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ORIGINAL ARTICLE

Calcium and Magnesium Metabolism in Pre-Eclampsia

Le Metabolisme du Calcium et du Magnesium dans la Pre Éclampsie

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ABSTRACT

BACKGROUND: **Preeclampsia is a multisystem disorder associated with high maternal and perinatal mortality and morbidity. The cause of the disorder is largely unknown and its pathogenesis is complex and poorly understood. Calcium and magnesium are divalent ions which may have roles to play in the manifestations of the disease. An understanding of their metabolism in preeclampsia may aid our management of pregnant women who develop the disease.**

OBJECTIVE: **To determine the plasma and urinary concentrations of calcium, magnesium and parathyroid hormone in women with mild, severe preeclampsia and in normal pregnancy.**

METHODS: **This is was a case control study of fifty women with mild preeclampsia, fifty women with severe preeclampsia and fifty women with normal pregnancy as controls, drawn from The Antenatal Clinic at the Lagos University Teaching Hospital, Lagos, Nigeria. The women were consecutively recruited after signing an informed consent form. Ethical approval was obtained from the medical ethics committee of the hospital.**

RESULTS: **The three groups of women were similar in their socio demographic characteristics. Plasma calcium was low in mild and severe preeclampsia compared to normal pregnancy controls (p=0.021). Urine calcium/creatinine ratio was lower in mild and severe preeclampsia compared to normal pregnancy controls (p= 0.030). Fractional excretion of calcium and levels of parathyroid hormone were similar across all three subgroups of women. Plasma magnesium was higher in mild and severe preeclampsia compared to normal pregnancy controls (p= 0.011) and showed a positive correlation with plasma creatinine (r=0.48, p=0.045). Parathyroid hormone levels were similar across the study groups.**

CONCLUSION: **Preeclampsia is associated with significant changes in calcium and magnesium metabolism. This study noted significant hypocalcaemia in mild and severe preeclampsia with significantly low urine calcium/creatinine levels. Calcium supplementation may have a place in patient's management. Hypermagnesemia was observed in mild and severe preeclampsia and appeared related to renal function. WAJM 2014; 33(3): 178–182.**

Keywords: **Calcium, magnesium, mild preeclampsia, severe preecalmpsia.**

RÉSUMÉ

CONTEXTE: La pré-éclampsie est une maladie multi- systémique associée à une forte morbidité et mortalité maternelle et périnatale. La cause de la maladie est largement inconnue et sa pathogénie est complexe et mal comprise. Le calcium et le magnésium sont des ions divalents qui peuvent avoir un rôle dans la manifestation de la maladie. Une bonne compréhension de leur métabolisme dans la pré-éclampsie peut aider notre prise en charge des femmes enceintes qui développent la maladie.

OBJECTIF: Pour déterminer les concentrations plasmatiques et urinaires du calcium, du magnésium et de l'hormone parathyroïdienne chez les femmes ayant une pré-éclampsie modérée, sévère, et une grossesse normale.

METHODES: Il s'agissait d' une étude de cas-témoin de cinquante femmes présentant une pré éclampsie modérée , de cinquante femmes présentant une préé clampsie sévère et de cinquante femmes ayant une grossesse normale comme témoins, prises à la clinique prénatale de l'Hôpital Universitaire de Lagos, Nigeria. Les femmes ont été recrutées de manière consécutive après avoir signé un formulaire de consentement éclairé. L'approbation éthique a été obtenue par le comité d'éthique médicale de l'hôpital.

RESULTATS: Les trois groupes de femmes étaient similaires dans leurs caractéristiques sociodémographiques. Le calcium plasmatiques était faible dans le pré éclampsie modérée et sévère par rapport aux témoins d'une grossesse normale (p = 0,021). Le rapport calcium/ créatinine urinaire était plus faible dans la pré éclampsie modérée et sévère par rapport aux témoins d ;une grossesse normale (p = 0,030). La fraction d'excrétion du calcium et les taux de l'hormone parathyroïdienne étaient similaires dans les trois sous-groupes de femmes. Le magnésium plasmatique était plus élevé dans la pré éclampsie modérée et sévère par rapport aux témoins d'une grossesse normale (p = 0,011) et a montré une corrélation positive avec la créatinine plasmatique (r = 0,48, p = 0,045). Les taux d'hormone parathyroïdienne étaient similaires dans les groupes d'étude.

CONCLUSION: La pré-éclampsie est associée à des changements importants du métabolisme du calcium et du magnésium. Cette étude a noté une hypocalcémie significative dans la pré éclampsie modérée et sévère avec des niveaux de calcium / créatinine significativement faibles dans l'urine. La supplémentation en calcium peut avoir une place dans la prise en charge de ces patients. L' hypermagnésémie a été observée dans la pré-éclampsie grave, et semblait liée à la fonction rénale. **WAJM 2014; 33(3): 178–182.**

Mots clés: calcium, magnésium, pré éclampsie modérée, pré éclampsie sévère.

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Abbreviations:

INTRODUCTION

Preeclampsia is the occurrence of new onset hypertension and proteinuria in the second half of pregnancy.[1] Environmental, genetic and immunologic mechanisms have been implicated in the pathogenesis of preeclampsia resulting in abnormal placentation with the release of various bioactive factors leading to vascular smooth muscle dysfunction, endothelial dysfunction and severe vasoconstriction.[2] Calcium and magnesium are dietary environmental risk factors which may have roles to play in the manifestations of the pathology of preeclampsia.

The role of calcium and magnesium in the pathology of preeclampsia has been the subject of much study.[3,4] Calcium and magnesium maintain membrane potential in nerves and muscles, influencing permeability and excitability of blood vessels and nerves.[5] It has been postulated that disorders of calcium and magnesium are implicated in the increased vascular sensitivity in pre eclampsia.[6]

Changes in plasma calcium and calcium metabolism in pregnancy have been reported[6,7] and the importance of adequate calcium intake in pregnancy has also been documented.[8] Low calcium and magnesium levels have been linked to the incidence of pre eclampsia.[4,6] Calcium supplementation have has been proffered to reduce the risk of developing preeclampsia especially in women who are calcium deficient.[9,10] Low urine levels of calcium have also been suggested as a marker for the early diagnosis of preeclampsia.[11]

The prevalence of preeclampsia is high in developing countries[12] and it is the second leading cause of maternal mortality and morbidity after obstetric hemorrhage.[13] There is the need to identify factors related to the disease in the local population. There are limited studies in the West African sub region on the metabolism of calcium and magnesium in preeclampsia. Both ions have been suspected to be related to the pathogenesis of the disease. Consequently, the aim of this study was to determine plasma and urine levels of calcium and plasma magnesium and parathyroid hormone levels in mild and severe preeclampsia and compare with levels in normal pregnancy.

MATERIALS AND METHODS

During the period of July 2012 to August 2013, gestational age matched (32 weeks), pregnant women who were attending The Antenatal Clinic at the Lagos University Teaching Hospital, Lagos, Nigeria, diagnosed with mild and severe pre eclampsia and pregnant women without hypertension or proteinuria as controls were consecutively recruited into the study. Severe preeclampsia was defined as systolic blood pressure $\geq$ 160 mmHgand/ or diastolic blood pressure $\geq$ 110mmHg and $\geq$ 2+ of proteinuria and mild preeclampsia was defined as systolic blood pressure $\geq$ 140 mmHg and/or diastolic blood pressure $\geq$ 90mmHg and $\geq$ 1+ of proteinuria.[14,15] Pregnant women with multiple gestation were excluded from the study. Approval was obtained from the ethics' committee of the hospital. Consenting subjects signed an informed consent form and filled a questionnaire. Information required included demographic information including age, ethnicity, level of education, marital status, medical history and history of index and previous pregnancies.

Pregnancy was dated from the last menstrual period and confirmed by clinical examination and ultrasonography scaning. Blood and urine were collected at 32 weeks gestation for biochemical analysis. Total calcium in plasma and urine were estimated from lithium heparin plasma by the orthocresolphthalein complexone method. Plasma and urine creatinine concentrations were estimated by the modified Jaffe kinetic method. Urinary calcium / creatinine ratio was calculated and the fractional excretion of calcium estimated.[16] Plasma magnesium was analysed from heparinised plasma using the colorimetric calmigate method. Parathyroid hormone levels were estimated in EDTA plasma using the enzyme linked immunosorbent assay method.[17]

The data were analyzed using the IBM SPSS version 19.0 package. One way ANOVA was used to test the differences in the mean values for the numerical variables. Chi square test was used to test the differences in proportion of the catergorical variables. Correlation analysis was done. Statistical significance was set at $p < 0.05$.

RESULTS

Fifty women with severe preeclampsia, fifty women with mild preeclampsia and fifty women with normotensive pregnancy participated in the study. The mean gestational age for all groups was thirty-two weeks. The study participants did not differ in their socio demographic characteristics. Ninety-six percent (96%) of the group with mild preeclampsia were married and four percent (4%) were unmarried. All the women with severe preeclampsia were married. In the normal pregnancy control group, ninety-two percent (92%) were married and eight percent (8%) unmarried. Fifty-two percent (52%) of the group with mild preeclampsia were of the Yoruba tribe, thirty-four (34%) were Igbo and fourteen percent (14%) were from other tribes, the group with severe preeclampsia had forty-six percent (46%) of the women being Yoruba, fifty percent (50%) of the women were Igbo and four percent (4%) belonged to other tribes. In the normal pregnancy control group, forty-four percent (44%) were Yoruba, forty-four percent (44%) were Igbo and twelve percent (12%) were from other tribes. The study participants also did not differ in age distribution nor in their educational status (Table 1).

Table 2 compared the clinical and laboratory characteristics of study groups and controls. The systolic and diastolic blood pressure values were higher in mild and severe preeclampsia compared with the normotensive pregnancy control group. Plasma calcium levels and urine calcium: creatinine ratio were significantly lower in the groups with preeclampsia compared to the control group. Plasma magnesium was significantly higher in the groups with preeclampsia.

The post hoc analysis showed that mild and severe preeclampsia contributed to the significantly higher levels of systolic and diastolic blood pressure and plasma creatinine. Both groups also contributed to the significantly lower plasma levels of calcium and albumin and urine levels of calcium:creatine ratio.

Table 1: Socio demographic Characteristics of the Study Participants

Characteristics	Control N=50(%)	Mild PET N=50(%)	Severe PET N=50(%)	P value
Age(years)				
20 – 30	18(36)	19(38)	20(40)	0.569
31 – 40	27(54)	31(62)	27(54)	
41 – 50	5(10)	0(0)	3(6)	
Tribe				
Yoruba	22(44)	26(52)	23(46)	0.993
Igbo	22(44)	17(34)	25(50)	
Others	6(12)	7(14)	2(4)	
Marital Status				
Married	46(92)	48(96)	50(100)	0.833
Single	4(8)	2(4)	0(0)	
Level of Education				
Primary	5(10)	7(24)	13(26)	0.217
Secondary	12(24)	17(34)	14(28)	
Tertiary	33(66)	26(52)	23(46)	

Table 2: Clinical and Laboratory Characteristics of the Study Groups and Controls

Characteristic	Control (50)	Mild PET (50)	Severe PET (50)	P-value
SBP (mmHg)	116.19 ± 12.0	149.4±53.3	156.48± 53.0	0.011*
DBP (mmHg)	71.25 ± 6.8	94.8±34.2	102.8±35.0	0.002*
Plasma Calcium(mmoles/L)	2.32 ± 0.4	2.29±0.3	2.023±0.3	0.021*
Urine calcium : creatinine ratio	0.142 ± 0.1	0.16±0.1	0.071±0.0	0.030*
Plasma creatinine (µmol/L)	59.77 ± 15.1	72.72±10.5	167.7±12.6	0.0001*
Fractional excretion of calcium	8.3 ± 8.4	11.78±8.5	11.62 ± 15.0	0.545
Plasma magnesium mmoles/L)	0.70 ± 0.2	0.84±0.4	1.1 ± 0.6	0.011*
Plasma albumin (g/L)	35.72 ± 2.9	32.78±4.5	31.52 ± 6.1	0.016*
Parathyroid hormone (pg/ml)	17.25 ± 4.1	16.48±2.3	17.63 ± 4.6	0.605

***-** *Statistically significant; PET – Pre eclampsia; Results expressed as mean ± SD*

Table 3: Correlation of Plasma Creatinine with Plasma Magnesium and Urine Variables in Mild, Severe Pre-eclampsia and Normal Pregnancy

	Pearson's Correlation Coefficient	
Variables	**Mild Pre-eclampsia**	**Severe Pre-eclampsia**
Plasma magnesium	0.18*	0.48*
Urine Calcium	0.09	0.20
Urine/calcium creatinine	–0.12	–0.04
Fractional excretion of calcium	–0.11	0.63*

-Statistically significant*

Severe preeclampsia alone was responsible for the higher levels of plasma magnesium observed between preeclampsia and normal pregnancy. There was no difference in fractional excretion of calcium and parathyroid hormone levels across the groups.

Table 3 shows the correlation of plasma creatinine with plasma magnesium and urine variables in mild, severe preeclampsia and normal pregnancy.

A positive significant relationship exists between plasma creatinine and plasma magnesium in mild and severe preeclampsia and between fractional excretion of calcium in severe preeclampsia.

DISCUSSION

This study noted a significantly lower plasma calcium levels in mild and severe preeclampsia compared to normal controls (p=0.021, Table 2) Similar findings were made by Kisters *et al*[18] and Sukonpan *et al.*[19] The low plasma calcium levels obtained in preeclampsia was suggested to contribute to the development in hypertension in pregnancy[18] and that hypocalcaemia may be a possible aetiology of preeclampsia.[19] Some other studies found no difference in the plasma calcium levels in preeclampsia and normal pregnancy,[3,20] this difference was attributed to the calcium values reported. Pedersten[20] corrected for individual variation in serum albumin and found that the hypoalbuminaemia of preeclampsia was related more to increased fluid retention. The free ionized calcium is the physiologically active fraction of calcium in plasma, not affected by levels of plasma albumin and fluid retention, Seely *et al,*[6] reporting ionised calcium, found significantly lower plasma ionised calcium levels in pre eclampsia compared to normal pregnancy controls.

Calcium is an essential dietary element crucial to skeletal development thus there is a higher demand for calcium in pregnancy. This increased demand for calcium in pregnancy, requires physiologic adaptation of the calcium homeostatic mechanisms in the mother in the areas of calcium turnover in the bones, intestinal absorption and urinary excretion. This adaptation may be inadequate in preeclampsia leading to significantly lower levels of plasma calcium. Preeclampsia is characterised by vascular smooth muscle dysfunction, endothelial dysfunction and severe vasoconstriction,[2] and low calcium levels in preeclampsia may contribute to these. However, whether the hypocalcaemia is a cause or a consequence of preeclampsia still remains to be clarified.

In this study there was a significant increase in plasma magnesium levels in

severe preeclampsia compared to normal pregnancy controls (p=0.011) Many studies found lower plasma magnesium levels in preeclampsia,[3,18] probably because these studies were carried out in women at an earlier gestational age.[3,18] The higher magnesium levels found in this study appeared related to declining renal function in severe preeclampsia (Table 3).

Magnesium sulphate is used extensively for the prevention and treatment of eclamptic seizures because of its vasodilatory action on cerebral and peripheral vessels to reduce arterial blood pressure and its action as an anticovulsant.[21] The total magnesium serum concentrations advocated for the treatment of eclamptic convulsions are 4.2 to 8.4 mg/dL,[22] which is usually obtainable with parenteral administration. The risk of magnesium toxicity however exists with the use of magnesium sulphate in preeclampsia and as such continuous monitoring of the patient during therapy is advocated.[21]

A significantly lower level of urine calcium/ creatinine ratio was obtained in this study between mild and severe preeclampsia and normal pregnancy (p=0.03) This is similar to findings by other authors.[6,11] The lower plasma calcium levels in preeclampsia may stimulate the calciotropic hormones to stimulate increased re absorption of calcium from urine.[6] A role for urine calcium/creatinine ratio in the early prediction of preeclampsia has been suggested.[11]

Fractional excretion of calcium was similar in all subgroups. Mandira *et al*[11] found an increased fractional excretion of calcium in preeclampsia at 34 weeks gestation which returned to normal pregnancy levels at term. The finding of similar levels of fractional excretion of calcium across the study subgroups with decreased urine calcium/creatinine ratio suggests adjustments in tubular re absorption to reflect changes in calcium homeostasis in preeclampsia. The urine calcium and urine calcium/creatinine ratio, correlated poorly with changes in plasma creatinine (Table 3) suggesting that the changes in urine calcium levels were not due to deteriorating renal function.

No difference was found in this study, in the parathyroid hormone levels between mild, severe preeclampsia and normal pregnancy (Tables 2). Seely *et al*[6] found higher levels of intact parathyroid hormones with lower plasma ionised calcium concentrations and lower urine calcium levels. He attributed the lower plasma ionised calcium levels to the lower 1,25 dihydroxycholecalciferol levels also found in the subgroup with preeclampsia. Pedersen[20] found similar parathyroid hormone levels in pre-eclampsia and normal pregnancy with normal corrected calcium levels and decreased levels of fractional excretion calcium. He attributed the findings of lower levels of fractional excretion calcium in preeclampsia and similar levels of parathyroid hormone and plasma calcium in normal pregnancy and preeclampsia, to changes in renal function. Our findings of similar parathyroid hormone levels in all study subgroups but lower plasma calcium and urine calcium/creatinine levels shows that the observed decrease in calcium levels may not be due to a significant increase in parathyroid hormone levels.

CONCLUSION

Preeclampsia, a hypertensive disorder of pregnancy has been associated with disorders of calcium metabolism. This study noted significant hypocalcaemia in mild and severe preeclampsia with significantly low urine calcium/creatinine levels. There may be a place for calcium supplementation in patients with preeclampsia. Hypermagnesemia was observed in severe preeclampsia and it appeared related to renal function.

The authors declare no conflict of interest.

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