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Serum Magnesium Levels in Second and Third Trimesters of Pregnancy in Patients That Developed Pre-Eclampsia and Feto-Maternal Outcome

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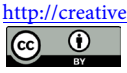

Abstract

Introduction: Pregnancy is a physiological process that may be complicated by a number of clinical conditions. Gestational diabetes and pre-eclampsia are known complications in pregnancy. Pre-eclampsia is a disease of hypothesis in which the pathogenesis is yet to be fully explained. The role of magnesium in the pathogenesis of pre-eclampsia has been suggested by studies and it is being investigated all over the world. The study aimed to compare serum magnesium levels in pre-eclampsia and control groups from second trimester of pregnancy and assessed maternofetal outcome. **Materials and Methods**: This was a nested case control study in which consenting three hundred and sixty (360) normal pregnant women were enrolled. These women were recruited in their second trimester of pregnancy. Blood samples for serum magnesium estimation were obtained from subjects and controls at recruitment and after development of pre-eclampsia. **Results**: Thirty seven pregnant women that developed pre-eclampsia were nested as cases and were matched with 37 controls (apparently healthy pregnant women). The mean serum magnesium at recruitment was 0.75 ± 0.028 mmol/l (cases) and 0.76 ± 0.036 mmol/l (controls) (P = 0.123); this became significant when diagnosis of pre-eclampsia were made with mean of 0.53 ± 0.06 mmol/l (cases) and 0.69 ± 0.08 mmol/l (controls), (P < 0.001). There was significant statistical relationship between preterm delivery, low birth weight and need for special care baby unit (SCBU) admission in newborn of mothers with low serum magnesium level (P = 0.001, 0.002 and 0.035 respectively). **Conclusion**: Findings from this study revealed that hypomagnesaemia appears to be a complication of pre-eclampsia. Serum levels of magnesium were normal until the develop-

ment of the disease. Serum level of this biomarker affects maternofetal outcome significantly.

Keywords

Pre-Eclampsia, Serum Magnesium, Pregnancy, Preterm Delivery

1. Introduction

Pre-eclampsia develops after 20 weeks of gestation [1]. Despite knowing the predisposing factors for its development, when the process starts and what initiates the development are still poorly understood. There are reports that the process of developing pre-eclampsia starts in first half of pregnancy; the woman that will develop pre-eclampsia can be predicted from first half of pregnancy [2] [3]. Preventive measures may be visible if the trend is detected early; this to a greater extent will reduce the burden of pre-eclampsia in our environment. The prevalence of pre-eclampsia is 7% - 18% in developing countries [4] [5] [6].

Some studies have reported that changes in serum levels of magnesium observed in pre-eclamptic patients may contribute to its pathogenesis [7] [8] [9] [10]. Meanwhile, a study in Nigeria reported no significant difference in serum magnesium level of women with pre-eclampsia [11].

The vasodilating effect of magnesium with consequent increase in blood flow has been shown to prevent pre-eclampsia, by selectively dilating cerebral vasculature and relieving cerebral spasm associated with pre-eclampsia/eclampsia [12]. Studies from different regions report a decline in serum magnesium levels during pregnancy [13] [14] [15] [16]. Magnesium deficiency during pregnancy may cause pre-eclampsia, preterm delivery and low birth weight babies [12] [14] [15] [16] [17].

The possible role of magnesium deficiency in the genesis of pre-eclampsia, preterm delivery and low birth weight babies continues to be the subject of considerable debate. Therefore, there is a need for this study to observe the serum magnesium levels early during pregnancy in our environment as it relates to the development of pre-eclampsia and its other effect on maternal and fetal health. In view of the above, this study was designed to compare serum levels of magnesium in patients that developed pre-eclampsia and its effect(s) on maternofetal outcome (which includes development of pre-eclampsia, preterm delivery, low birth weight and need for special care baby unit (SCBU) admission).

2. Methodology

This was a nested case control study comparing the association between those who developed pre-eclampsia and those who did not in Osogbo over eight months period (between July 2017 and February 2018). The study was carried out in the Departments of Obstetrics and Gynaecology of Ladoke Akintola Uni-

versity of Technology (LAUTECH) Teaching Hospital, Osogbo and Chemical Pathology of Ekiti State University Teaching Hospital (EKSUTH), Ado-Ekiti. Three hundred and sixty (360) apparently normal pregnant women in their second trimester (17 - 23 weeks of gestation) were recruited at booking and during routine antenatal clinic visits into the study after obtaining written informed consent.

Sample size was determined using a statistical calculator for comparing two means. Considering a mean serum level of 0.58 mmol/L in pre-eclamptic women compared to 0.73 mmol/L in healthy pregnant women and standard deviation for an outcome of interest (serum magnesium concentration in patients with pre-eclampsia) of 0.17 from a previous study [16], at a power of 90% and 5% significance level. The minimum sample size calculated was 30 per group. Thirty seven (37) pregnant women that developed pre-eclampsia were compared with thirty seven (37) age and gestational age match controls. Exclusion criteria were chronic hypertension, chronic renal disease, pre-gestational diabetes, sickle cell anaemia, multiple pregnancy, patients on magnesium and or calcium supplements. Patients who developed pre-eclampsia before recruitment were also excluded.

Venous blood sample (5 mls) was drawn from pregnant women at recruitment and after development of pre-eclampsia using routine aseptic procedure of phlebotomy.

The samples were left undisturbed for between 30 and 60 minutes to clot and retract. Subsequently these were centrifuged at 3000×g for 10 minutes; the supernatant (serum) was then extracted into another plain specimen bottle. All the batches of serum samples were kept frozen (at temperature of −20˚C) till the time of analysis. Serum magnesium was analyzed by the use of Atomic Absorption Spectrophotometer [18].

Statistical analysis was done using statistical package for social science (SPSS) version 23. Results were tested for statistical significance using the student t-test, chi-square test and multivariate analysis. The significant value was put at 5%. Ethical clearance for this study was obtained from the research and ethical review committee of the LAUTECH Teaching Hospital Osogbo (PROTOCOL NUMBER LTH/EC/2017/02/292).

3. Results

Thirty seven patients (10.27%) developed pre-eclampsia out of 360 women recruited for this study. Majority (48%) of the study population was between ages of 20 and 29 years, majorly are of Yoruba ethnicity (90%), Christianity accounted for 58%, followed by Islam 41%, others are traditional worshipers (1%). Other demographic characteristics of the study population are as shown in **Table 1**.

The study showed no statistical significant difference in the mean age of the case and control groups 30.00 ± 5.06 and 30.08 ± 5.20 year respectively (P =

Table 1. Socio-demographic characteristic of the subjects.

Variables	Patients (%)	Control (%)
Parity		
Nullipara	14 (37.8)	14 (37.8)
Para 1	18 (48.7)	18 (48.7)
Multipara	5 (13.5)	5 13.5)
Total	37	37
Age (years)		
<20	1 (2.7)	1 (2.7)
20 - 29	18 (48.7)	18 (48.7)
30 - 39	16 (43.2)	16 (43.2)
40 and above	2 (5.4)	2 (5.4)
Total	37 (100)	37 (100)
Delivery EGA		
<36	25 (67.6)	4 (10.8)
37 and above	12 (32.4)	33 (89.2)
Total	37 (100)	37 (100)
Social class		
1	6 (16.2)	4 (10.8)
2	21 (56.8)	20 (54.0)
3	9 (24.3)	10 (27.0)
4	1 (2.7)	2 (5.4)
5	0	1 (2.7)
Total	37 (100)	37 (100)
BMI		
<18.5	1 (2.7)	1 (2.7)
18.5 - 24.9	15 (40.5)	18 (48.7)
25.0 - 29.9	12 (32.4)	10 (27.)
30 - 34.9	6 (16.2)	6 (16.2)
35.0 - 39.9	3 (8.2)	2 (5.4)
Total	37 (100)	37 (100)

BMI = Body mass index; EGA = Estimated gestational age (weeks).

0.946). Also there were no statistical differences between the body mass index, estimated gestational age at recruitment, mean blood pressure at recruitment and social class of the study groups ($P > 0.05$). The mean systolic and diastolic blood pressure became statistically significant between the two groups at the point of diagnosis of pre-eclampsia and remained so at delivery ($P < 0.001$) as shown in Table 2.

Table 3 shows comparison of serum magnesium levels in cases and controls

Table 2. The demographic and obstetrics characteristics of the study population.

Variables	Patients (n = 37) Mean ± SD	Control (n = 37) Mean ± SD	"t" value	P value
Age (years)	30.00 ± 5.06	30.08 ± 5.20	−0.68	0.946
Parity	1.13 ± 1.13	1.32 ± 1.08	−0.73	0.465
BMI (kg/m^2)	27.2 ± 4.50	25.2 ± 5.32	1.75	0.84
Gestational Age (Recruitment)	20.37 ± 1.67	20.10 ± 1.64	0.70	0.486
Social Class	2.10 ± 0.73	2.4 ± 0.86	−1.73	0.87
Recruitment Systolic Bp (mmHg)	106.48 ± 11.15	105.18 ± 9.36	0.54	0.59
Recruitment Diastolic BP (mmHg)	64.05 ± 6.43	66.10 ± 6.94	−1.32	1.91
Diagnosis/control systolic BP	161.08 ± 8.0	110.81 ± 9.80	24.02	0.000
Diagnosis/control diastolic BP	102.70 ± 6.90	67.83 ± 5.80	23.40	0.000
Delivery systolic BP	144.32 ± 11.43	122.10 ± 6.80	10.14	0.000
Delivery diastolic BP	90.27 ± 7.60	74.32 ± 6.0	9.97	0.000

SD = Standard deviation; BMI = Body mass index; Kg/m^2 = kilogram per meter square; BP = Blood pressure; mmHg = Millimeter of mercury.

Table 3. Comparison of serum magnesium levels in disease and control groups.

Parameters	Patients (n = 37) Mean ± SD	Control (n = 37) Mean ± SD	"t" value	P value
Mg (mmol/l) at Recruitment	0.75 ± 0.028	0.76 ± 0.036	−1.523	0.123
Mg (mmol/l) at diagnosis/control	0.53 ± 0.06	0.69 ± 0.08	−9.52	0.000

Mg = magnesium; mmol/l = Millimole per liter.

which was not significant at recruitment (0.75 ± 0.028 mmo/L vs. 0.76 ± 0.036 mmol/L, P = 0.123) but became significant at the point of diagnosis of pre-eclampsia (0.53 ± 0.06 mmol/L vs. 0.69 ± 0.08 mmol/L, P < 0.001), while Figure 1 illustrate relationship between serum levels of magnesium and the degree of hypertension in pre-eclampsia group. Twenty seven out of 28 patients that developed severe systolic hypertension (≥160 mmHg) had low serum level of magnesium (<0.63 mmol/l) and all the nine patients with mild systolic hypertension (140 - 159 mmHg) had low serum magnesium level at diagnosis, however this was not statistically significant (P > 0.05). Also twelve of 13 patients that developed severe diastolic hypertension (≥110 mmHg) had low serum magnesium level and all the 24 patients with mild diastolic hypertension (90 - 109 mmHg) had low serum magnesium level with Pearson Chi-square value of 1.89 (P > 0.05).

Table 4 presents significant relationship between preterm delivery, low birth weight and need for special care baby unit (SCBU) admission in new born of mothers with low serum magnesium. Twenty four babies (54%) of mothers with low magnesium level were born preterm as compared with 5 babies (17%) of

Table 4. Relationship between serum magnesium level and fetal outcome.

Fetal outcome	Low magnesium level	Normal magnesium level	Pearson Chi-square	P value
Preterm	24	5	10.740[a]	0.001
Term	20	25		
Total	44	30		
low birth weight	17	2	9.554[b]	0.002
Normal birth weight	27	28		
Total	44	30		
Live birth	43	29	0.76	0.782
Still birth	1	1		
Total	44	30		
SCBU Admission	8	1	4.426[c]	0.035
No SCBU Admission	34	28		
Total	42	29		

SCBU = Special care baby unit; a = likelihood ratio (11.43); b = likelihood ratio of (10.90); c = likelihood ratio of 5.20.

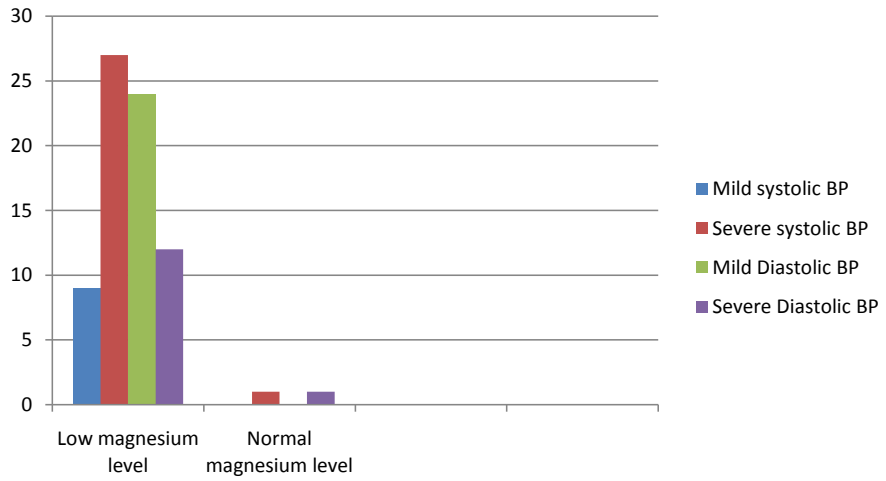

Figure 1. Relationship between serum levels of magnesium and degree of hypertension in pre-eclampsia group. Mild systolic BP = 140 - 159 mmHg; Severe systolic BP ≥ 160 mmHg; Mild diastolic BP 90 - 109 mmHg; Severe diastolic BP ≥ 110 mmHg. The relationships were not statistically significant (P > 0.05).

mothers with normal serum magnesium level (P = 0.001), 17 babies (39%) of mothers with low magnesium level had low birth weight compared with 2 (7%) babies of mothers with normal magnesium level (P = 0.002) and 9 (21%) babies of mothers with low magnesium were admitted into SCBU as compared with a baby (3%) of mothers with normal magnesium level (P = 0.035), however after a multivariate analysis of covariance was performed to control for pre-eclampsia, these differences became insignificant (P = 0.388, 0.808 and 0.695 for preterm delivery, low birth weight and SCBU admission respectively). There was no sig-

nificant relationship between serum level of magnesium and being live or stillbirth (P = 0.782).

4. Discussion

The global incidence of pre-eclampsia ranges between 3% and 18% [4] [5]. Pre-eclampsia is referred to as the "disease of theories" making its prevention and management an ongoing global challenge [6]. Its etiology is yet to be elucidated, some studies have reported that changes in levels of blood metals including magnesium observed in pre-eclamptic patients may contribute to its pathogenesis [7] [8] [9] [10].

The reduced serum magnesium level observed in patient with pre-eclampsia in our study is in agreement with reports from various studies [14] [15] [19]. The study of Adekanle *et al.* [16] also observed a significant low level of serum magnesium in patient with pre-eclampsia. Patients were recruited early in their pregnancy in this study, at a time when they had not developed pre-eclampsia. At recruitment there was no significant difference in the serum magnesium levels in study groups. However, both case and control groups had lower serum magnesium at diagnosis than at recruitment. It is shown in this study that apparently healthy pregnant women also have a decrease in serum magnesium level as pregnancy advances. This is in agreement with previous studies [13] [15] [17] and it is explained to be due to increase in demand for mother and growing fetus, increase renal excretion through increased glomerular filtration rate and haemodilution which is seen more in third trimester of pregnancy.

Pre-eclampsia is diagnosed in a pregnant woman with onset of hypertension (systolic and diastolic blood pressure of ≥140 and 90 mmHg, respectively on two occasions, at least 6 hours apart and urine protein of ≥300 mg in 24 hour urine sample, or a dipstick of ≥2+), this usually occurs above 20 weeks of gestation. Serum magnesium level along with calcium has roles to play in regulation of blood pressure through modification of vascular system [12] [20].

Magnesium is an intracellular ion that is important for cellular metabolism such as muscle contractility and neuronal activity. A proper balance between it and calcium is vital to regulation of blood pressure, while calcium enables the blood vessels to contract, magnesium is required for the vascular relaxation [12]. Magnesium acts as calcium channels blocker by opposing calcium dependent arterial constriction thus antagonizes increase in intracellular calcium concentration leading to vasodilatation [12] [20]. The vasodilating effect of magnesium aside increase in blood flow, has been shown to prevent pre-eclampsia/eclampsia by selectively dilating cerebral vasculature and relieving cerebral spasm associated with pre-eclampsia [12].

The majority of patients in this study were of low parity. This finding is not different from reports from literature [14] [15] [16] [19]. It is known that women who are carrying pregnancy for the first time are more prone and likely to develop pre-eclampsia. However, our study observed further, more women in their second pregnancy developed pre-eclampsia contrary to higher prevalence

reported in nulliparous women. This finding may be linked with the outcome of their first pregnancy which probably was complicated with pre-eclampsia. Women with pre-eclampsia in their first pregnancy have increased risk of having their next pregnancy complicated as such [21]. Also, a woman with increased number of risk factors for developing pre-eclampsia can have the disease even in her subsequent pregnancies especially when inter-pregnancy interval is short (less than 18 months) [21] [22].

Contrary to the belief that women of low socio-economic status have higher risk of developing pre-eclampsia [15] [23], our study observed no significant difference in social classes of the study groups.

Low serum level of magnesium at diagnosis shows significant relationship with preterm delivery which corroborates the finding of Okunade *et al.* [24] However Parizadeh and co-workers found no significant association between low serum magnesium and preterm delivery [25]. Also there was significant relationship between low serum levels of magnesium and low birth weight as well as SCBU admission. These findings may be related to intervention offered to patients with pre-eclampsia, which is the delivery of the fetus, because the only known curative treatment is the delivery of the placenta which is an important cause of preterm delivery leading to low birth weight and need for SCBU admission. Further analysis to control for the effect of pre-eclampsia on preterm delivery, low birth weight and the need for SCBU admission seen in our study shows that these findings were only indirectly related to low serum magnesium levels in mothers who developed pre-eclampsia. While low serum magnesium level is directly linked with the development of pre-eclampsia in this study, preterm delivery, low birth weight and the need for SCBU admission appeared to be a direct effect/complication of pre-eclampsia and its management rather than low serum magnesium.

The perinatal death and stillbirth observed in our study could be due to any causes other than pre-eclampsia or low serum magnesium level. They were observed in both groups. However, it is not out of place to think that the stillbirth observed in case group was due to pre-eclampsia or low serum magnesium levels and that observed in control group was due to other causes. Gibbins *et al.* [26] observed in their study that placental insufficiency is often implicated in stillbirth, especially in women with preeclampsia.

5. Conclusion

Findings from this study revealed that hypomagnesaemia appears to be a complication of pre-eclampsia. Serum levels of magnesium were normal until the development of the disease. Serum level of this biomarker affects maternofetal outcome significantly; however further studies are needed to establish direct relationship or otherwise between hypomagnesaemia and these fetal outcomes.

Limitations

1) Outcome of previous pregnancies was not taken into consideration espe-

cially for multiparous women that developed pre-eclampsia.

2) The nested case-control design used in this study has inherent limitation of inefficiency due to the alignment of each selected control subject to its matched case.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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