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Original article

Maternal Serum Calcium and Magnesium levels in women presenting with preeclampsia: Case -Control study in Greater Accra and Ashanti Regions of Ghana

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ABSTRACT

Background: Preeclampsia is a medical condition which arises in pregnancy and associated with high blood pressure and significant amount of protein in urine of pregnant women. It is a multisystem disease of pregnancy of unknown cause. The study was aimed to determine the association between serum Calcium and Magnesium levels with preeclampsia. **Methods:** A Case-Control study of two hundred primigravidae, singleton and second trimester pregnant women with preeclampsia (case) age-matched with two hundred normotensive pregnant women in the same trimester (controls), were recruited from the Obstetrics and Gynaecology Departments of the Komfo Anokye Teaching Hospital, Kumasi and Ridge Regional Hospital, Accra, all in Ghana. Socio-demographics, blood pressure, urine protein, calcium and magnesium levels of both groups were collected. **Results:** Serum Calcium and Magnesium levels were significantly lower in the Case group than the controls (1.53 ± 0.90, 2.36± 0.17)and (0.56 ± 0.08, 0.88 ± 0.08) ($p < 0.001$).The mean systolic, diastolic blood pressure and BMI were significantly higher in the case group than the control ($p < 0.001$).The mean hemoglobin (Hb) was significantly lower among the cases (10.01 ± 0.73) than the controls (13.76 ± 0.80) ($p < 0.001$). Prevalence of hypocalcaemia, hypomagnesaemia and anaemia were(51.75%), (50.0%) and (42.5%) respectively. **Conclusion:** The current study reports a significant reduction of serum Calcium and Magnesium levels in preeclamptic women at the second trimester. Altered levels of serum calcium and magnesium may be important in the development of preeclampsia.

KEYWORDS: preeclampsia, calcium ions, magnesium ions, proteinuria.

INTRODUCTION

Preeclampsia is a medical condition which arises in pregnancy and it is highly associated with high blood pressure and significant amount of protein in the urine of pregnant women. Preeclampsia is a multisystem disease of pregnancy of unknown cause. It is a maternal syndrome, which is characterized by increased blood pressure, edema, proteinuria and abnormal clotting, liver and renal functions all of which may be due to the release of placental toxic factors into the mother's circulation.

The only effective therapy to this complication is to facilitate the delivery (induction of labour, cesarean section).The epidemiology of this multisystem disorder, varying between little systemic involvements to multi organ failure, is complicated by differences in definition, inaccuracy of diagnosis and the outcomes. Unfortunately, there has been little progress in predicting the disorder compared to advances made in eliminating other serious medical conditions such as malaria, TB and HIV in Ghana.

The magnitude of the problem and the impact on the mother and the neonate as well as the nation needs to be highlighted and updated especially in a developing country like Ghana

where the incidences are high(Obed and Aniteye, 2007)[1]. In addition to the immediate burden, there are long-term consequences of the disease such as chronic kidney disease (CKD) and other heart related illnesses on the mother as well as the baby. Unless effective prevention strategies are developed and implemented, the huge cost of critical care for the mother, the newborn and the long-term problems in the premature or intrauterine growth retarded baby will continue to impact negatively on health systems and the economy at large (Lopez et al, 2004)[2].

Pregnancy induced hypertension (PIH) or gestational hypertension is the development of blood pressure of greater than 140/90Mm of Hg after 20 weeks of gestation and eclampsia is defined as the occurrence of one or more convulsions usually superimposed on pre-eclampsia (Papageorghiou et al, 2001)[3]. Pre-eclampsia is a frequent disorder with a reported incidence of 2-8% among pregnancies worldwide and 2-10% in Ghana with over 50,000 maternal mortalities especially in developing countries(Obed and Aniteye, 2007)[[1].

Preeclampsia is diagnosed when a pregnant woman develops new onset of significant proteinuria of more than 300mg /hr after 20 weeks of gestation. This usually occurs over several days to weeks but sometimes occur more quickly(Papageorghiou et al, 2001)[[3]. The occurrence of fits in pregnant women has been documented as early as 4th Century B.C. by Hippocrates (O'Dowd and Philip 1994) [4], hence the condition termed ECLAMPSIA, a Greek word which literally means ''shine forth'', depicting an abrupt development. It was recognized also that hypertension and albuminuria herald the onset of fits in these pregnant women as such the term PREECLAMPSIA was devised (Lewis and Chamberlain, 1990)[5]. Preeclampsia is a clinical condition of pregnancy characterized by hypertension and proteinuria.

Different studies clearly show that the uteroplacental blood flow, its vascular resistance, endothelial integrity, endothelial damage, the platelets and coagulation system, and neutrophils all interact in preeclampsia (Turpin et al, 2008)[6]. It is most probable that unless more is known about the dynamics of uteroplacental blood flow, flow behaviour and its influence on the vascular endothelium, confusion and inconsistency will continue. It is therefore, understandable why this condition is sometimes referred to as ''the disease of theories''.

Several risk factors have been suggested as contributing to the development of PE. These include: nulliparity, family and previous history of preeclampsia, diabetes mellitus, BMI higher than normal, multiple pregnancies, renal disease, hydatidiform mole, hydrops foetalis, donor insemination, chronic hypertension and chronic autoimmune disease(Dekker and Sibai, 2001, Owiredu et al, 2012)[7, 8]. The management of eclampsia is mostly done in Ghana by the use of Magnesium and Calcium therapies, as a result the protocol for the administration is pasted on all notice boards of the two facilities in this study, and hence this study was to measure the serum levels of both Magnesium and Calcium ions in both preeclamptics and normotensives.

MATERIALS AND METHODS

Study Design and Study site

This Case-Control study was conducted at the Komfo Anokye Teaching Hospital and the Ridge Regional Hospital in Kumasi and Accra respectively. Two hundred primigravidae with singleton pregnancy presenting with preeclampsia (cases) and two hundred normotensive pregnant women (controls) visiting the Obstetrics and Gynaecology Departments of the study sites were consecutively selected and recruited in the second trimester for this study.

Ethical Considerations: The study was approved by the Committee on Human Research Publication and Ethics of the School of Medical Science, Kwame Nkrumah University of Science and Technology and the Komfo Anokye Teaching Hospital, Kumasi (CHRPE).

Selection Criteria: The participation of all subjects was voluntary and informed consent was obtained from each respondent. The diagnosis of Preeclampsia during pregnancy was assessed by qualified Obstetrician/Gynaecologist at the respective facilities. The presence of high blood pressure on two occasions six hours apart and proteinuria level of 2+ or more positive result on a dipstick, were also considered as presenting with preeclampsia (PE). Each subject had a questionnaire-based interview, which was conducted privately and in person and lasted approximately 30 minutes. Information was obtained on maternal lifestyle factors such as smoking and alcohol consumption during pregnancy, demographic data, educational level, recent medical history, a complete present and past obstetric history, occupational factors, exercise and information on the parents.

Exclusion Criteria: Pregnant women who were more than 40years or less than 20 years old, chronic hypertension, diabetes mellitus, chronic renal disease, connective tissue diseases, hyperthyroidism, hypothyroidism, cardiac disease, HIV/AIDS, anaemia (Hb<10.0 g/dL), malaria during the index pregnancy, alcohol abuse, cigarette smoking and any visible disease were excluded from the study.

Inclusion Criteria: Primigravidae who were between the ages of 20 and 40years and in their second trimester and were either Preeclamptics or normotensives were recruited in to the study.

Anthropometric measurements:

Anthropometric measurements included height, measured without shoes and weight measured in kilograms with light clothing. Subjects were weighed on a scale (Zhongshan Electronic Co. Ltd, China) and their height measured with a wall-mounted ruler. Body mass index (BMI) was calculated by dividing weight (kg) by height squared (m^2).Blood pressure was taken by trained personnel using a mercury sphygmomanometer and stethoscope. Measurements were taken from the left upper arm after subjects had rested for 15 min in accordance with the recommendation of the American Heart Association. Triplicate measurements were taken with a 5 min rest interval between measurements and the mean value was recorded to the nearest 2.0 mm Hg.

Biochemical analysis: Venous blood samples were drawn after the participants have rested for about 15munites. About 5 ml of venous blood was drawn and dispensed into EDTA and gel separator vacutainer® tubes respectively. The samples in the gel separator tubes were then taken to the laboratory and centrifuged and sera separated, aliqouited and keptfrozen at -21^{O}C until analysis was done; the whole blood in the EDTA tubes were used for Hemoglobin determination whiles the sera were used for the assay of the serum Calcium and Magnesium.

The serum Mg^{2+} and Ca^{2+} were assayed using a commercial test kit obtained from GenWay Biotech, Inc., San Diego, USA by the use of Selectra Junior manufactured by Vital Scientific, Ekkerstijt, Netherlands. The Hemoglobin was determined by the use of Mindray BC-3600 heamatology analyser manufactured by Mindray Chiana Ltd.

Urine Protein Determination: Urine samples (10ml) were also taken in to sterile containers provided for the measurement of urine protein in all participants. Urine protein was determined using the dip-stick qualitative method (Rapid Lab Ltd, unit 2 hall farm, little Bentley.uk).

Statistical Analysis: Data was entered unto a Microsoft Office Excel 2013 and SPSS Version 20 program for the data analysis. The values were expressed as mean plus or minus standard deviations (mean ± SD). Student *t*-test was used for comparison of means of variables between case and control subjects. The level of statistical significance was set at $p<0.05$ for all tests and at 95% confidence interval (CI).

RESULTS

Subjects with no formal education were significantly higher in the cases as compared to the controls51.5% vrs 26.5%(Table 1). Tertiary education was higher in the controls than the cases (5.5 % vrs 1.0%) (Table 1).Secondary/ Vocational education was also higher in the controls than the cases 24.0% vrs 10% (Table 1). Employment washigher amongst the controls than the cases 75% vrs 47.5 % (Table 1). Late booking visit was also higher in the cases as compared to the controls 7.5% vrs 0.0% (Table1). There were higher prevalence of normal weight among the controls when compared with the cases (95% vrs 5.5%) (Table 1). Higher prevalence of overweight was seen amongst the cases when compared with the controls (80.5% vrs 5%) (Table1). However, it was only the cases that showed a prevalence of 14.0% obesity (Table1).

Table 1. Clinical and Socio-demographic parameters of study population

Variable	Controls, N= 200 n (%)	Cases, N= 200 n (%)	p - value
Age(years)			
20 – 25	20(10.0)	25(12.5)	0.055
26 – 35	133(66.5)	150(75.0)	
>35	47(23.5)	29(14.5)	
Educational status			
No formal education	53(26.5)	103(51.5	<0.001
Basic	88(44.0)	75(37.0)	
Sec/Vocational	48(24.0)	20(10.0)	
Tertiary	11(5.5)	2(1.0)	
Employment Status			<0.001
Employed	150(75.0)	95(47.5)	
Unemployed	50(25.0)	105(52.5)	
BODY MASS INDEX			
Normal	155(95.0)	11(5.5)	<0.001
Overweight	10(5.0)	161(80.5)	
Obese	0(0.0)	28(14.0)	
Booking Visits(weeks)			<0.001
8 - 16.	190(95.0)	42(21.0)	
17 - 24.	10(5.0)	143(71.5)	
>24	0(0.0)	15(7.5)	
Proteinuria			<0.001
<2+	199(99.5)	0(0.0)	
2+	1(0.5)	52(26.0)	
>2+	0(0.0)	48(74.0)	

*CONTROL= Women without preeclampsia. CASES= Women with preeclampsia, N = Population size, n = proportion prevalence.

The mean age of the controls and cases did not show any significant difference, p = 0.074 (Table 2). The mean systolic and diastolic blood pressure for the cases was significantly higher than that of the controls (160.8 ± 10.4, 107.4 ± 8.4) and (121.1 ± 7.5, 88.0 ± 7.8) respectively (p < 0.001) (Table2). The mean serum Mg^{2+} and Ca^{2+} were both significantly higher in the controls than the cases (0.88 ± 0.08, 0.56 ± 0.08) and (2.36 ± 0.17, 1.53 ± 0.90) respectively (P < 0.001) (Table 2). The mean Hb was also significantly lower in the cases when compared with the controls (10.01 ± 0.73) and (13.76 ±0.80)p<0.001(Table 2). The mean Urine Protein was also significantly higher in the cases as compared to the controls (2.95 ± 0.69) and (0.26 ± 0.45)(p<0.001) (Table 2). The cases showed higher prevalence of hypomagnesaemia, hypocalcaemia and anaemia when compared with the controls (100% vrs 0%, 99.0% vrs 4.5% and 82.5% vrs 2.5%) (Table3).

Table 2 Comparison of clinical and biochemical variables of the study population

Parameter	Control (N=200)	Case (N=200)	95% CI of mean difference	p-value
Age (years)	30.83 ± 4.03	31.08 ± 4.5	0.31- 1.99	0.074
BMI (Kg/m^2)	22.63 ± 2.08	26.62 ± 2.14	3.57- 4.40	<0.001
SBP (mmHg)	121.07 ± 7.51	160.78 ± 10.38	37.93 - 41.49	<0.001
DBP (mmHg)	88.03 ± 7.81	107.44 ± 8.36	17.82 - 21.00	<0.001
Ca^{2+}(Mmol/ml)	2.36 ± 0.17	1.53 ± 0.90	0.71 – 0.96	< 0.001
Mg^{2+}(Mmol/ml)	0.88 ± 0.08	0.56 ± 0.08	0.30- 0.33	<0.001
Proteinuria	0.26 ± 0.448	2.95 ± 0.685	2.576 - 2.803	<0.001
Hb (g/dl)	13.76 ± 0.80	10.01 ± 0.73	3.56 – 3.86	< 0.001

*CASE = women with preeclampsia. Control =Women without preeclampsia. UP= urine protein, BMI = Body Mass Index, SBP = Systolic blood pressure, DBP=Diastolic blood pressure, Mg2+ = Magnesium ions, Ca2+ = Calcium ions, Hb=haemoglobin.

Table 3. Prevalence of hypocalcaemia, Anaemia and hypomagnesaemia amongst the study population

Variables	**Control N = 200**	**Case N=200**	**Prevalence**
Mg^{2+} (mmol/l) n (%)			
< 0.7	0 (0.0)	200 (100.0)	200 (50.0)
≥ 0.7	200 (100)	0 (0.0)	200 (50.0)
Ca^{2+}(mmol/l) n (%)			
< 2.1	9 (1.0)	198 (99)	207 (51.75)
≥ 2.8	191 (99.0)	2 (1.0)	193 (48.25)
Hb (g/dl) n (%)			
< 11.0	5 (2.5)	165 (82.5)	170 (42.5)
≥ 11.0	195 (97.5)	35 (17.5)	230 (57.5)

BMI = Body Mass Index, Mg2+ = Magnesium, Ca2+ Calcium,HB=haemoglobin, N = Population size, n = proportion prevalence

DISCUSSION

This study reports for the first time the levels of macro-elements in preeclamptic women in two regions of Ghana. Our study has clearly shown that Preeclamptic women have low levels of serum calcium and magnesium. The decrease in the calcium and magnesium levels among the Preeclamptics in the second trimester indicate the possible role of electrolytes in the pathogenesis of Preeclampsia. Serum magnesium and calcium areimportant for metabolism within the cell and are also vital for muscle contraction, neuronal activity and cell death(Sandip et al, 2013) [9]. The low Ca^{2+} and Mg^{2+} levels observed in this study are in agreement with other studies on hypertensive disorders in pregnancy (Owiredu et al, 2012, Abdallah and Abdrabo 2014, Sayyed and Sonttake 2013, Indumati et al, 2011) [8, 10, 11, 12].

A possible reason to this observation may be that when serum calcium levels decrease, the levels of intracellular calcium increase, leading to constriction of smooth muscles in blood vessels and therefore an increase vascular resistance culminating in a raised systolic and diastolic blood pressure (Ingec et al, 2006, Lopez 2000, Szmidt et al, 2006) [13, 14, 15].Furthermore, previous reports suggest that altered calcium homoeostasis, as exhibited by increase calcium excretion, is associated with higher blood pressure levels (Kesteloot et al, 2011) [16]. Low serum calcium levels may also increase blood pressure by stimulating parathyroid hormone and rennin release, which in turn increases intracellular calcium in smooth muscle, leading to vasoconstriction (Selina et al, 2011) [17].This implies that calcium and magnesium levels may play a role in pregnancy.

The observed low levels of magnesium in women with preeclampsia could be due to decrease dietary intake, increase clearance by the kidneys, and associated haemodilution due to expansion of the extracellular space and increased consumption of minerals by the growing foetus (Indumati et al, 2011) [12]. The lowered magnesium together with lowered calcium levels play a role in the development of hypertensive disorders in pregnancy. Other researchers have proposed that a reduction in the level of extracellular Mg^{2+}causes partial membrane depolarization and decreased repolarisation along with opening of Ca^{2+} membrane channels, leading to an intracellular Ca^{2+} shift. Furthermore, the existing increase in the foetal Ca^{2+} demand may also block bone resorption of Ca^{2+} with a concurrent intracellular pull (Indumati et al, 2011) [12]. This phenomenon produces vasoconstriction together with an increase in the blood pressure, as seen in this study.

The BMI of the cases were higher as compare to the controls. A study in the U S A also showed that preeclampsia risk is doubled from a BMI of 26 and nearly tripled at a BMI of 30 (Neal and Klark, 2004)[18]. Similar observations were made in other studies (O'Brien,2003, NHLBI,1998, Douglas and Redman, 1994) [19, 20,21]. A significant difference was observed between the mean Hb of the control group and the cases in this study. Several studies have highlighted the fact that severe anaemia (Hb < 10g/dl) is associated with a higher risk for preeclampsia and poor perinatal outcomes(Neal and Klark, 2004, NHLBI,1998, Osungbade and Ige,2011,Poon et al, 2010) [18, 21, 22, 23].

The decreased Hb may be as a result of poor nutrition and prenatal care and non-supplementation of ion during pregnancy and this can influence the hemoglobin values of especially the preeclamptic women.TheSystolic blood pressure (SBP) and the Diastolic blood pressure (DBP) were significantly raised in individuals with preeclampsia as compared to the controls.Several studies have highlighted the fact that blood pressure greater than or equal to 160/110mmHg at the second trimester is associated with preeclampsia (Owiredu et al, 2012, Neal and Klark, 2004)[8, 18]. During gestation, placental tissue cells called trophoblasts act like invaders, attacking the maternal blood vessels that supply blood to the embryo in an effort to draw even more nutrients to the placenta to increase the supply of nutrients.

The high blood pressure in pregnancy strains the mother's kidneys. The process of opening up the arteries fails, this leads to the rise in blood pressure(Poon et al, 2010)[23].The formation of a uteroplacental vasculature is insufficient to supply adequate blood to the developing fetus which results in feto -placental hypoxia, leading to imbalances in the release and metabolism of prostaglandins, endothelia, and nitric oxide by placental and extraplacental tissues (Sibai and Caritis, 2003) [24].These, as well as enhanced lipid peroxidation and other undefined factors contribute to the hypertension, platelet activation and systemic endothelial dysfunction which are characteristics of preeclampsia (Sibai and Caritis, 2003) [24].

The results of this study shows that subjects with lower levels of education or no formal education are at a higher risk of developing preeclampsia, this agree with other studies such as (Davies et al, 1970) [25] and more recently(Haelterman et al, 2003)[26] who found that relative to women with a higher educational level, those with a low educational level had a higher risk of pre-eclampsia. But it conflicts a study by (Nelson 1995)[27], who studied maternal social class as measured by the husband's occupation in relation to the incidence of pre-eclampsia, and found no association.

The association of the low educational level with higher risk of preeclampsia could be due to the fact that such pregnant women do not start antenatal early and the late booking visit could also lead to high blood pressure and other related p14regnancy issues. The low educational levels also suggest that they may not appreciate the value of regular exercises and they may also indulge in sedentary life style which are all risk factors for obesity and subsequently they could develop preeclampsia during pregnancy.

This study reports for the first time the levels of macro-elements in preeclamptic individuals in two regions of Ghana. Low levels of Magnesium and Calcium may affect maternal health in general and supplementation during pregnancy may contribute to reduction in preeclampsia and its related complications in Ghana.

CONCLUSION

The current study reports a significant reduction of serum Calcium and Magnesium in Preeclamptic women at the second trimester of pregnancy. Altered levels of serum calcium and magnesium may be important in the development of preeclampsia.

Competing interest: The authors declare that they have no competing interests.

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