Study on comparison of serum levels of calcium, magnesium, and uric acid in mild preeclamptics, severe preeclamptics, and normal pregnant women in Ilorin, Nigeria

Omokanye Lukman Omotayo, Abdul N Kareem, A W O Olatinwo, I F Abdul, K A Durowade[1], S A Biliaminu[2]

Departments of Obstetrics and Gynaecology and [2]Chemical Pathology and Immunology, College of Health Sciences University of Ilorin, Kwara State, [1]Department of Community Medicine, Federal Teaching Hospital, Ido-Ekiti, Ekiti State, Nigeria

Address for correspondence:
Dr. Omokanye Lukman Omotayo, Department of Obstetrics and Gynaecology, College of Health Sciences, University of Ilorin, Kwara State, Nigeria.
E-mail: omostuff1111@yahoo.com

Abstract

Background: Preeclampsia is pregnancy-specific syndrome and contributes about 15% of maternal mortality and preterm deliveries. **Objective:** To compare the serum levels of calcium, magnesium, and uric acid in mild preeclamptics, severe preeclamptics, and normal pregnant women. **Materials and Methods:** A cross-sectional study conducted at the Department of Obstetrics and Gynaecology of the University of Ilorin Teaching Hospital (UITH) Ilorin. The data were collected from 64 normal pregnant women, 64 mild preeclamptic women, and 64 severe preeclamptic women who presented at the Department of Obstetrics and Gynaecology, UITH between June 2013 and January 2014. The data were analyzed using analysis of variance. **Results:** The mean serum calcium concentration in severe preeclamptics and mild preeclamptics was significantly reduced (1.75 ± 0.63 mmol/L and 1.90 ± 0.44 mmol/L vs. 2.28 ± 0.24 mmol/L, $P = 0.00$) compared with serum calcium concentration in normal pregnant controls. The serum magnesium concentration among severe preeclamptics was also significantly reduced (0.84 ± 0.44 mmol/L versus 1.05 ± 0.28 mmol/L, $P = 0.00$) compared with serum magnesium among normal pregnant controls. However, there was no statistically significant difference in serum magnesium concentration between mild preeclamptic women and normal pregnant women (1.01 ± 0.26 mmol/L vs. 1.05 ± 0.28 mmol/L). The serum uric acid concentration was significantly elevated among both mild and severe preeclamptic women compared with the serum uric acid concentration among normal pregnant control (0.89 ± 0.63 mmol/L and 1.25 ± 0.68 mmo/L vs. 0.21 ± 0.19 mmol/L). **Conclusions:** It is concluded that while reduced serum calcium levels and elevated serum uric acid levels correlate with etiopathogenesis of preeclampsia, reduced serum magnesium correlates with severity of preeclampsia.

Key words: Preeclampsia, pregnancy, serum calcium, serum magnesium, uric acid

INTRODUCTION

Preeclampsia is a pregnancy-specific syndrome and one of the leading causes of maternal, fetal, and neonatal mortality and morbidity.[1,2] Preeclampsia complicates 6-8% of gestations.[3,4] It is responsible for approximately 50,000 maternal deaths yearly worldwide, 25% of all cases of intrauterine growth restriction, and 15% of preterm births in developed countries.[1-3] Clinically, preeclampsia

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as defined by the International Society for the Study of Hypertension in Pregnancy is the presence of hypertension with proteinuria and/or edema after 20 weeks gestation in a previously normotensive woman that resolves completely by 6th postpartum week.[2,3] However, preeclampsia is a complex multisystemic syndrome and far more than simple gestational/hypertension and proteinuria.[2-4]

The exact etiology of preeclampsia is still unknown, despite active research for many years. However, certain contributory factors include primigravidity, primipaternity, obesity, low socioeconomic status, diabetes mellitus, vascular diseases, and alteration in the maternal serum levels of magnesium, calcium, and uric acid.[1] Other factors include teenage pregnancy, pregnancy in the elderly, multiple gestation, and molar pregnancy.[4-10]

The results from some clinical studies have concluded that changes in the blood levels of certain metals in the maternal serum observed in preeclamptic patients may be implicated in the pathogenesis and severity of preeclampsia.[2,9] Few studies showed an association between maternal serum concentration of these elements and the occurrence of preeclampsia.[6,10,11] Interestingly, variable levels of serum calcium, magnesium, and uric acid are found in preeclamptic mothers.

On the physiological basis, calcium plays an important role in muscle contraction and regulation of water balance in the cells. Modification of plasma calcium concentration leads to alteration of blood pressure. The changes in serum calcium, the increased intracellular calcium, and associated hypocalcemia can be responsible for enhanced vascular contractility and an elevated blood pressure in preeclamptic mothers.[2,11,13,14] In general, magnesium has been known to be an essential cofactor for many enzyme systems. It plays an important role in neurochemical transmission and peripheral vasodilatation. Magnesium sulfate appears to be safe and effective in prevention and treatment of seizure and has been used as the drug of choice in severe preeclampsia and eclampsia.[13]

As first reported many years ago, increased serum uric acid is another common clinical finding in women with clinically evident preeclampsia.[11] Since that time, the clinical utility of increased serum uric acid in preeclampsia has been actively debated.[11,12] Uric acid is a marker of oxidative stress, tissue injury, and renal dysfunction; it is possible that uric acid merely identifies a more severe form of preeclampsia.[12] However, increased serum uric acid is also an independent risk factor for cardiovascular diseases and is proposed to mediate altered vascular function and inflammation.[8,11,12]

These elements and uric acid could be useful prognostic indices in preeclampsia. However, the role and status of serum calcium, magnesium, and uric acid in preeclampsia is still being investigated. Therefore, this study was conducted to compare the serum levels of calcium, magnesium, and uric acid in mild preeclamptics, severe preeclamptics, and normal pregnant women seen at the UITH, Ilorin, Nigeria.

MATERIALS AND METHODS

The study was a cross-sectional study conducted between 1st June 2013 and 31st January 2014 at the Department of Obstetrics and Gynaecology of UITH, Ilorin Kwara State, Nigeria, which is the major referral center for Kwara, Niger and parts of Kogi, Oyo, Osun, and Ekiti states in Nigeria. Pregnant women who presented at antenatal clinic and emergency section of the Department of Obstetrics and Gynaecology of UITH Ilorin, who satisfy the inclusion criteria for the study were recruited.

Subjects' selection was done purposively in all pregnant women diagnosed with preeclampsia, presenting within the period of the study. The controls were selected by probability simple random selection of the first two normal pregnant women matched for gestational age with the subjects who presented at each of the four antenatal clinic sessions every week in the hospital.

Participants were pregnant women who were at 20 weeks gestation or more diagnosed with mild preeclampsia or severe preeclampsia. Mild preeclampsia is defined as a blood pressure of 140/90 mmHg or more measured on two occasions at least 6 h apart, accompanied by proteinuria of at least 300 mg/24 h, or 1 + on dipstick testing. Severe preeclampsia is defined as having one or more of the following criteria in a patient diagnosed with preeclampsia: - Blood pressure 160/110 mmHg or more measured on two occasions at least 6 h apart, proteinuria of more than 5 g/24 h, or at least 3 + on dipstick testing, Oliguria of <500 mL/24 h, cerebral or visual disturbances, pulmonary edema, epigastric or right upper quadrant pain, intrauterine growth restriction, impaired liver function, or thrombocytopenia.

Blood pressure measurements were taken using mercury sphygmomanometer in a quiet room with the subject seated, and the arm supported at heart level. Arm circumference was measured at the approximate midpoint of the upper arm to determine the appropriate cuff size to be used. Two cuff sizes were available: Normal adult (22-32 cm) and large adult (32-42 cm). Auscultatory readings were taken using Littmann® Stethoscope and Korotkoff five was used to identify the diastolic pressure. Screening for proteinuria in a random midstream urine by visually read dipstick was done in all subjects given its comparable sensitivity and specificity to other methods, its convenience and low cost. Also, mode of delivery and perinatal outcomes that is, fetal birth weight at delivery, apgar scores at 1st and 5th min, and need for Neonatal Intensive Care Unit (NICU) admission was assessed and were

compared between mild and severe preeclamptic patients. Excluded from the study were pregnant women with a previous history of chronic hypertension on antihypertensive, transient hypertension, multiple gestation, history of renal disease, preexisting cardiovascular disease, diabetes mellitus, and other preexisting medical conditions, history of smoking, and gestational age less 20 weeks.

On diagnosis of preeclampsia and recruitment of the patient into the study, a venous blood sample was collected with the patient in supine position, prior to commencement of intravenous therapy or any intervention. The sample of the controls was also collected once they were recruited into the study. About 10 mL of venous blood was withdrawn from every patient for the estimation of serum calcium, magnesium, and uric acid. The sample was taken using a plastic disposable syringe and needle from a suitable vein in patient forearm or antecubital fossa. A soft tubing tourniquet was applied in the upper arm or not at all (in case of serum calcium estimation: Blood meant for serum calcium estimation was collected devoid of the use of tourniquet so as not to give false result). Blood sample was collected at 7 am in the morning after overnight fasting using a plastic disposable syringe and needle, from a suitable vein in the patient forearm or antecubital fossa. A: The puncture site was cleaned with ethanol and allowed to air dry before the blood was withdrawn. With the thumb of one hand holding down the skin below the puncture site, venepuncture was made with the bevel of the needle directed upward in the line of the vein. The plunger of the syringe was then steadily withdrawn at the speed it took the vein to fill the syringe. The needle was removed from the puncture site, which was then pressed with a cotton wool. The needle was also removed from the syringe, and the specimen placed in a plain specimen bottle and immediately sent to the laboratory for analysis.

The estimation was performed in the clinical chemistry laboratory of the hospital by a trained chemical pathologist. At the time of the blood collection, urine protein, edema, and deep tendon reflexes were also assessed. Urine protein was measured by dipstick and graded on a scale of 0-3 + (0 implied none protein; 1 + implied 30 mg/dl; 2 + implied 100 mg/dl; and 3 + implied 500 mg/dl). Deep tendon reflexes were assessed by striking the patella tendon with tendon hammer and grading the response as; A: Absent response (no movement), B: Brisk response (marked leg movement), D: Diminished response (mild leg withdrawal) and E: Exaggerated response (abrupt leg jerk and extension). The clinical characteristics, which include gestational age, body mass index, blood pressure, placental weight, birth weight, and 1st and 5th min apgar scores, were determined. The blood sample obtained on admission was sent for determination of packed cell volume and estimation of serum calcium, magnesium, and uric acid.

Laboratory Procedure

Blood samples were allowed to clot at room temperature then centrifuged at 3,000 rpm for 7 min. Serum aliquots were harvested with a clean Pasteur pipettes and immediately stored frozen at −2°C until analysis. Serum calcium was measured by the complexometric method. This is based on the principle that calcium (Ca^{2+}) reacts with cresolphthalein complex one in an alkaline medium to give a purple color, which is estimated colorimetrically at a wavelength of 580 nm. Eight-hydroxyquinoline binds the Mg^{2+} effectively, hence, preventing interference from this ion. Diethylamine maintains the alkaline pH between 10 and 12. Reagent sample mixture was incubated for 5 min at room temperature. The absorbance of standard and that of the sample was measured against the reagent blank at a specific wavelength of 580 nm using a spectrophotometer. The calcium concentration was calculated by the formula:

$$\text{Calcium concentration (mmol / L)} = \frac{OD\ test \times \text{concentration of the standard}}{\text{OD standard}}$$

Where OD = Optical density.

Serum uric acid was measured by modified Caraway method, which is based on the principle that phosphotungstic acid is reduced by uric acid in the presence of sodium carbonate to give a blue complex, which could be measured colorimetrically. The reagent sample mixture was incubated for 5 min at room temperature. The absorbance of standard and that of the test sample was measured against the reagent blank at a specific wavelength of 520 nm using spectrophotometer. The uric acid concentration was then measured using the formula:

$$\text{Uric acid (mmol / L)} = \frac{\text{Test} - \text{blank} \times 0.6}{\text{Standard} - \text{blank}}$$

Serum magnesium was measured by xylidyl blue test. Magnesium reacts with xylidyl blue to form a colored compound in alkaline solution. The intensity of the color formed is proportional to the magnesium concentration in the sample. Reagent sample mixture was incubated for 5 min at 37°C. The absorbance of the standard and the sample was measured against reagent blank at a specific wavelength of 560 nm using a spectrophotometer. Magnesium concentration was calculated as follows:

$$\text{Magnesium concentration (mg / dl)} = \frac{\text{Absorption of sample} \times \text{standard concentration}}{\text{Absorption of standard}}$$

Data were analyzed using the Statistical Package for Social Science software (SPSS 17.00) and expressed in terms of mean (m) and standard deviation. Continuous variables of the serum calcium, magnesium, and uric acid concentrations and others of the three groups were compared by the F-test from analysis of variance and *t*-test where applicable. Demographic and AQ3

obstetric variables for both cases and control were compared using χ^2-test. In all variables $P = 0.05$.

RESULTS

The study enrolled 192 subjects (64 mild preeclamptics and 64 severe preeclamptics) and 64 controls. The mean age of mild and severe preeclamptics were 25.75 ± 5.56 and 26.36 ± 5.34 years, respectively, while the mean age of the controls was 24.89 ± 4.68 years, $P = 0.423$. The mean parity for the controls was 2.06 ± 0.85 while the mean parity for the mild preeclamptics was 1.88 ± 1.28, and the mean parity for the severe preeclamptics was 1.58 ± 1.21. Other sociodemographic variables are in Table1.

The mean gestational age of the control was 38.72 ± 2.1.90 weeks, while the mean gestational age of mild and severe preeclamptics were 37.95 ± 2.82 and 37.00 ± 3.52 weeks ($P = 0.18$), respectively. The mean systolic blood pressure for controls was 109.06 ± 9.38 mmHg, and 144.83 ± 6.16 and 172.34 ± 21.06 mmHg ($P = 0.003$) for mild and severe preeclamptics, respectively. The mean diastolic blood pressure for controls was 69.53 ± 7.8 mmHg while for mild and severe preeclamptics were 94.92 ± 6.64 and 109.22 ± 15.1 mmHg ($P = 0.005$), respectively. The mean difference in packed cell volume and cesarean section rate was statistically significant among the three groups [Table 2].

The mean birth weight for the controls was 3.21 ± 0.39 kg, while that of mild and severe preeclamptics were 3.15 ± 0.69 and 2.67 ± 0.87 kg ($P = 0.144$), respectively. The NICU admissions were highest among infants of severe preeclamptics with 23 (35%) admissions, while NICU admissions were lowest among the controls with 2 (3.1%) admissions [Table 3].

The mean serum calcium concentration in the normal controls was 2.28 ± 0.24 mmol/L while among mild and severe preeclamptics were 1.90 ± 0.44 and 1.75 ± 0.63 mmol/L ($P = 0.0163$), respectively. The mean serum uric acid concentration among controls was 0.21 ± 0.19 mmol/L, and for mild and severe preeclamptic women were 0.89 ± 0.63 and 1.25 ± 0.68 mmol/L ($P = 0.037$), respectively [Table 4].

The mean serum calcium concentration was reduced among both mild and severe preeclamptics compared with that in normal controls (1.90 ± 0.44 mmol/L vs. 2.28 ± 0.24 mmol/L $P = 0.003$ and 1.75 ± 0.63 mmol/L vs. 2.28 ± 0.24 $P = 0.002$). There was no statistically significant difference in mean serum magnesium concentration of the controls when compared the serum magnesium concentration of mild preeclamptics

Table 1: Sociodemographic characteristics of the study population

Variable	Controls (A) (%)	Severe preeclamptics (B) (%)	Mild preeclamptics (C) (%)	P
Age (mean±SD)	24.89±4.68	26.36±5.34	25.75±5.56	0.423
Parity (mean±SD)	2.06±0.85	1.58±1.21	1.88±1.28	0.006
Para 0	18 (28.1)	47 (73.4)	38 (59.4)	0.0015
Para 1	27 (42.2)	7 (10.9)	9 (14.1)	
Para 2	16 (25.0)	5 (7.8)	9 (14.1)	
Para ≥3	3 (4.7)	5 (7.8)	8 (12.5)	
Booking status				
Booked	56 (87.5)	18 (28.1)	38 (59.4)	0.009
Unbooked	8 (12.5)	46 (71.9)	26 (40.6)	
Ethnicity				
Yoruba	53 (82.8)	56 (87.5)	38 (59.4)	0.008
Others	11 (17.2)	8 (12.5)	26 (40.6)	

SD = Standard deviation

Table 2: Maternal clinical characteristics of the study population

Variable	Controls (A)	Severe preeclamptics (B)	Mild preeclamptics (C)	P
Gestational age (week) (mean±SD)	38.72±1.90	37.00±3.35	37.95±2.82	0.183
BMI (kg/m²) (mean±SD)	27.30±2.58	30.67±5.15	30.21±4.12	0.580
BP (mmHg) (mean±SD)				
SBP	109.06±9.38	172.34±21.06	144.83±6.16	0.003
DBP	69.53±7.85	109.22±15.10	94.92±6.64	0.005
PCV (%) (mean±SD)	30.48±2.66	35.13±4.79	30.32±2.69	0.047
Mode of delivery (%)				
Vaginal	60 (93.8)	40 (62.5)	52 (81.2)	0.258
Instrumental	Nil	5 (6.5)	2 (3.8)	0.007
CS	4 (6.2)	19 (31.0)	10 (15.0)	0.002

SD = Standard deviation, BMI = Body mass index, SBP = Systolic blood pressure, DBP = Diastolic blood pressure, PCV = Packed cell volume, CS = Cesarean section, BP = Blood pressure

(1.05 ± 0.28 mmo/L vs. 1.01 ± 0.26 mmol/L $P = 0.111$). However, the mean serum magnesium concentration was significantly reduced in severe preeclamptics when compared with that of normal pregnant controls (0.84 ± 0.46 mmol/L vs. 1.05 ± 0.28 mmol/L $P = 0.00$). The mean serum uric acid concentration of the mild and severe preeclamptics were significantly elevated compared with the mean serum uric acid concentration of the controls (0.89 ± 0.63 mmol/L vs. 0.21 ± 0.19 mmol/L $P = 0.00$ and 1.25 ± 0.68 mmol/L versus 0.21 ± 0.19 mmol/L $P = 0.00$) [Table 5].

DISCUSSION

In this study, no difference was observed in the mean ages of the respondents probably because the study focused on women of reproductive age group (15-49 years). However, significant differences were found in the booking status with 87.5% of the women booked. This could be due to the fact that the study is hospital-based, conducted in a tertiary health facility offering specialized obstetrics care.

The mean serum calcium concentrations in severe and mild preeclamptic women were 1.90 ± 0.44 mmol/L and 1.75 ± 0.63 mmol/L, respectively. Both levels were significantly less than the mean serum calcium concentration in normal pregnant control. This result is consistent with the report of other studies.[2,19,23] This may be related to the disease progression. Similar findings were also reported from Nigeria by Idogun *et al.*[27] at Benin and Akinloye *et al.*[29] at Osogbo.

The mean serum magnesium concentration among severe preeclamptic patients was significantly reduced compared with the mean magnesium concentration of normal pregnant controls. While the exact etiology of preeclampsia is elusive to scientific knowledge, abnormally low maternal serum concentration of magnesium and calcium are thought to be implicated.[4,10,16] Studies have also elucidated the nature and effect of magnesium and calcium ions at the neuromuscular and prejunctional neuronal sites in association with muscular activity.[30] Magnesium competes with calcium for prejunctional sites. High magnesium concentration inhibits the release of acetylcholine thereby promoting muscular relaxation while high calcium concentration enhances the release of acetylcholine from the prejunctional nerves, thereby promoting muscular contraction.

Evidence has also shown that cellular injury and death are associated with the influx of calcium ions into the cells and subsequently loss of calcium homeostasis.[29,30] Vasospasm, ischemia, and hypoxia are associated with reversible cell injury. Since magnesium antagonizes the effect of calcium, there is also influx of magnesium into the cells. This may explain the reduced serum levels of both magnesium and calcium among preeclamptic mothers. It also forms the basis for use of magnesium sulfate in prevention and control of convulsion in preeclampsia/eclampsia.[10] Magnesium ions also block the entry of calcium ions into the neuronal cells through the N-methyl-D-Aspartate receptors on the neuronal cells.[10]

Table 3: Perinatal clinical characteristics of the study population

Variable	Controls (A)	Severe preeclamptics (B)	Mild preeclamptics (C)	P
Birthweight (kg) (mean±SD)	3.21±0.39	2.67±0.87	3.15±0.69	0.144
Apgar score at 5 min	9.23±0.81	7.03±1.93	8.72±1.03	0.072
NICU admission (%)				
Yes	2 (3.1)	23 (35)	9 (14.1)	0.036
No	62 (96.9)	41 (65)	53 (82.8)	0.112

SD = Standard deviation, NICU = Neonatal Intensive Care Unit

Table 4: The mean serum concentration of calcium, magnesium, and uric acid in preeclamptics and controls

Variable (mmol/L)	Controls (A)	Severe preeclamptics (B)	Mild preeclamptics (C)	P
Serum calcium	2.28±0.24	1.75±0.63	1.90±0.44	0.016
Serum magnesium	1.05±0.28	0.84±0.46	1.01±0.26	0.111
Serum uric acid	0.21±0.19	1.25±0.68	0.89±0.63	0.037

Table 5: Comparison of serum calcium, magnesium, and uric acid between preeclamptics and normal controls

Variable (mmol/L)	Controls (A)	Severe preeclamptics (B)	Mild preeclamptics (C)	P
Serum calcium	2.28±0.24	1.75±0.63	1.90±0.44	A versus B=0.00
				A versus C=0.00
Magnesium	1.05±0.28	0.84±0.46	1.01±0.26	A versus B=0.00
				A versus C=0.11
Serum uric acid	0.21±0.19	1.25±0.68	0.89±0.63	A versus B=0.00
				A versus C=0.00

Low maternal serum calcium and magnesium concentrations among preeclamptics were found by Kanchapan and Phupong[19] in Thailand and Vahidrodsari[26] in Iran. Akinloye *et al.*[28] and Idogun *et al.*[27] both in Nigeria also found low serum calcium and magnesium concentrations among preeclamptics compared with normal control. This is not unexpected as population for both studies were from the same geographical location.

However, Chanvitya *et al.*[2] found a statistically insignificant difference in mean maternal serum magnesium concentration of both mild and severe preeclamptics when compared with normal pregnant control. Villanueva found elevated serum magnesium and no difference in serum calcium in 15 severe preeclamptics compared to 20 normal controls. This may not be unrelated to the small sample size used in the study.

More so, in this study, there was no statistically significant difference in maternal serum concentration of magnesium between mild preeclamptics and normal pregnant controls (1.05 ± 0.28 mmol/L vs. 1.19 ± 0.26 mmol/L $P = 0.11$). This could be explained by the fact that preeclampsia is a progressive disease, and influx of the calcium into the cell is not severe enough to trigger the subsequent magnesium influx in the cells. Therefore, magnesium levels have not changed significantly.

Furthermore, in this study, the maternal serum uric acid among both mild and severe preeclamptics was found to be significantly elevated compared to normal controls. This is consistent with findings reported by Chanvitya *et al.*[2] and Gulati[30]. Chanvitya *et al.*[2] reported elevated serum uric acid concentration among severe preeclamptic patients though, there was statistically insignificant levels of serum uric acid among mild preeclamptics compared to normal controls. Elevated maternal serum uric acid is a common finding among preeclamptic patients and is said to be due to decreased renal uric acid clearance, increased purine breakdown, and inflammation in the ischemic placenta.[11,12,31] Soluble uric acid impairs nitric oxide (vasodilator) generation allowing the unopposed effect of vasoconstors.[31]

The findings of this study clearly attest to the input/interplay of serum calcium, magnesium, and uric acid in the etiopathogenesis of preeclampsia. With this, there seems to be evidence that serial measurement/assay of these aforementioned blood parameters may be strongly predictive and of utmost relevance in the prevention and management of preeclampsia. Furthermore, randomized control trials might be needed to evaluate the effect of multiple agent supplementations with calcium and magnesium in the prevention and management of preeclampsia/eclampsia.

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Conflicts of Interest
There are no conflicts of interest.

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