.001*
Selenium (μg/dL) (Ref. Range: 60–120 μg/dL)	76.46 ± 16.58 95% CI: 71.33, 81.59	107.79 ± 16.19 95% CI: 102.78, 112.80	0.001*
Copper/Zinc Ratio (Ref. Range 0.7 -1.5)	2.86 ± 0.04 95% CI: 2.85, 2.87	1.05 ± 0.02 95% CI: 1.04, 1.06	0.001*

*$P < 0.05$, statistically significant.

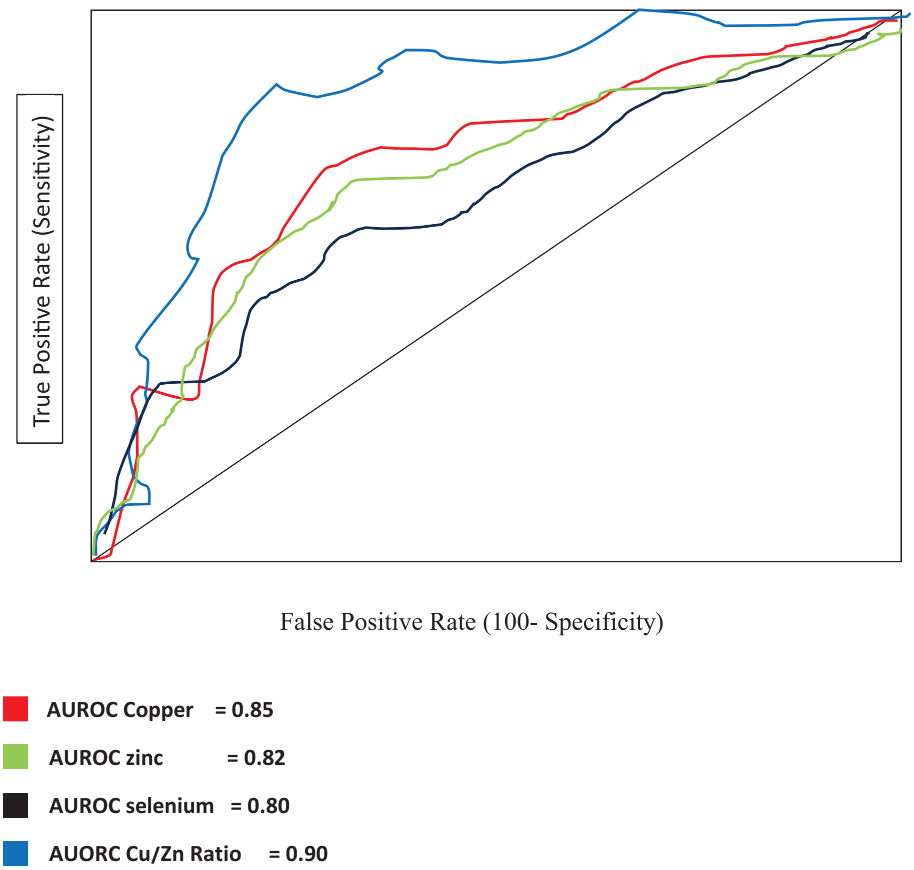

Fig. 1. The Area Under the Receiver Operating Characteristic (AUROC) curves for copper, selenium, zinc, and Cu/Zn ratio.

for age and BMI, the mean Cu/Zn β = 0.28, 95% CI: 2.85, 2.87, $P < 0.01$ remained independently associated with pre-eclampsia. Using pre-eclampsia and control as binary dependent variables in a logistic regression, the Area Under the Receiver Operating Characteristic (AUROC) curves for copper, selenium, zinc, and the Cu/Zn ratio are provided in Fig. 1. The AUROC for Cu/Zn was the highest at 0.9, indicating a better model for differentiating between pre-eclampsia and control.

Discussion

Preeclampsia is one of the major causes of high morbidity and mortality among pregnant women worldwide, especially in developing countries like Nigeria [20]. The risk factors of preeclampsia, such as oxidative stress, inflammation, dyslipidemia, cytokine production and elevated homocysteine, have been documented [21]. While research exists linking micronutrient levels to preeclampsia [18, 19], there is a significant lack of information on the metal fingerprint associated with preeclampsia among pregnant women in Nigeria.

Our findings reveal a clear pattern of micronutrient dysregulation among women with preeclampsia: a notable reduction in serum zinc and selenium levels, contrasted with a significant rise in serum copper levels. The observed decrease in zinc and selenium in pregnant women with preeclampsia compared to controls is particularly concerning. Zinc acts as a crucial cofactor for the enzyme superoxide dismutase (SOD), while selenium is essential for glutathione peroxidase (GPx). Both zinc and selenium are fundamental components of the body's antioxidant defence system. Their reduced levels indicate a severely weakened defence mechanism against the increased oxidative stress that is characteristic of preeclampsia pathology. This deficiency likely hinders the neutralisation of detrimental free radicals, exacerbating endothelial injury and contributing to the clinical symptoms of the disease.

These findings are consistent with previous findings [22, 23], though there have been some conflicting results regarding the levels of these micronutrients in preeclampsia [24, 25]. A study has documented reduced levels of zinc, copper, and selenium in preeclampsia [25], while other studies have documented an increase in the levels of these micronutrients [26, 27]. Micronutrient deficiencies or toxicity has been reported to disrupt biochemical processes that can potentially predispose pregnant women to high pressure and preeclampsia [28].

Citation: Journal of Global Medicine 2026, 6: 355 - http://dx.doi.org/10.51496/jogm.v6.355

In addition, the notably elevated Cu levels in pregnant women with preeclampsia compared to the control group exacerbate the issue. Although copper is a vital nutrient, an excess or inadequately high level of copper can function as a pro-oxidant [29–31].

The findings regarding the Cu/Zn ratio lend substantial empirical support to the comprehension of trace element imbalance in hypertensive disorders of pregnancy, particularly within the Nigerian context. The Cu/Zn ratio is recognised as a significant clinical indicator of oxidative stress and inflammation [32, 33]. The observation of a significantly elevated ratio indicated that pre-eclampsia is marked by a systemic imbalance between antioxidants and oxidants. This finding is consistent with global patterns [13–15] and provides specific baseline values pertinent to the Nigerian population.

A notable strength of this study is the multivariate linear regression analysis. By controlling for age and BMI, it has shown that the Cu/Zn ratio is not simply a consequence of maternal obesity or age, but rather an independent biological factor associated with the condition.

Also, the Cu/Zn ratio with AUC = 0.90 indicates that the ratio may be a strong predictor or can accurately distinguish between women with pre-eclampsia and normotensive pregnant women. This advancement elevates the ratio from a mere observation to a potentially valuable predictive biomarker. It also holds considerable promise as a novel, cost-effective, and easily measurable biomarker for risk evaluation in the management of preeclampsia. Employing this 'metal fingerprint' in clinical settings could facilitate earlier interventions, especially in resource-constrained areas such as Nigeria.

Research on trace elements during pregnancy frequently presents contradictory findings influenced by geographic and dietary differences. The narrow confidence intervals (95% CI: 2.85−2.87) indicate a high level of precision in the analytical technique. This contributes high-quality data points to the African regional literature, where such precise profiling of trace elements is occasionally deficient. It establishes a clear benchmark that future research in similar populations can utilise for comparative purposes.

Given that elevated copper levels are often associated with increased ceruloplasmin (an acute-phase reactant), these findings reinforce the notion that pre-eclampsia represents a state of chronic systemic inflammation. Therefore, the data presented imply that the presence of inflammation is statistically correlated with the clinical presentation of pre-eclampsia.

The findings from a tertiary healthcare facility in Edo State, Nigeria, validate global patterns and offer essential, region-specific insights. The high occurrence of micronutrient deficiencies in certain demographics may render these findings particularly relevant. The Cu/Zn ratio not only indicates the concentrations of specific trace elements but also seems to significantly influence metabolism, implying that these trace elements are crucial in the development of diseases [34]. The reference ranges for the Cu/Zn ratio (0.54–1.68) in plasma and 0.13–0.25 in whole blood have been recorded among Chinese women [35]. The authors proposed that this information could be utilised to evaluate the clinical health and body burden of the population studied [35]. Future research should focus on determining the optimal cut-off value for the Cu/Zn ratio to establish its sensitivity and specificity as a diagnostic tool for preeclampsia, paving the way for its clinical application.

In this study, we conclude that preeclampsia in the Nigerian population is significantly associated with severe systemic disruption of the homeostasis of essential micronutrients. An imbalanced Cu/Zn ratio in the endothelial lining of blood vessels impairs the vessels' ability to produce vasodilators (such as nitric oxide), leading to vasoconstriction [36]. The narrowing of blood vessels leads to increased blood pressure, directly contributing to the hypertension observed in preeclampsia [37].

Numerous studies have noted a positive correlation between a high Cu/Zn ratio and elevated systolic and diastolic blood pressure [26, 38]. Since the body's circulating copper naturally rises during a typical pregnancy (due to increased oestrogen stimulating the carrier protein, ceruloplasmin), measuring copper alone can be deceptive. However, when zinc levels do not adequately compensate or decrease significantly, the resulting high ratio is regarded as a more reliable indicator of pathological imbalance and vascular complications than either trace element alone [38].

Limitations of the study

Despite the important discoveries concerning the Cu/Zn ratio, several limitations must be recognised. First, the cross-sectional nature of this study prevents the establishment of a definitive causal relationship. Although a distinct 'metal fingerprint' was identified in mothers with preeclampsia, it remains unclear whether these imbalances in trace elements are a primary cause of the condition or a secondary physiological response to it.

Second, the research was conducted in a single-centre setting, which may limit the generalisability of the results. Given regional differences in dietary habits, soil composition, and environmental exposures across Nigeria, the results may not accurately reflect the wider national population.

Lastly, the relatively small sample size may have constrained the statistical power to detect more subtle correlations, especially when analysing data by severity or onset timing of preeclampsia. Future longitudinal, multi-centre research with larger participant groups is necessary to confirm these findings and assess the predictive significance of the Cu/Zn ratio during early pregnancy.

Conclusion

The identified markedly reduced levels of antioxidant zinc and selenium, alongside significantly elevated pro-oxidant copper levels, induce a critical condition of oxidative stress and heightened inflammatory susceptibility. Importantly, the notably increased Cu/Zn ratio acts as a powerful and unique 'metal fingerprint' for preeclampsia. This ratio is statistically significant when comparing women with preeclampsia to normotensive controls, highlighting its capacity to reflect the severity of the underlying redox imbalance.

Finally, the Cu/Zn ratio presents significant potential as an accessible, cost-effective, and highly predictive biomarker for the prompt detection and risk assessment of preeclampsia in pregnant mothers, especially in high-risk areas such as Nigeria. Further clinical validation is necessary to incorporate this influential metabolic signature into standard antenatal screening practices.

Authorship contribution statement

Mathias A. Emokpae, Micheal C. Oyana, Irabonosa Asiriuwa, Loveth A. Emokpae, Nosakhare O. Enaruna conceived, designed the experiments, performed the analysis and wrote the manuscript; Mathias A. Emokpae, Irabonosa Asiriuwa, Loveth A. Emokpae performed the data gathering, analysis and assisted in the writing of the manuscript. All authors have read and agreed to the published version of the manuscript.

Acknowledgements

We appreciate the contributions of the clinical, nursing and laboratory staff of the University of Benin Teaching Hospital, Benin City for their assistance toward the completion of the study.

Conflicts of interest and funding

The authors declare no conflict of interest. This research received no external funding.

Ethics declarations

Ethics approval and consent to participate.

The study protocol was reviewed and approved by the Ethics Committee of Edo State Ministry of Health, Health Research Ethics Committee, Benin City (HA/737/25/D/09230937 dated 23rd September 2025), and all participants gave informed consent before the commencement of specimen collection.

Consent for publication

Not applicable.

References

1. Poon LC, Shennan A, Hyett JA, Kapur A, Hadar E, Divakar H, et al. The International Federation of Gynecology and Obstetrics (FIGO) initiative on preeclampsia (PE): a pragmatic guide for first trimester screening and prevention. International journal of gynaecology and obstetrics: the official organ of the Int Fed Gynaecol Obstet 2019; 145(Suppl 1): 1. doi: 10.1002/ijgo.12802
2. Turbeville HR, Sasser JM. Preeclampsia beyond pregnancy: long-term consequences for mother and child. Am J Physiol Renal Physiol 2020; 318(6): F1315–26. doi: 10.1152/ajprenal.00071.2020
3. Narkhede AM, Karnad DR. Preeclampsia and related problems. Indian J Crit Care Med 2021; 25(Suppl 3): S261. doi: 10.5005/jp-journals-10071-24032
4. Oluwole AA, Ugwu AO, Soibi-Harry AP, Garba SR, Okunade KS, Makwe CC, et al. Maternal outcomes of eclampsia at the Lagos University Teaching Hospital: a six-year retrospective review. West Afr J Med 2022; 39(1): 20–3. doi: 10.56167/jjms.2022.0302.05
5. Olaoye T, Oyerinde OO, Elebuji OJ, Ologun O. Knowledge, perception and management of pre-eclampsia among health care providers in a maternity hospital. Int J Matern Child Health AIDS 2019; 8(2): 80. doi: 10.21106/ijma.275
6. Martini C, Saaed Z, Simeone P, Palma S, Ricci M, Arata A, et al. Preeclampsia: insights into pathophysiological mechanisms and preventive strategies. Am J Prev Cardiol 2025; 3: 101054. doi: 10.1016/j.ajpc.2025.101054
7. Al-Mubarak AA, van der Meer P, Bomer N. Selenium, selenoproteins, and heart failure: current knowledge and future perspective. Curr Heart Fail Rep 2021; 18(3): 122–31. doi: 10.1007/s11897-021-00511-4
8. Cheng Y, Chen H. Aberrance of zinc metalloenzymes-induced human diseases and its potential mechanisms. Nutrients 2021; 13(12): 4456. doi: 10.3390/nu13124456
9. Afrose D, Alfonso-Sánchez S, McClements L Targeting oxidative stress in preeclampsia. Hypertens Pregn 2025; 44(1): 2445556. doi: 10.1080/10641955.2024.2445556
10. Ajayi DD, Awoleke JO, Adewara EO, Ajayi OB, Adeniji AK. Influence of trace and heavy metals on semen quality of infertile men in Ado-Ekiti, South Western Nigeria. FUOYE J Pure Appl Sci 2024; 9(2): 141–57. doi: 10.55518/fjpas.UTJU4097
11. Vo TT, Peng TY, Nguyen TH, Bui TN, Wang CS, Lee WJ, et al. The crosstalk between copper-induced oxidative stress and cuproptosis: a novel potential anticancer paradigm. Cell Comm Signal 2024; 22(1): 353. doi: 10.1186/s12964-024-01726-3
12. Grzeszczak K, Kwiatkowski S, Kosik-Bogacka D. The role of Fe, Zn, and Cu in pregnancy. Biomolecules 2020; 10(8): 1176. doi: 10.3390/biom10081176
13. Emokpae MA, Fatimehin EB. Copper-to-zinc ratio as an inflammatory marker in patients with sickle cell disease. Science 2020; 2(4): 89. doi: 10.3390/sci2040089
14. Fabiola ME, Barrado E, Parodi-Román J, Escobedo-Monge MA, Torres-Hinojal MC, Marugán-Miguelsanz JM. Copper and copper/Zn ratio in a series of children with chronic diseases: a cross-sectional study. Nutrients 2021; 13(10): 3578. doi: 10.3390/nu13103578
15. Ivanova ID, Pal A, Simonelli I, Atanasova B, Ventriglia M, Rongioletti M, et al. Evaluation of zinc, copper, and Cu: Zn ratio in serum, and their implications in the course of COVID-19. J Trace Elem Med Biol 2022; 71: 126944. doi: 10.1016/j.jtemb.2022.126944

16. Gohari H, Khajavian N, Mahmoudian A, Bilan di RR. Copper and zinc deficiency to the risk of preterm labor in pregnant women: a case-control study. BMC Preg childbirth 2023; 23(1): 366. doi: 10.1186/s12884-023-05625-2
17. Hulsbosch LP, Boekhorst MG, Gigase FA, Broeren MA, Krabbe JG, Maret W, et al. The first trimester plasma copper-zinc ratio is independently related to pregnancy-specific psychological distress symptoms throughout pregnancy. Nutrition 2023; 109: 111938. doi: 10.1016/j.nut.2022.111938
18. Enebe JT, Dim CC, Ugwu EO, Enebe NO, Meka IA, Obioha KC, et al. Serum antioxidant micronutrient levels in preeclamptic pregnant women in Enugu, south-East Nigeria: a comparative cross-sectional analytical study. BMC Preg Childbirth 2020; 20(1): 392. doi: 10.1186/s12884-020-03081-w
19. Enebe JT, Dim CC, Omeke AC. Maternal antioxidant micronutrient deficiencies among pre-eclamptic women in Enugu, Nigeria: a cross-sectional analytical study. J Int Med Res 2023; 51(11): 03000605231209159. doi: 10.1177/03000605231209159
20. Tanner MS, Davey MA, Mol BW, Rolnik DL The evolution of the diagnostic criteria of preeclampsia-eclampsia. Am J Obstet Gynecol 2022; 226(2): S835–43. doi: 10.1016/j.ajog.2021.11.1371
21. Yusuf H, Subih HS, Obeidat BS, Sharkas G. Associations of macro and micronutrients and antioxidants intakes with preeclampsia: a case-control study in Jordanian pregnant women. Nutr Metab Cardiovasc Dis 2019; 29(5): 458–66. doi: 10.1016/j.numecd.2019.01.008
22. Rana AM, Shahzad M, Iftikhar B, Ullah Z, Shaheen B, Hussain S. Serum iron, copper and zinc levels in preeclampsia and normotensive Primigravida females: serum iron, copper and zinc levels in preeclampsia. Pak Bio-Med J 2022; 276–81. doi: 10.54393/pbmj.v5i5.440
23. Hamdan HZ, Hamdan SZ, Adam I. Association of selenium levels with preeclampsia: a systematic review and meta-analysis. Biol Trace Elem Res 2023; 201(5): 2105–22. doi: 10.1007/s12011-022-03316-1
24. Rezende VB, Barbosa Jr F, Palei AC, Cavalli RC, Tanus-Santos JE, Sandrim VC. Correlations among antiangiogenic factors and trace elements in hypertensive disorders of pregnancy. J Trace Elem Med Biol 2015; 29: 130–5. doi: 10.1016/j.jtemb.2014.06.011
25. Nwatah AJ, Ugwu GO, Ugwu CE, Meludu SC. Serum immunoglobulins, C-reactive protein, and trace element level in preeclamptic Nigerian subjects. Niger J Clin Prac 2022; 25(9): 1405–12. doi: 10.4103/njcp.njcp_1455_21
26. Moravvej Z, Baradaran- Rahimi V, Azari A, Rahsepar AA, Ghayour-Mobarhan M, Salehi M, et al. Changes in serum zinc and copper concentrations in patients with cardiovascular disease following cardiac surgery. Physiol Rep 2022; 10(19): e15483. doi: 10.14814/phy2.15483
27. Gul AZ, Atakul N, Selek S, Atamer Y, Sarıkaya U, Yıldız T, et al Maternal serum levels of zinc, copper, and thiols in preeclampsia patients: a case-control study. Biol Trace Elem Res 2022; 200(2): 464–72. doi: 10.1007/s12011-021-02660-y
28. Cholik R, Suliburska J. Association between zinc, copper, iron, calcium, magnesium, and preeclampsia development: a narrative review. J Elementol 2025; 30(3): 493. doi: 10.5601/jelem.2025.30.1.3545
29. Sailer J, Nagel J, Akdogan B, Jauch AT, Engler J, Knolle PA, et al. Deadly excess copper. Redox Biol 2024; 275: 103256. doi: 10.1016/j.redox.2024.103256
30. Jomova K, Alomar SY, Valko R, Nepovimova E, Kuca K, Valko M. The role of redox-active iron, copper, manganese, and redox-inactive zinc in toxicity, oxidative stress, and human diseases. EXCLI J 2025; 24: 880. doi: 10.17179/excli2025-8449
31. Fu Y, Hou L, Han K, Zhao C, Hu H, Yn S. The physiological role of copper: dietary sources, metabolic regulation, and safety concerns. Clin Nutr 2025; 48: 161–79. doi: 10.1016/j.clnu.2025.03.023
32. Kunutsor SK, Voutilainen A, Laukkanen JA. Serum copper-to-zinc ratio and risk of incident pneumonia in caucasian men: a prospective cohort study. Biometals 2022; 35(5): 921–33. doi: 10.1007/s10534-022-00414-4
33. Ullah MI, Manni E, Shakil M, Hussain S, Awan AN, Hussain S, et al. Association of serum copper, zinc and copper to zinc ratio in patients with acute myeloid leukemia. Sci Rep 2025; 15(1): 1–9. doi: 10.1038/s41598-025-14812-4
34. Hamasaki H, Kawashima Y, Yanai H. Serum Zn/Cu ratio is associated with renal function, glycemic control, and metabolic parameters in Japanese patients with and without type 2 diabetes: a cross-sectional study. Front Endocrinol 2016; 7: 147. doi: 10.3389/fendo.2016.00147
35. Zhang H, Cao Y, Man Q, Li Y, Lu J, Yang L. Study on reference range of zinc, copper and copper/zinc ratio in childbearing women of China. Nutrients 2021; 13(3): 946. doi: 10.3390/nu13030946
36. Cao H, Xiong SF, Dong LL, Dai ZT. Study on the mechanism of lipid peroxidation induced by carbonate radicals. Molecules 2024; 29(5): 1125. doi: 10.3390/molecules29051125
37. Jenner B. Hypertension in pregnancy and pre-eclampsia. Medicine 2024; 52(10): 620–6. doi: 10.1016/j.mpmed.2024.07.011
38. Lu CW, Lee YC, Kuo CS, Chiang CH, Chang HH, Huang KC. Association of serum levels of zinc, copper, and iron with risk of metabolic syndrome. Nutrients 2021; 13(2): 548. doi: 10.3390/nu13020548

***Mathias A. Emokpae**
Department of Medical Laboratory Science,
School of Basic Medical Sciences
College of Medical Sciences,
University of Benin, Benin City,
Nigeria
Email: mathias.emokpae@uniben.edu
Orcid: 0000-0002-6266-1774