Original Article

A comparative study of serum magnesium between normal healthy pregnant women and pre-eclamptics in a Nigerian teaching hospital

Headindueme Charles Nwogu[1], Sotonye Fyneface-Ogan[2], Sunday Osabuohien Imasuen[1]

[1]Department of Anaesthesia, Rivers State University Teaching Hospital, Port Harcourt; [2]Department of Anaesthesia, Faculty of Clinical Sciences, University of Port Harcourt, Port Harcourt.

Abstract

Background: Low serum magnesium levels have been implicated in the prevalence of pre-eclampsia. However, these levels are not routinely assessed amongst parturients.

Aim: The study was to compare the serum magnesium levels between normal healthy pregnant and pre-eclamptic women.

Methods: A total of one hundred and forty-four pregnant women aged 18 to 45 years in their third trimester were recruited from the antenatal clinic into this prospective comparative study by convenient sampling method and assigned into two groups of 72 women each. One group was made up of healthy pregnant women while the other group had diagnosed pre-eclamptics women. Blood samples were collected and analysed by the attending Chemical Pathologist for serum magnesium levels. The results of serum magnesium were entered into the data bank and analysed.

Results: The mean magnesium levels in normal healthy pregnant women and pre-eclamptic pregnant women were 0.99 ± 0.28 and 0.79±0.24mmol/l respectively. There were significantly lower mean serum magnesium levels among pre-eclamptic compared to normal healthy pregnant women (t=4.516, p=0.000013). Pre-eclampsia patients had much lower serum magnesium levels than normal, healthy pregnant women, according to observations made at the University of Port Harcourt Teaching Hospital (UPTH).

Conclusion: Pre-eclampsia patients in this study showed significantly decreased serum magnesium levels when compared to the healthy population of pregnant women; hence the need for a routine magnesium screening of women during pregnancy.

Keywords: **Serum magnesium, healthy pregnant women, pre-eclamptic women, antenatal clinic**

Address for correspondence: Dr. Headindueme Charles Nwogu, Department of Anaesthesia, Rivers State University Teaching Hospital, Port Harcourt

Email: nwoguheadinduemecharles@yahoo.com

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INTRODUCTION

Magnesium is well well-known essential macronutrient which plays a significant role in over 300 enzyme reactions in the human body. This element is essential in muscle and nerve function, regulating blood pressure, and supporting the immune system. During pregnancy normal serum level of this element is needed to maintain a healthy parturition and foetal health. One study has demonstrated that magnesium supplementation in pregnant women might reduce the risk of intrauterine growth retardation of the foetus, increase birth weight, and reduce by half the incidence of eclampsia.[1] Monitoring the mother's health throughout the pregnancy is especially important to prevent complications like pre-eclampsia and preterm labour, among others, which can have serious implications for the health of both the mother and the baby.[2] Normal healthy pregnant women are those who do not exhibit any significant medical conditions or complications during pregnancy.[3] They are deemed to have a low-risk pregnancy and are expected to have an uncomplicated labour and delivery process.

Pre-eclampsia is a complex pathology that specifically arises after 20 weeks gestation, affecting multiple organs and foetal outcomes.[4-6] Studies by Nygaard *et al*.,[7] Catov *et al*., [8] and Roberts *et al*.[9] have indicated that a deficiency of magnesium may be a factor in the onset of pre-eclampsia. Recently, maternal biochemical macronutrients such as magnesium and calcium have gained prominence in the pathogenesis and management of pre-eclampsia.

There is currently no conclusive evidence to support the regular use of magnesium supplements for all pregnant women. However, various studies have found lower levels of magnesium during pregnancy, and even worse levels in cases of pre-eclampsia.[7-9] Therefore, these conflicting findings highlight the need to compare the serum magnesium levels between normal healthy pregnant women and pre-eclamptic women in our sub-region.

METHODS

After obtaining approval from the University of Port Harcourt Teaching Hospital's Research Ethics Board (REB approval reference number UPTH/ADM/90/S.II/VOL.XI/1101/2023) and obtaining informed consent from each participant, participants aged 18 to 45 years in their third trimester were enrolled over six-month period by purposive sampling method (in which the researchers intentionally selected participants with specific characteristics related to the research question) into this prospective comparative single-blind study. The researchers considered 80% power, and sample was calculated for 95% confidence which gave a sample of 62 patients per group. However, we decided to recruit 72 participants per group after using 10% (7.5, rounded up to 8) attrition rate was added making the total sample size 144. While 72 of the pregnant women with diagnosed pre-eclampsia were assigned to group A, 72 of the healthy pregnant women were assigned to group B. Only the Chemical Pathologist who analyzed the sample was blinded throughout the study to the group each sample fell into. For this study, normal healthy pregnant women were in good health with normal blood pressure and no evidence of proteinuria, whereas pre-eclamptic women had hypertension and significant proteinuria.

Included in the study were healthy pregnant women and diagnosed pre-eclamptics without any other inter-current disease. Women with other pre-existing medical conditions such as diabetes mellitus, renal failure, heart failure, or ischaemic heart disease were excluded. Furthermore, pregnant women with chronic hypertension on antihypertensive therapy, eclampsia, autoimmune disease, or renal disease were excluded from the study. Also excluded were patients who declined to participate and patients taking magnesium sulphate and/or calcium lactate supplements and women with multiple gestations.

For the purpose of this study, the researchers assumed that Nigeria has five socioeconomic classes and these are: class I (Upper class), class II (Upper middle class), class III (Lower middle class), class IV (Working class) and class V (The underclass).[10]

Following recruitment by the researchers, 5ml of fasting venous blood was collected during the third trimester of pregnancy and centrifuged at

300 rpm for 5 minutes and serum was aspirated into a plain tube and analysed immediately using CONTEC Semi-Auto biochemistry analyser, model: BC300 (CONTEC medical systems LTD. China) or stored at -20°C.

Before entering the data into the IBM Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM Corporation, New Orchard Road Armonk, NY 10504, USA) the collected data was double-checked for completeness. Student's *t*-test for normally distributed data was used when appropriate. Fisher's exact test and Chi-square test was used to look for differences in the discrete variables. The significance level was considered to be $p<0.05$.

Table 1: Comparison of pre-eclamptic and normal healthy pregnant women socio-demographic characteristics

Socio-demographic	Normotensive N (%)	Pre-Eclamptic N (%)	Chi-Square[a]	p-Value
Age (Years)				
20 – 29	17 (23.3)	20 (30.3)	3.575[f]	0.163
30 – 39	47 (65.7)	44 (66.7)		
40 and above	8 (11.0)	2 (3.0)		
Education				
Primary	0 (0.0)	6 (9.1)	8.078[f]	0.014*
Secondary	24 (32.9)	25 (37.9)		
Tertiary	48 (67.1)	35 (53.0)		
Socio-economic Status				
Class I	3 (4.1)	0 (0.0)	19.134[f]	0.001*
Class II	12 (16.4)	28 (42.4)		
Class III	32 (45.3)	14 (21.2)		
Class IV	22 (30.1)	24 (36.4)		
Class V	3 (4.1)	0 (0.0)		
Occupation				
Business Owner	32 (61.1)	21 (38.9)	9.781	0.043*
Trader	11 (37.9)	18 (62.1)		
Civil Servant	13 (72.2)	5 (27.8)		
Teacher	8 (53.3)	7 (46.7)		
Others	8 (34.8)	15 (65.2)		

[a]Chi-square test statistic;*Significant at the 0.05 level; [f]Fischer's Exact test

Table 2: Comparing normal healthy pregnant women and pre-eclamptic biological characteristics

	Normotensive (Mean)	Pre-eclamptic (Mean)	*t*-test[a]	p-value
Age of Participants (Years)	33.12	32.32	0.96	0.338
Gestational Age (Weeks)	38.11	34.54	6.80	<0.000*
BMI (Kg/m^2)	30.84	32.02	-1.22	0.225
Systolic Blood Pressure (mmHg)	128.29	167.45	-14.30	<0.000*
Diastolic Blood Pressure (mmHg)	78.25	104.20	-13.43	<0.000*
Mean Arterial Pressure (mmHg)	92.30	123.48	-13.55	<0.000*

[a]*t*-test statistic *Significant at the 0.05 level

Table 3: Comparing pre-eclamptic and normal healthy pregnant women obstetric characteristics

Variables	Pre-eclampsia (%)	Normotensive (%)	Chi-Square[a]	p-value
Parity				
Para 0	31(47.0)	21(28.8)	26.40[f]	0.000*
Para 1	15 (22.7)	22 (31.5)		
Para 2	2 (3.0)	20 (27.4)		
Para 3	15 (22.7)	7 (9.6)		
Para 4	0 (0.0)	2 (2.7)		
Para 6	3 (4.5)	0 (0.0)		
Urine Protein				
Negative	0 (0.0)	72 (100.0)	139.00	<0.000*
1+	20 (30.3)	0 (0.0)		
2+	31 (47.0)	0 (0.0)		
3+	15 (22.7)	0 (0.0)		

[a]Chi-square test statistic; *Significant at the 0.05 level; [f]Fisher's exact test

Table 4: Mean serum magnesium levels among pre-eclamptic and normal healthy pregnant women

Serum magnesium (mmol/L)	Normotensive	Pre-Eclamptic	t-test[a]	p-Value
N	**72**	**66**		
Mean ± SD	0.99 ± 0.28	0.79 ± 0.24	4.516	0.000*
Minimum	0.55	0.22		
Maximum	1.83	1.42		

[a]*t*-test statistic; *Significant at the 0.05 level

Table 5: Comparison of Mean Serum magnesium levels and severity of pre-eclampsia

Serum (mmol/L)	Mild pre-eclampsia	Severe pre-eclampsia	t-test[a]	p-Value
N	**39**	**27**		
Mean ± SD	0.83 ± 0.25	0.73 ± 0.22	11.67	0.000*
Minimum	0.28	0.22		
Maximum	1.42	1.08		

[a]*t*-test statistic; *significant at the 0.05 level

RESULTS

A total of 144 pregnant women were recruited into this study. Out of the number recruited, one hundred and thirty-eight (95.83%) participants completed the study. Six (4.17%) pregnant women from the pre-eclamptic group were excluded from the study as they had already commenced magnesium treatment.

Table 1 shows that there was no difference in age categories between the normotensive pregnant women and pre-eclamptics groups (χ^2=3.575, p=0.163). However, there was a statistically significant difference in the levels of education as more pre-eclamptics have only primary levels of education as compared to the normotensive patients. On comparative analysis, socioeconomic status (χ^2=19.134, p<0.001), and occupation were statistically significantly

different between the normotensive and pre-eclamptic groups (χ^2=9.781, p=0.043).

Pre-eclamptic patients had higher systolic (t = -14.30, p<0.0001), diastolic (t = -13.43, p<0.0001), and mean arterial pressure (t = -13.55, p<0.0001), compared to normotensive patients. On average their gestational ages were significantly lower at the time of recruitment (34.54 weeks vs 38.11 weeks) (t = 6.8, p<0.0001). There was no significant difference in the BMI or age between the two groups and these are summarized in Table 2.

On observation of obstetric characteristics, nullipara accounted for (52, 37.5%) of all participants, followed by para 1 (38, 27.3%). Out of the 66 pre-eclamptics analysed for urine protein, (20, 30.3%) had 1 plus, (31, 47%) and (15, 22.7%) had 2 and 3 pluses proteinuria respectively. Pre-eclamptic women had a significantly greater proportion of nulliparous women compared to normal healthy pregnant women (χ^2=26.4, p=0.000), as summarized in Table 3.

The mean magnesium levels in normal healthy pregnant women and pre-eclamptic pregnant women were 0.99±0.28 and 0.79±0.24 respectively, there were significantly lower mean serum magnesium levels among pre-eclamptic compared to normal healthy pregnant women (t =4.516, p=0.000), these are summarized in Table 4. Serum magnesium levels varied significantly between patients with mild and severe pre-eclampsia. (F=11.67; p<0.005) as summarized in Table 5.

DISCUSSION

This study shows that there was a significant difference in mean serum magnesium levels between the normotensive and pre-eclamptic populations with the latter group maintaining a lower plasma level. This finding was similar to the study by Sukonpan *et al*[11] in Thailand, who observed a significant difference in serum magnesium levels between the two groups. Unlike in this present study, there was an attempt by the researchers to account for diet as a confounder by measuring and comparing magnesium intake between both groups. However, this present study did not take dietary measurements and could not ascertain if there were differences in dietary intake of magnesium in both groups which could have alternatively explained this difference.

Unlike the finding of the present study, Kanagal *et al*,[12] did not observe any difference in serum magnesium levels between pre-eclamptic and normotensive pregnant women. Several reasons could have accounted for these differences in findings. Firstly, the current study had a comparatively larger sample size compared to the Indian study[13] and, was more powered to detect any difference if one existed. Secondly, differences in the population exist as the former study recruited their sample from rural coastal India while the current study population were from a metropolitan hospital based in Nigeria. Socio-demographic characteristics could account for differences in dietary intake of pregnant women who are already prone to dietary deficiency of magnesium[14, 15] and could have accounted for conflicting results.

In sub-Saharan Africa, contrasting findings have been reported. While a comparative cross-sectional study conducted at the Korle-Bu Teaching Hospital, Ghana,[16] reported no significant difference in serum magnesium in pre-eclamptic women compared to normal pregnant women, another conducted in the Cape Coast metropolis of Ghana, [17] reported a significant difference as observed in this index study. The sample size in the Korle-Bu study was less than half of the index study and could have led to their non-significant differences. The Cape Coast Ghana study[17] which reported similar significant findings had a larger sample size and also accounted for the effect of confounding by matching their controls for age. Even though controls were not age-matched in the present study, it is unlikely that age confounded the relationship between magnesium levels and pre-eclampsia as there was no significant difference observed in the ages among both groups.

The use of a tourniquet which was reported in

their study could have resulted in cell lysis with a resultant elevation in serum magnesium and calcium levels leading to erroneous results. It is well known that the mechanism of cell lysis could be related to tourniquet application during blood collection, pneumatic tube transport, or centrifugation during the transport and preparation for running the test in the laboratory.[18] The use of a tourniquet was discouraged in this index study to avoid a false negative result of raised calcium and magnesium levels.

In Nigeria, Idogun *et al*[19] in a cross-sectional study at the University of Benin Teaching Hospital in the South-South region reported a contrasting result of non-significant differences in serum magnesium among pre-eclamptic and normotensive pregnant women. However, when CSF magnesium was analysed in the same study, the magnesium levels were significantly different among both groups. The present study did not measure magnesium level in CSF thus, it is difficult to compare this result. However, it can be inferred since the pathology of pre-eclampsia is mostly in the cerebral vasculature, that CSF levels of magnesium are an important biomarker to measure and more research should be done in this area to ascertain its sensitivity.

Magnesium is well known to be a unique calcium antagonist as it can act on most types of calcium channels in vascular smooth muscle and as such would be expected to decrease intracellular calcium.[20] Although serum calcium levels were not measured in our study, one major effect of decreased intracellular calcium would be the inactivation of calmodulin-dependent myosin light chain kinase activity and decreased contraction, causing arterial relaxation that may subsequently lower peripheral and cerebral vascular resistance, relieve vasospasm, and decrease arterial blood pressure. This mechanism of action could reduce the occurrence of preeclampsia. However, the importance of magnesium-induced vasodilation in the treatment and prevention of preeclampsia is yet to be fully elucidated.

The nutritional requirements of magnesium in pregnancy are still poorly understood. The serum magnesium level has been shown to fall during pregnancy,[21] and this could be due in part to haemodilution associated with the physiological changes. However, there should always be a balance of calcium and magnesium to maintain blood pressure which is a result of adequate balance between blood vessel constriction and relaxation mediated by calcium and magnesium respectively. Magnesium does this by directly blocking calcium channels responsible for arterial constriction thus inhibiting the release of acetylcholine.[22] It has been proven that an inverse association exist between Ca^{2+} intake and the development of pre-eclampsia.[23] In pre-eclampsia, there is an initial vasospasm, ischaemia and cellular hypoxia which may lead to reperfusion injury when normal blood flow has been established.[24] Magnesium also flows into the cell to mitigate this ill effect by antagonising the effect of calcium.[25] This could explain the low levels of magnesium in pre-eclamptic patients compared to normotensive pregnant women as observed in our study.

It has been observed that only less than 1% of the total body magnesium is present in serum, the serum magnesium concentration does not correlate with and is a poor predictor of the total body or intracellular magnesium content.[26] Therefore, cell magnesium is the true reflection of magnesium level. Red cell magnesium is found to be the most commonly measured using atomic absorption spectrophotometry, which is available commercially. This is reported to be a highly sensitive, accurate, and precise method that is amenable to automation.[27]

However, a semi-biochemistry autoanalyzer was used in this index study, hence measuring only 1% of the total body magnesium. There have been no large population studies currently, to determine a standard reference range, and it could be possible that such a range would differ in the pregnant population. The determination of normal reference ranges for the general population and pregnant women would guide for diagnosis of magnesium deficiency. Therefore, the gold standard of magnesium measurement involves magnesium loading and subsequent

measurement of urinary excretion, but this is rarely done in most clinical settings.

Semi-auto analyser-based biochemical reporting of routine parameters could have comparable and dependable results if provisions are made for continuous, coordinated, and comprehensive care by primary care physicians and staff. The inferior quality of care and results obtained emphasise the role of attending laboratory physicians in the screening and diagnosis of laboratory findings. In this index study, the biochemical laboratory is manned by Laboratory Physicians who run the investigations.

This index study had some limitations. Firstly, the dietary intake of calcium and magnesium among the recruited pregnant women was not determined. Nutritional deficits are widespread during pregnancy and pregnant women in low-income countries have been documented to consume diets that are deficient in minerals and vitamins; although a study showed no difference in magnesium levels following dietary intake.[28] Secondly, there was no socioeconomic status among the variables measured as this is a well-known confounder of dietary patterns. It would have been more informative to compare the socioeconomic status of cases and controls to establish an association with pre-eclampsia. Thirdly, samples could not be taken close to the point of analysis for rapid delivery without widespread routine use of point-of-care testing, which has its difficulties. Lastly, the serum magnesium level obtained in our study did not demonstrate the total magnesium level in the body. Laboratories could optimise carrying conditions and educate users: more systematic use of insulated specimen boxes in practices and temperature-controlled transport systems in collection vans and pneumatic tube transportation could have improved the outcome of the results of this index study.

Further studies using the atomic absorption spectrophotometry to assay the total magnesium level are recommended on a much larger study population. This investigation should be carried out by laboratory physicians for a proper diagnosis to be achieved.

CONCLUSION

Our study showed significantly decreased serum magnesium levels amongst preeclamptic women when compared to the healthy population of pregnant women; hence the need for a routine magnesium screening of women during pregnancy.

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Conflicts of interest
There are no conflicts of interest

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