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Exploring Maternal Biomarkers and Risk Factors in Preeclampsia: Insights from a Ghanaian Case-control Study

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Authors' contributions

This work was carried out in collaboration among all authors. Author NA supervised the research; Authors MAA and NA conceived the idea. Author MAA experimented and collected the data. Authors MAA, MB and IAAN performed the statistical analysis, interpreted the results and wrote the first draft manuscript. All authors provided critical feedback and approved the final manuscript.

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ABSTRACT

Aims: The involvement of maternal sociodemographic, obstetric, clinical, anthropometric and biochemical variables in preeclampsia has been demonstrated in previous studies. However, there are intra- and inter-population variabilities in study findings due to differences in genetic and environmental factors. This requires population-specific studies to aid the formulation of local protocols for the early detection and management of preeclampsia.
Study Design: This was a case-control study
Place and Duration of Study: The study was conducted at the Bolgatanga Regional Hospital between January and December 2022. The women were aged between 16 and 41 years and were receiving antenatal care at the hospital.

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Aim of Work: The current study sought to determine variations in maternal sociodemographic, clinical, obstetric and biochemical characteristics in preeclampsia. To achieve this, women with and without preeclampsia were recruited and compared.
Methodology: The study included 100 and 150 pregnant women with and without preeclampsia respectively. Sociodemographic, birth outcomes and obstetric data were collected from participants' medical records. Venous and placental blood samples were collected at delivery and analyzed for biochemical variables and malaria parasites.
Results: The results showed that the maternal and gestational ages did not differ between the pregnant women with and without preeclampsia. However, caesarean delivery ($\chi2=14.275$, $P<0.001$), preterm birth ($\chi2=12.209$, $P=0.001$) and .placental malaria ($\chi2=5.335$, $P=0.032$) were associated with preeclampsia. In addition, maternal body mass index and lipid variables such as total cholesterol, and LDL cholesterol were significantly higher in preeclampsia. The study also observed higher serum levels of aspartate and alanine aminotransferases in preeclampsia. Moreover, serum creatinine, blood urea nitrogen, urea and uric acid levels were also higher in preeclampsia. However, preeclampsia was characterized by lower serum HDL cholesterol as well as a lower estimated glomerular filtration rate.
Conclusion: Maternal anthropometric, obstetric and clinical variables are associated with preeclampsia. In addition, there are variations in serum lipids and renal and hepatic variables between preeclampsia and normotensive pregnancy. These findings are useful for assessing the risk of preeclampsia in the local population.

Keywords: Preeclampsia; body mass index; cholesterol; caesarean section; placental malaria; Ghana.

1. INTRODUCTION

Preeclampsia is a placental syndrome that occurs in pregnancy and has an estimated global prevalence of about 2-8%, accounting for significant maternal-foetal morbidity and mortality [1]. The impact of preeclampsia on maternal-foetal health shows regional variations with low and middle-income countries accounting for much of the global prevalence due to adequate health facilities and personnel for early detection and management. The real impact of preeclampsia in most developing countries may not be known as most cases go undetected or detected [2].

The pathophysiology of preeclampsia remains elusive, although several mechanisms have been suggested. It has been demonstrated that the clinical symptoms in women diagnosed with preeclampsia get resolved or improve after delivery; a clear indication of placental involvement in the pathophysiology of preeclampsia [3]. Human and animal studies have implicated ischemia of the placenta, poor trophoblast invasion and endothelial dysfunction in the pathophysiology of preeclampsia [4]. However, the involvement of environmental factors, the liver, the kidney and lipid metabolism have been suggested as possible contributors to the development of preeclampsia [5].

Previous studies have indicated that maternal sociodemographic variables such as age, economic and education status, ethnicity etc.; obstetric variables such as parity, gravidae, caesarean delivery, preterm etc.; anthropometric variables such as body mass index; clinical conditions such as placental malaria are associated with preeclampsia [3,6]. Sub-Saharan Africa accounts for about 90% of the global burden of malaria. Malarial endemicity poses an additional risk to the development of preeclampsia for women in Ghana and other tropical countries. The massive sequestration of the malarial parasite in the placenta may serve as a precursor to the development of preeclampsia [1].

Preeclampsia is also characterized by alterations in lipid metabolism, and liver and renal dysfunctions. Cohort and meta-analytic studies indicate that women with a history of preeclampsia increased risk of developing cardiovascular diseases (CVDs) as compared to normal pregnancy [7,8]. The increased risk of CVDs in preeclampsia may be attributable to the increased plasma levels of atherogenic LDL cholesterol and triglycerides while the levels of cardio-protective HDL cholesterol may be reduced in preeclampsia. Aside from the reduction in HDL levels, its role in cholesterol efflux from macrophages may also be impaired in preeclampsia [7,9]. Hepatic hypoxia, anatomical and histological changes in the liver and kidneys as a result of endothelial dysfunction and the increased release of proinflammatory cytokines may also lead to dyslipidaemia, and increased

serum liver enzymes, creatinine and uric acid in preeclampsia [8,10,11,12].

There has not been a consensus on the pathophysiology of preeclampsia given to genetic and environmental variabilities. Previous studies in Africa showed that seasonal variations in the prevalence of preeclampsia where more women develop the condition in the rainy season than in the dry season [11]. Nutritional involvement in preeclampsia has been suggested in the literature. Due to the multiplicity and variability of factors associated with preeclampsia, there is a need for population-specific studies to inform local policy in the management of preeclampsia. The current study sought to determine variations in maternal sociodemographic, clinical, obstetric and biochemical characteristics in preeclampsia. To achieve this, women with and without preeclampsia were recruited and compared.

2. MATERIALS AND METHODS

2.1 Study Design and Population

This was a case-control study from January to December 2022 at the Bolgatanga Regional Hospital. The Bolgatanga Regional Hospital is the secondary-level health facility that serves as the main referral hospital in the Upper East Region. In this study, 100 pregnant women who were diagnosed with preeclampsia were included. Another 150 pregnant women without preeclampsia were also recruited as controls. The women were between 16 and 41 years old. Preeclampsia was described as the sudden onset of systolic blood pressure surpassing 140mmHg, diastolic blood pressure over 90mmHg, and persistent proteinuria of 300 mg protein/24 hours in urine samples, excluding urinary tract infection, occurring after the 20th week of pregnancy [13]. Pregnant women with twin pregnancies or with a history of preexisting chronic conditions such as chronic hypertension, hepatitis, chronic kidney disease and dyslipidaemia were excluded from the study. In addition, participants with missing data or incomplete records were also excluded.

2.2 Sample Size Determination

The mode of delivery was used as an exposure variable in calculating the sample size. A previous study in Ghana found that 65.79% of women with preeclampsia delivered by caesarean but only 14.89% of pregnant women without preeclampsia [14]. The following assumptions were made using the Kelsey formula in Epi Info v7 (https://www.cdc.gov/epiinfo/pc.html):
From the analysis, the minimum sample size = 65 (cases=22 and controls=43).

$$\text{Sample size} = \frac{r+1}{r}\frac{(p^*)(1-p^*)(Z_{\beta}+Z_{\alpha/2})^2}{(p_1-p_2)^2}$$

r = Ratio of control to cases which is 2.0
p* = Average proportion exposed = proportion of exposed cases + proportion of control exposed/2
Z_{β} = Standard normal variate for power = 80%
$Z_{a/2}$ = Standard normal variate for the level of significance as mentioned in the previous section.
$P_1 - P_2$ = Effect size or difference in proportion expected

The margin of error (α)=5% (95% confidence interval)

2.3 Data Collection

The sociodemographic, obstetric, clinical and anthropometrical data of the participants were collected from their hospital records and soon after delivery. Venous blood samples were aseptically collected immediately after delivery and dispensed into K_3EDTA anticoagulated and gel-separator vacutainer tubes. Blood samples were also collected from the placental tissue. The placental and foetal variables were also measured and documented. Thick and thin blood films were prepared from the anticoagulated blood from venous and placental sources, dried, fixed and stained with a 1:10 working solution of Giemsa Stain and then examined for the presence of malarial parasites. The blood in the gel-separator tube was allowed to clot before being centrifuged at 3000xg for 10 minutes to obtain serum. The serum samples were analyzed for biochemical lipids, and liver and renal function assessment using an automated biochemistry analyzer.

2.4 Statistical Analysis

The data were collected into a Microsoft Excel Spreadsheet before analysis in SPSS (v27). The normality of the scale variables was assessed using the Kolmogorov-Smirnov test. Subsequently, categorical variables were summarized as frequencies and percentages while the scale variables were summarized as mean ± standard deviation. The differences in data distribution between preeclampsia and normotensive pregnancy regarding scale

variables were determined using an unpaired student t-test (2-tailed). The association between preeclampsia and those maternal clinical and obstetric variables were determined using the Chi-Square of Fisher's Exact tests as appropriate. Statistical significance was established at a P-value <0.050.

3. RESULTS

3.1 The Sociodemographic, Anthropometric and Obstetric Parametric Variables of the Study Population

From Table 1, it was observed that there were no significant differences in maternal and gestational age between normotensive pregnancies and those complicated by preeclampsia. However, women with preeclampsia had significantly higher BMI when compared to those with normotensive pregnancy (28.6±6.6 vs 25.0±4.5; P=0.027).

3.2 The Sociodemographic, Clinical and Obstetric Categorical Variables of the Study Population

From Table 2, there was a significant difference in the mode of delivery between women with normotensive pregnancy and preeclampsia (χ2=14.275, P<0.001). While the majority of the women with NP had a normal vaginal delivery (86.7%), the majority of those with preeclampsia (PE) had either CS or assisted delivery (65%). In addition, only women diagnosed with PE had preterm birth as compared to those with NP (χ2=12.209, P=0.001). Moreover, PE was associated with abnormal birth outcomes (χ2=12.286, P<0.001). Finally, women who were diagnosed with PE were also found to have a higher frequency of placental malaria than their counterparts with NP (χ2=5.335, P=0.032).

3.3 Comparison of Fasting Lipids and Renal Variables between Normotensive Pregnancy and Preeclampsia

The fasting lipids, liver and renal function variables were compared between preeclampsia and normotensive pregnancy (Table 3). It was observed that fasting total cholesterol, LDL, aspartate aminotransferase, alanine aminotransferase, serum urea, creatinine, blood urea nitrogen and uric acid levels were significantly higher in preeclampsia. However, serum fasting HDL level and the estimated glomerular filtration rate were significantly lower in preeclampsia.

Table 1. Descriptive statistics of the study population stratified by preeclampsia status

Variables	NP	PE	*t*	P-value
Maternal age (years)	26.8±6.4	29.4±6.6	-1.389	0.171
Gestational age (weeks)	38.2±1.5	36.4±6.2	1.574	0.122
BMI (Kg/m^2)	25.0±4.5	28.6±6.6	-2.275	0.027
Birth weight (Kg)	3.1±0.6	2.9±0.9	1.081	0.285
Placental length (cm)	20.0±3.4	20.2±5.9	-0.107	0.915
Placental weight (Kg)	0.6±0.2	0.6±0.2	1.032	0.307
BW/PW	5.1±1.2	5.2±1.5	-0.14	0.889
Cord length (cm)	50.1±10.9	52.3±1.0	-0.656	0.515
Cord diameter (cm)	1.2±0.6	1.2±0.5	-0.031	0.975

The results are summarized as mean ± SD. The differences between mean values were determined using an unpaired t-test (2-tailed)

Table 2. The sociodemographic, clinical and obstetric categorical variables of the study population

Variables	NP	PE	χ2, df	P-value
Parity			2.824, 2	0.244
Nulliparous	70(46.7)	25(25.0)		
Primiparous	30(20.0)	20(20.0)		
Multiparous	50(33.3)	55(55.0)		
Gravida			1.751, 1	0.237
Primigravida	65(43.3)	25(25.0)		
Multigravida	85(56.7)	75(75.0)		
Anti-malarial prophylaxis			4.787, 1	0.058
No	0(0.0)	15(15.0)		

Variables	NP	PE	χ2, df	P-value
Yes	150(100)	85(85.0)		
Folic acid			1.531, 1	0.400
No	0(0.0)	5(5.0)		
Yes	150(100)	95(95.0)		
Sickle cell trait			2.219, 1	0.289
No	145(96.7)	85(85.0)		
Yes	5(3.3)	15(15.0)		
Mode of delivery			14.275, 1	<0.001
Normal (vaginal)	130(86.7)	35(35.0)		
CS/Assist	20(13.3)	65(65.0)		
Preterm birth			12.209, 1	0.001
No (≥37)	150(100)	65(65.0)		
Yes (<37)	0(0.0)	35(35.0)		
Birth outcome			14.286, 1	<0.001
Normal	150(100)	60(60.0)		
abnormal	0(0.0)	40(40.0)		
Cord insertion			4.829, 1	0.090
Central	90(60.0)	85(85.0)		
Paracentral	35(23.3)	15(15.0)		
Others	25(16.7)	0(0.0)		
Peripheral malaria			0.059, 1	0.808
No	140(93.3)	95(95.0)		
Yes	10(6.7)	5(5.0)		
Placental malaria			5.335, 1	0.032
No	145(96.7)	75(75.0)		
Yes	5(3.3)	25(25.0)		

The results are summarized as frequency (per cent). Measures of association were determined using Chi-Square or Fishers exact as appropriate

Table 3. Differences in fasting plasma lipids, renal and liver function variables between preeclampsia and normotensive preeclampsia

Variables	NP	PE	*t*	P-value
TCHOL (mmol/L)	4.3±0.4	4.7±1.0	-2.115	0.040
HDL (mmol/L)	1.0±0.1	0.8±0.2	2.363	0.022
LDL (mmol/L)	2.5±0.4	3.3±0.7	-6.013	<0.001
VLDL (mmol/L)	0.7±0.2	0.6±0.2	1.333	0.189
TRIG (mmol/L)	1.9±0.4	1.8±0.6	1.241	0.221
AST (IU/L)	56.3±29.6	126.2±38.6	-7.234	<0.001
ALT (IU/L)	45.8±8.5	81.7±19.5	-8.927	<0.001
UREA (mmol/L)	30.3±8.4	35.6±9.1	-2.485	0.016
CRT (µmmol/L)	63.3±16.1	71.0±6.0	-2.023	0.049
BUN (mmol/L)	5.0±1.4	6.1±1.6	-2.548	0.014
Uric acid (mg/dL)	5.1±2.0	10.7±6.5	-4.45	<0.001
eGFR (min/mL/1.73m^2)	103±20	102±11	2.173	0.035

The results are presented as mean ± SD. The differences between means were determined using an unpaired t-test (2-tailed)

4. DISCUSSION

Preeclampsia may be characterized by altered lipid homeostasis, and liver and renal dysfunction. It may also be associated with maternal sociodemographic, anthropometric and clinical characteristics. The study sought to determine variations in fasting lipids, and liver and renal parameters between preeclampsia and normotensive pregnancy. Results indicated that mothers with preeclampsia had higher body mass index and higher levels of total cholesterol and LDL but lower levels of HDL. In addition, the serum AST and ALT as well as the levels of serum creatinine, urea and BUN were higher in preeclampsia. Moreover, the GFR was significantly lower in preeclampsia.

It was observed that preeclampsia was characterized by lower fasting HDL cholesterol and higher total cholesterol and LDL cholesterol. Previous primary studies, systematic reviews and meta-analyses have sought to implicate dyslipidaemia in the pathophysiology of preeclampsia in Africa and other parts of the world [8,10,9]. One of the mechanisms in lipid homeostasis is cholesterol efflux or reverse cholesterol transport where atherogenic

cholesterol particles such as LDL are transported from systemic circulation back to the liver by HDL cholesterol particles for conversion into bile acids. Previous studies have shown a reduction in HDL cholesterol levels in preeclampsia and a reduction in HDL cholesterol efflux capacity even after 6 months postpartum; an indication of impaired function of HDL cholesterol in preeclampsia [7]. The reduction in HDL cholesterol particle number, coupled with a reduction in its cholesterol efflux capacity will culminate in higher levels of serum total and LDL cholesterol as has been reported in the current and previous studies. Preeclampsia is a common risk factor for cardiovascular diseases even after parturition. The cardiovascular disease risk posed by preeclampsia may be largely due to the observation that women whose pregnancies are complicated by preeclampsia tend to have higher body mass index, increased levels of atherogenic LDL cholesterol and a marked reduction in HDL cholesterol levels [7,1,6].

The current study also observed a higher level of liver aminotransferases in preeclampsia. This finding is consistent with previous studies [11]. Preeclampsia has been said to increase hypoxia emanating from endothelial dysfunction with the subsequent reduction in prostacyclin but an increase of thromboxane levels. The state of hypoxia and vasoconstriction of hepatic blood vessels may lead to necrosis of hepatic cells and the release of aminotransferases such as AST and ALT into systemic circulation [11]. Preeclampsia may also be associated with renal dysfunction as indicated by higher serum levels of creatinine, uric acid, urea, blood urea nitrogen and a reduced estimated glomerular filtration rate. A common indicator of renal dysfunction in preeclampsia is proteinuria which is one of the diagnostic criteria of the disease [9]. Preeclampsia may lead to structural changes in the kidney that may impair its function. Anatomical and histological studies have shown that the kidney is enlarged alongside the glomeruli in preeclampsia given to the swelling of the capillary cells, encroaching on the capillary lumen which leads to obstruction and hypoxia [5]. This phenomenon may lead to a condition termed pouting where there is herniation of the tuft into the proximal tubule which may also lead to glomerular endotheliosis. Aside from the structural changes of the kidney in preeclampsia, the net blood flow and glomerular filtration rates also decrease in preeclampsia largely due to the reduction in the effective plasma flow in the kidney [4]. The impaired function of the kidney may hurt protein and uric acid handling as the permeability of the glomeruli is increased which may account for the observed proteinuria and uricaemia in preeclampsia [5].

Results in the current study also indicated an association between preeclampsia and maternal variables such as delivery by caesarean, preterm births and placental malaria. Previous studies have shown significant associations between preeclampsia and placental malaria [1]. While the mechanism of the involvement of placental malaria in preeclampsia is not clear, it has been suggested that increased sequestration of malaria parasites in the placenta may lead to the loss of integrity and ischemia of the placenta [1]. The increased sequestration of the malarial parasites in the placenta may elicit the increased production of proinflammatory cytokines and endothelial dysfunction. Increased blood pressure in primigravidae pregnant women with placental malaria has been associated with the inflammatory mediator, vascular endothelial growth factor and its inhibitor, soluble vascular endothelial growth factor receptor 1 in an African study; which may be indicative of the interaction between placental malaria and inflammatory markers in the pathophysiology of preeclampsia. Evidence of the involvement of malaria in the prevalence of preeclampsia may be adduced from the observation that the prevalence of preeclampsia in some African countries is higher during the rainy season when malaria transmission peaks [1]. Preeclampsia and caesarean delivery may have a bi-directional relationship. Pregnant women with a history of preeclampsia have an increased tendency to undergo caesarean delivery while women with a previous history of caesarean delivery have a heightened of preeclampsia [3]. Preeclampsia is largely attributable to the presence of the placenta and the removal of the placenta tends to mark the end of the disease. To reduce the risk to maternal-foetal health and well-being in preeclampsia, caesarean delivery may be ordered as an intervention. This may also explain the increased number of preterm births in preeclampsia which may occur as spontaneous delivery or induction by healthcare providers for the well-being of the mother and foetus [3,15].

The current study adds to the limited information in the Upper East Region of Ghana on variations in maternal clinical, obstetric and biochemical variables in preeclampsia. This is mostly important as the pathophysiology of preeclampsia is impacted by environmental and

genetic factors and therefore exhibits population and geographic variabilities [2,13]. The study could not determine changes in maternal variables as the design was case-control and not a longitudinal cohort study. In addition, the findings may not be generalizable to population variabilities.

5. CONCLUSION

The findings indicated that maternal clinical and obstetric variables are significantly associated with preeclampsia. In addition, preeclampsia may be characterized by altered lipid homeostasis, and renal and liver dysfunction. These findings may however be interpreted while considering the population of study as these findings may vary from one population to another.

ETHICAL APPROVAL AND CONSENT

The study followed the recommendations of the 1964 Helsinki Declaration and its later amendments on the use of human subjects in research. Institutional guidelines were followed for all procedures and approval was given by the Navrongo Health Research Centre Institutional Review Board (Ref#: NHRCIRB378). A written informed consent was obtained from all the adults. Where the woman was below the age of consent, written informed consent was obtained from her legal parent or guardian.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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