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Decreased Serum Magnesium Level among Nigerian Women with Late Onset Pre-eclampsia

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Authors' contributions

This work was carried out in collaboration among all authors. Author FNO designed the study, wrote the protocol and performed the statistical analysis. Author ASA wrote the first draft of the manuscript. Authors FNO, ASA, JIC, JM and IAOU managed the analyses of the study and the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Pre-eclampsia is a common medical complication of pregnancy associated with increased maternal and perinatal mortality and morbidity. Its etiology is unknown, although several evidences indicate that deficiency of various nutritional elements might play important role.
Aims: To compare the serum magnesium levels in a group of pre-eclamptic and normotensive pregnant Nigerian women in Jos, Nigeria.
Study Design: This was a descriptive cross-sectional study.
Place and Duration of Study: Department of Obstetrics and Gynaecology, Jos University Teaching Hospital, Jos, between May 2011 and April, 2012.

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Methodology: We included 50 pre-eclamptic patients and 50 controls in the study. A structured questionnaire was administered directly on each subject. For each recruited pre-eclamptic patient, the next eligible normotensive patient matched for age, occupation, educational status, socioeconomic status, parity and gestational age was recruited as control. Venous blood samples were collected from pre-eclamptic and normotensive pregnant women. The sera from the samples were analyzed for magnesium using a photometric colorimetric analyzer (*Diagnosticum Zrt; Budapest*). The data were analyzed using Epi info 3.5.1 software (CDC, Atlanta Georgia, USA). Tests of associations were done using Student's t-test and chi square test. P value < 0.05 was considered statistically significant.

Results: Mean serum magnesium level in pre-eclamptic women was 0.89±0.10 mmol/l compared to 1.07±0.12 mmol/l in the normotensive pregnant women (p = 0.001).The range of serum magnesium in the pre-eclamptics was 0.73 – 0.96 mmol/l while that in normotensive pregnancies was 0.95 – 1.26 mmol/l. In patients with mild pre-eclampsia, the mean serum magnesium was 0.93±0.09 mmol/l while it was 0.81±0.08 mmol/l in those with severe pre-eclampsia (p < 0.0001). Also there was an inverse relationship between serum magnesium and systolic blood pressure (r = -0.404, p = 0.004) as well as serum magnesium and diastolic blood pressure (r = -0.462, p = 0.001).

Conclusion: Serum magnesium level in pre-eclamptics was significantly lower than those in normotensive pregnant women. This finding supports the hypothesis that hypomagnesaemia may be a contributor to the etiology of pre-eclampsia. Introduction of magnesium supplementation in diet may help reduce the incidence of pre-eclampsia in at risk women.

Keywords: Pre-eclampsia; serum magnesium; pregnancy; Nigeria.

1. INTRODUCTION

Pre-eclampsia is one of the most common causes of maternal and perinatal morbidity and mortality with incidence of between 2 – 8% of pregnancies [1,2,3]. It is estimated to cause about 100,000 maternal deaths annually worldwide [4]. This multi-systemic pregnancy related disorder has been dubbed the “disease of theories” as multiple hypotheses have been proposed to explain its occurrence [5,6]. The pathophysiologic abnormalities of the disorder are numerous but central to them is placental ischaemia leading to the release of circulating factor(s) causing widespread endothelial cell damage and activation of the coagulation system [7,8].

Despite active research for many years, the aetiology of this disorder remains unknown [7,9,10], although contributory factors include young maternal age, nulliparity, obesity, diabetes mellitus, older maternal age, job stress, multiple pregnancy, molar pregnancy, chronic hypertension, renal diseases, antiphospholipid antibody syndrome, family history of pre-eclampsia, collagen vascular diseases as well as nutritional deficiencies including that of magnesium and calcium [7-10]. Recently, pre-eclampsia has been characterized into two different disease entities with two different pathophysiological disorders. It consists of early onset pre-eclampsia which develops before 34 weeks of gestation and late onset pre-eclampsia, developing at or after 34 weeks of gestation [11]. Though they present with overlapping clinical features, they are associated with different maternal and fetal outcomes, heritability and biochemical markers. Also a report of differences in metabolomic profiles between the two types of pre-eclampsia exist, suggesting metabolites such as specific lipids and amino acids are differently expressed in early onset disease [12].

Clinical features of pre-eclampsia including increased neuromuscular irritability, seizures, vasoconstriction, elevated blood pressure, and increased vascular sensitivity to pressor agents are also characteristic of hypomagnesaemia, all of which respond to magnesium therapy [13,14]. Epidemiological data suggest an inverse correlation between dietary magnesium intake and incidence of pre-eclampsia [6,9,13,15]. Among the advocated modalities of prevention of pre-eclampsia is calcium and magnesium supplementation [9,16].

High prevalence of pre-eclampsia in developing countries have forced some authors to conclude that malnutrition is a risk factor in the aetiology of the disorder and deficit intake of magnesium, calcium and zinc has been implicated [17,18]. Identifying low serum magnesium as a risk factor for developing pre-eclampsia is essential for

developing intervention strategies designed to reduce the incidence and complications of pre-eclampsia. While most studies on magnesium levels in pre-eclamptic women were carried out mostly in developed nations, there has been paucity of literatures from developing nations where most of the maternal deaths from pre-eclampsia and eclampsia occur [19]. Few data exist regarding serum magnesium levels in pre-eclamptic and normotensive pregnant women in our obstetric population and few studies conducted in Nigeria were mainly from the southern part of the country. It is therefore pertinent to study the levels of serum magnesium in women with pre-eclampsia and compare with that of normotensive pregnant women in Jos, North-central Nigeria. The findings of the study may be contributory toward health planning with respect to effective interventions for the prevention and control of pre-eclampsia.

2. MATERIALS AND METHODS

2.1 Study Area

This was a hospital-based cross-sectional study conducted at the maternity unit of the Department of Obstetrics and Gynaecology, Jos University Teaching Hospital (JUTH), a tertiary health institution situated in the central part of Jos, Plateau State. JUTH serves as a referral center for neighbouring states of Bauchi, Gombe, Benue, Kogi, Nasarawa, Taraba, Adamawa and southern part of Kaduna State.

2.2 Study Population

The study population comprised of 50 pre-eclamptic women with singleton pregnancy and 50 normotensive pregnant women as controls, both at gestational ages greater than 20 weeks. Pre-eclampsia was diagnosed as the occurrence of hypertension with blood pressure of ≥ 140/90 mmHg in combination with significant proteinuria (≥ ++), developing after 20 weeks of gestation in a previously normotensive, non-proteinuric patient. Severe pre-eclampsia was diagnosed based on presence of systolic blood pressure of ≥ 160 mmHg or diastolic blood pressure of ≥ 110 mmHg as well as presence of symptoms and signs including headache, visual symptoms, vomiting, epigastric pain, oliguria and intra-uterine growth restriction. Exclusion criteria included pregnant women with multiple pregnancies, chronic hypertension and renal disease. Informed consent was obtained from the women before recruitment into the study. For each recruited pre-eclamptic patient, the next eligible normotensive patient matched for age, occupation, educational status, socioeconomic status, parity and gestational age was recruited as control.

2.3 Sample Size

The sample size was determined using the mean and standard deviation of serum magnesium levels in pre-eclamptics and controls from a previous study [20], with power of 80% and a confidence interval of 95%. The following formula was used for calculation of the sample size [21].

$$2N = \frac{4(Z\alpha + Z\beta)^2 (\sigma_1 + \sigma_2)^2}{\Delta^2}$$

Sample size of 50 (25 cases and 25 controls) were needed for the study, however 100 (50 cases and 50 controls) were recruited.

2.4 Data Collection

The purpose of the study and the procedure were explained to the subjects and data was collected using interviewer administered questionnaire. Information sought for included socio-demographic and obstetric features of the women. Also documented were their weights and packed cell volumes (PCV). Blood pressure measurement was taken using mercury sphygmomanometer and Korotkoff sound V (disappearance of the sound) was used to obtain the diastolic blood pressure because of its reproducibility. Two blood pressure measurements were taken at least five minutes apart and the average of these was calculated. Urine protein estimation was carried out using dipstick measurement of clean catch mid-stream urine specimen.

Then two millilitres (mL) of blood sample from each subject for magnesium estimation was drawn from the ante-cubital vein and emptied into plain test tubes without the use of tourniquet to avoid blood stasis and hypoxia leading to acidaemia (H^+). This was aimed at minimizing the effect of hydrogen ions (H^+) competing and displacing mg^{2+} ions from the plasma protein binding sites which may lead to false increased free plasma magnesium. The blood samples were allowed to clot, sent to the laboratory and the sera were separated by centrifugation for 10 minutes at 3000 rpm into plain test tubes and

stored at -20ºC until time of analysis for magnesium.

2.5 Laboratory Magnesium Estimation

Sera magnesium levels were estimated by photometric colorimetric test for magnesium using a standard kit and Magnesium liquid supplied by *Diagnosticum Zrt; Budapest*. The test principle is based on the formation of a colored complex when magnesium ion is combined with xylidyl blue under alkaline conditions. The intensity of the developed color is proportional to the magnesium ion concentration of the sample. The reagent was prepared by mixing equal volumes of the TRIS buffer and xylidyl blue. A pipette was then used to measure 10 microlitre (0.01 ml) of distilled water (blank) into a test tube and 1 ml of the reagent added. Another pipette was used to measure 0.01 ml of a standard solution of magnesium (with a known concentration of magnesium) into a second test tube and 1 ml of the reagent added to it. Separate pipette was used to measure 0.01 ml of serum (sample) into a third test tube and 1 ml of the reagent was also added. Using the spectrophotometer, the absorbance of the sample and the standard solution were read against that of the blank after 5 minutes at a wavelength of 500 nm.

The concentration of serum magnesium was calculated from the formula:

Magnesium concentration (mmol/l) =

[(Absorbance of sample solution/Absorbance of standard) X Concentration of standard]

This method is highly sensitive as it accurately measures magnesium level as low as 0.004 mmol/l.

2.6 Statistical Method

All results were transferred into the proforma designed for the study. The data were entered and analyzed using Epi info 3.5.1 software (CDC, Atlanta Georgia, USA). The mean and standard deviation of maternal age, parity, gestational age at diagnosis/enrolment, weight, systolic blood pressure, and diastolic blood pressure were calculated. Test of association between mean serum magnesium of both groups was assessed using student t-test. Categorical variables were compared using Chi-square test. A P value < 0.05 was considered significant.

3. RESULTS

One hundred patients were evaluated consisting of 50 pre-eclamptic women (cases) and 50 normotensives (controls). Table 1 depicts the obstetric and socio-Demographic characteristics of pre-eclamptic cases and normotensive controls. Mean age of pre-eclamptic patients was 25.92±5.37 years while that of the control was 25.48±5.41 years (P = 0.684). The mean parity of the cases was 0.64±0.96 while that of the controls was 0.74±1.03 (P = 0.408). The mean gestational age at diagnosis/enrolment were 36.82±2.75 weeks and 36.72±3.23 weeks respectively for the cases and controls (P = 0.691). Also with respect to their educational status and occupation, there was no significant difference between the cases and the controls (P = 0.369 and P = 0.544 respectively).

Table 2 shows the clinical features and packed cell volume (PCV) among the pre-eclamptic and control groups. The mean weight for the cases and controls were 81.07±19.21 kg and 71.27±9.76 kg respectively (P = 0.002). Statistical analysis also showed marked significant difference in the mean systolic and diastolic blood pressures between cases and control.

The mean serum magnesium levels in the pre-eclamptics (cases) was 0.89±0.10 mmol/l while that of the normotensive women (controls) was 1.07±0.12 mmol/l (P = 0.001). The range of serum magnesium in the pre-eclamptics was 0.73 – 0.96 mmol/l while that of normotensive women was 0.95 – 1.26 mmol/l. Serum magnesium tend to be lower with increasing severity of pre-eclampsia. The mean level of serum magnesium among patients with mild pre-eclampsia was 0.93±0.09 mmol/l while those with severe pre-eclampsia was 0.81±0.08 mmol/l (p = 0.001).

Table 3 shows the correlation between serum magnesium level and blood pressure of pre-eclamptic patients. There was a significant inverse relationship between serum level of magnesium and systolic blood pressure (r = -0.404, P = 0.004) as well as serum magnesium and diastolic blood pressure (r = -0.462, P = 0.001).

4. DISCUSSION

The major finding in this study was that of statistically significant decreased mean serum magnesium among pre-eclamptic patients

Table 1. Obstetric and socio-demographic characteristics of pre-eclamptic patients (cases) and normotensive pregnant women (control)

Characteristics	Cases (n = 50)	Control (n = 50)	P-value
Age	25.92±5.37	25.48±5.41	0.684
Parity	0.64±0.96	0.74±1.03	0.408
Gestational age	36.82±2.75	36.72±2.80	0.600
Education level			
Illiterate	2(50.0)	2(50.0)	0.369
Primary	7(77.8)	2(22.0)	
Secondary	21(45.7)	25(54.1)	
Tertiary	20(48.8)	21(51.2)	
Occupation			
Housewife	13(59.1)	9(40.9)	0.544
Student	11(61.1)	7(38.9)	
Trader	3(37.5)	5(62.5)	
Self-employ	12(48.0)	13(52.0)	
Civil servant	11(40.7)	16(59.3)	

Table 2. Clinical characteristics and packed cell volume of the study populations

Characteristics	Cases (Mean)	Control (Mean)	P-value
GA at sample collection (weeks)	36.82±2.75	36.72±3.23	0.691
Weight (Kg)	81.07±19.21	71.27±9.76	0.002
Systolic BP (mmHg)	158.20±13.05	106.80±8.19	0.001
Diastolic BP (mmHg)	104.40±9.72	66.20±6.35	0.001
PCV (%)	36.20±2.62	34.24±2.04	0.001

P< 0.05 is considered significant

Table 3. Correlation between serum magnesium level and blood pressure of pre-eclamptic patients

Parameter	Correlation coefficient (r)	P
Serum magnesium (mmol/l)	1.00	-
Systolic blood pressure	-0.404	0.004
Diastolic blood pressure	-0.462	0.001

P< 0.05 is considered significant

compared to normotensive women (P = 0.001). This is consistent with previous studies conducted in other parts of Nigeria [5,20,22,23]. Again, it is similar to studies reported from India, Thailand and USA [10,15,24].

However, this is in contrast with studies from other countries [6,25–27] where they found no significant difference in mean serum magnesium between preclamptics and controls. There was significantly lower level of mean serum magnesium in severe pre-eclamptics compared to those with mild disease. This finding is consistent with the study reported from India [10].

The fact that our patients presented as late onset pre-eclampsia, lower serum magnesium found in this study among pre-eclamptic patients compared to the controls could suggest a possible involvement of magnesium in the pathophysiology of late onset pre-eclampsia. The clinical implication of this finding could be that screening for hypomagnesaemia at late second or early third trimesters especially among women at risk of the disorder may predicts women that will develop late onset pre-eclampsia. However, this result must be interpreted with caution, as the study did not analyze the dietary intake of pre-eclamptic women to confirm whether or not the reduced reported levels of magnesium was

due to nutritional deficiency. In our environment, diets rich in magnesium including rice, cassava, beans, soya beans, beef, vegetable and yam flour are widely available. Obviously, most of our staple foods are rich in magnesium [20], therefore attributing dietary deficiency of magnesium being responsible for the low level of this element among pre-eclamptic patients as found in this study is unlikely. However, it has been estimated that magnesium intake has declined by more than half during this century [9], because of reduced magnesium in the ecosystem with resultant poor magnesium content of food items [9,28]. The magnesium content of food is further compromised with overcooking, processing and reprocessing of food products [9,28].

Magnesium has established role in obstetrics with respect to both fetal and maternal wellbeing. Low concentration of magnesium in serum exposes the patient to risk of pregnancy complications including pre-eclampsia. This is usually due to a defect in an enzymatic process as a result of low circulating magnesium which functions as a co-factor [23]. Thus, the success of magnesium therapy for prevention of convulsion in pre-eclamptic patients, as a treatment for eclamptic seizures and its known effect on vascular responses in-vitro suggest that magnesium might be deficient in women with pre-eclampsia [23] as noted in this study. Unavailability of this element due to nutritional deficiency or decrease concentration in the ecosystem may be a predisposing factor in the development of pre-eclampsia or a contributing factor in its pathogenesis [3,9,15,27,29]. The consequences of low magnesium may lead to a reduction in cerebral blood flow, cerebral vasospasm and increase in neuronal burst [9] leading to seizures as typically seen in eclampsia, a condition usually preceded by severe pre-eclamptic state. This hypothesis of the role of hypomagnesaemia in pre-eclampsia is also supported by the fact that women with severe pre-eclampsia in this study had significantly lower mean serum magnesium compared to those with mild disease. This suggests that the lower the serum magnesium level, the more severe the pre-clamptic disease.

Macdonald et al. [30] have shown experimentally that magnesium has a vasoprotective effects. This explains the use of magnesium sulphate as a neuroprotectant and antivasospastic agent in women with pre-eclampsia and eclampsia. Magnesium (mg++) may increase cerebral blood flow and reduce contraction of cerebral arteries caused by various stimuli [9,30]. The suggested clinical implication of low magnesium seen in our patients may be increased vascular contractility leading to increased blood pressure as noted in this study, low cerebral blood flow and a tendency to eclamptic fits. Physicians now agree that the medication for prevention of seizures in pre-eclampsia and treatment of eclamptic fits is magnesium sulfate [9,24]. The systemic effects of magnesium which include vasodilatation and increase in blood flow prevent eclampsia by selectively dilating cerebral vasculature and relieving cerebral vasospasm associated with pre-eclampsia. In eclamptic patients, it prevents recurrent seizures which is beneficial in reducing mortality and morbidity in both mother and fetus [9,24]. Other studies have also demonstrated that magnesium has neuro-protective effects as well as protective against vasospasm [9,29]. The consequences of magnesium deficiency may therefore be responsible for the clinical manifestations that are observed in this disease, since magnesium ions are important in cellular and neuronal metabolism as well as cell membrane stability [28].

Magnesium depletion also increases the susceptibility of cells to oxidative stress which on its own can negatively affect the cardiovascular system and enhance accelerated atherosclerosis [22]. It is convincible therefore that the vascular syndromes of pre-eclampsia namely pathologic vasospasm, increased peripheral resistance and ischaemic damage may be related to extracellular magnesium depletion as found in this study.

There was a significantly higher PCV level among women with pre-eclampsia compared to controls in this study. This is known to be attributed to relative intravascular volume depletion (haemoconcentration) seen in pre-eclampsia leading to increased haemoglobin levels in these women [31]. Also in this study, there was inverse relationship between serum magnesium and blood pressure of pre-eclamptic women. Magnesium has been suggested to play important role in vascular biology by regulating the vascular tone [32]. Hence hypomagnesaemia is linked to hypertension as a result of increased vascular tone [33] and this may explain the inverse relationship between low serum magnesium and blood pressure noted in this study and by extension the pathologic vasospasm usually seen in pre-eclampsia and eclampsia. Despite the suggestion emerging

from this study of a role of magnesium in the regulation of blood pressure (BP) in pregnancy and pre-eclampsia, some caution need to be considered. There is the need to obtain longitudinal data serially during pregnancy to ascertain whether or not the development of magnesium depletion necessarily correspond with increasing blood pressure throughout pregnancy and thus in particular, whether pre-eclamptic pregnancies can be distinguished by decreasing serum magnesium before the onset of clinical signs and symptoms.

Though there is no reliable marker for prediction of pre-eclampsia, the finding in this study suggests that low level of free magnesium in pre-eclampsia is more than a casual relationship and hypomagnesaemia may in fact be a marker for the disorder. Recent studies by other workers have raised the possibility that magnesium supplementation may be useful in the prevention of pre-eclampsia [20,34].

The major limitation of this study is that it did not analyze the dietary intakes of pre-eclamptic and normotensive pregnant women to confirm whether or not the reduced levels of magnesium found in this study was due to nutritional deficiencies in the pre-eclamptics.

5. CONCLUSION

The study shows that mean serum magnesium level in pre-eclamptic women was significantly lower compared to normotensive women in this group of pregnant Nigerians as well as inverse relationship between serum magnesium and blood pressure among women with pre-eclampsia. This finding supports the hypothesis that hypomagnesaemia is a possible contributor to the aetiology of pre-eclampsia, and dietary supplementation of this element may help in preventing the disorder among women at risk.

6. RECOMMENDATIONS

Dietary supplementation with magnesium in at risk patients should be considered as a modality in preventing pre-eclampsia so as to reduce the high mortality and morbidity from the disease. Also, a longitudinal research is required to estimate serum magnesium in a cohort of women at risk or among primigravidae before 20 weeks of gestation to determine its association with the development of pre-eclampsia.

CONSENT

Informed consent was obtained from the subjects before enrolment into the study.

ETHICAL APPROVAL

Approval for the study was granted by the Research and Ethical Committee of Jos University Teaching Hospital, Jos, with ethical clearance number JUTH/DCS/ADM/127/XIX/29516.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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