

Clinical significance of low serum magnesium in pregnant women attending the University of Benin Teaching Hospital

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Abstract

Objective: Magnesium level is known to decline during pregnancy. A suggested role for magnesium deficiency in conditions like pre-eclampsia and pre-term birth has prompted studies with conflicting evidence. The primary objective of this study was to determine the prevalence of hypomagnesemia in pregnancy, while the secondary objectives attempted to define maternal and fetal outcome due to hypomagnesemia.

Subjects and Methods: A pilot study was performed to determine the mean serum magnesium level for the population of female patients attending the University of Benin Teaching Hospital. The result of the pregnant population in the pilot study was used as a reference for hypomagnesemia in this study. Thereafter, a prospective cohort study of antenatal women recruited in the second trimester and followed-up till delivery and 1 week post-partum was done. Serum magnesium estimates were done with samples collected at recruitment and delivery. The magnesium levels determined at recruitment were used to divide the subjects into two groups of hypomagnesemic and normomagnesemic patients. Their sociodemographic and clinical characteristics were used to generate a database for analysis.

Results: The prevalence of magnesium deficiency was 16.25%. Hypomagnesemia was significantly correlated with the occurrence of pre-eclampsia ($P = 0.011$), leg cramps ($P = 0.000$) and pre-term birth ($P = 0.030$). A logistic regression analysis showed that hypomagnesemia had an Odds ratio of 22 for pre-eclampsia. There was no maternal mortality or early neonatal death.

Conclusion: Pre-eclampsia and pre-term birth are associated with hypomagnesemia in pregnancy; hence, magnesium supplementation or magnesium-rich diet consisting of green leafy vegetables, soy milk and legumes may improve outcome.

Key words: Hypomagnesemia, pre-eclampsia, pre-term birth, University of Benin Teaching Hospital

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Introduction

Magnesium deficiency is not readily detectable as less than 1% of the total body magnesium is found in the plasma and red blood cells;^[1,2] moreover, ionized magnesium assays are non-routine and expensive.^[3] Studies from different regions report a decline in magnesium levels during pregnancy,^[4,5] with values reaching their lowest point at the end of the first trimester.^[4] Olatunbosun *et al.*^[5] in Nigeria found an average serum magnesium level of 1.03 mg/dl (0.87 mEq/L)

in the 8th month of pregnancy, dropping from a non-pregnant average of 1.47 mg/dl (1.24 mEq/L).

The frequency of magnesium deficiency in pregnancy has been variously reported to be between 4.6% and 48%.^[6-8] Gestational magnesium deficiency is able to induce maternal, fetal, neonatal and pediatric consequences, which

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may last throughout life. Evidence from animal studies suggest that hypomagnesemia has marked effects on the processes of parturition, post-partum uterine involution and fetal growth and development.^[9] Many researchers have thus associated lack of magnesium with pre-term birth, increased incidence of leg cramps and constipation during pregnancy,^[10,11] development of pre-eclampsia and fetal growth restriction,^[11] as well as the sudden infant death syndrome.^[10,12] However, the role of magnesium deficiency in adverse pregnancy outcome in our environment has been insufficiently studied.

Many studies showing that magnesium levels decline as pregnancy advances have also reported improvements in magnesium status with supplementation leading to significant improvements in maternal and perinatal outcomes.^[12-16] Magnesium intake plays a crucial role in magnesium status; hence, a positive magnesium balance can be readily achieved through supplementation or consumption of a magnesium-rich diet consisting of green leafy vegetables, legumes and soy milk. Considering the level of poverty and other social deprivations in our environment, it is important to examine the significance of magnesium deficiency in pregnancy vis-à-vis maternal and perinatal health.

The frequency of magnesium deficiency in pregnancy and the role of hypomagnesemia in the development of adverse outcomes in pregnant Nigerian women are evaluated in this study. The findings are expected to direct attention to the burden of hypomagnesemia in pregnancy in our environment.

Materials and Methods

A prospective cohort study of patients attending antenatal care at the University of Benin Teaching Hospital (UBTH), Benin City, was conducted between June and December 2011 with approval of the Institutional Ethics Committee. The subjects were healthy pregnant women with uncomplicated pregnancies at the time of recruitment. Peptic ulcer disease patients placed regularly on magnesium-containing antacids and patients with multiple pregnancy, pre-gestational diabetes, chronic hypertension, chronic renal disease, sickle cell anemia, intrauterine growth restriction, retroviral infection or acquired immune deficiency syndrome were excluded.

A pilot study involving both pregnant and non-pregnant women attending the outpatient clinic in UBTH found the mean serum magnesium level of the pregnant population to be 2.01 ± 0.49 mEq/L. Thus, in this study, hypomagnesemia was defined as serum magnesium level lower than (the mean -2 SD), i.e., 1.03 mEq/L.

The sample size was calculated^[17] based on a previous

study that reported 43.6%^[7] hypomagnesemia in the rural pregnant Indian population. We aimed at detecting a 50% decrease in pregnant Nigerian women in the current study, who were largely urban dwellers. Accepting a statistical power of 80% and confidence interval of 90%, with the level of significance set at 0.05, and up to 10% of the participants expected to drop out, a sample size of 160 patients was obtained.

All patients who met the inclusion criteria were recruited after obtaining an informed written consent. Due counseling on the nature of the study, the quantity of blood to be taken, the details of the subsequent follow-up, and the time of termination of the study for each patient was given. The eligible patients had their venous blood taken for serum magnesium measurement at recruitment. Subsequently, they were followed-up till delivery, when a repeat serum magnesium assay was done, and to discharge from hospital or up to 1 week post-delivery if they stayed longer on admission.

Five milliliters of venous blood was taken from each patient in the antenatal side laboratory at recruitment and subsequently in the labor ward at delivery for assay of serum magnesium. The blood was collected in a 20-ml plain plastic container and immediately transferred to the clinical chemistry laboratory where serum was separated by centrifugation at 2000 rpm following clot retraction. The separated serum was then frozen at -80°C until the time for analysis. Analysis was done by a direct measurement (Calmagite method) in the clinical chemistry laboratory using the kit manufactured by Teco Diagnostics, California, USA, which defines the adult reference range as 1.3-2.5 mEq/L.^[18]

The primary outcome measure was the prevalence of hypomagnesemia in pregnancy. The hypomagnesemic and normomagnesemic groups were also compared for maternal and perinatal clinical outcome. Evaluation of the patients commenced between 24 and 26 weeks gestation. The participants were told to take only the routine hematinics given to them in the clinic. All complications in pregnancy and outcome of delivery were then noted. In particular, the patients were assessed for occurrence of leg cramps in pregnancy; after delivery, the presence of and need to treat uterine cramps were evaluated. Following delivery, the mothers were followed-up in the lying-in ward along with their babies. For the babies admitted to the special care baby unit (SCBU), their follow-up was done in conjunction with the neonatologists.

For all participants, sociodemographic data including age, parity, occupation and level of education of the patient and her spouse, estimated gestational age, as well as relevant clinical parameters were entered into a proforma, and the information was used to generate a database. The social

classes of the women were determined using the Olusanya *et al.*^[19] classification, making use of the educational status of the woman and her husband's occupation.

The subjects were divided into two groups at the end of the study depending on the determination of their serum magnesium levels at recruitment. The study thus comprised: Group A with those who had serum magnesium levels less than two standard deviations (SD) below the mean of the pilot study; and Group B were patients with serum magnesium levels from two SD below the mean to above the mean.

Statistical analysis was done with a personal computer using the SPSS (SPSS Inc., Chicago Ill, 2006) for Windows version 15.0 and GraphPad InStat 3 softwares. Categorical variables were expressed as absolute numbers and percentages and significant differences were determined using the Chi square test or fisher exact test where appropriate, while continuous variables were presented as means with SDs and significant differences being determined with the Student *t* test. The level of significance was set as $P < 0.05$.

Results

The mean serum magnesium level at recruitment was 1.54 ± 0.46 mEq/L, and at delivery it was 1.37 ± 0.45 mEq/L ($P = 0.001$). The prevalence of hypomagnesemia was 8% higher at delivery than at recruitment (25% vs. 16.25%; $P = 0.072$, Table 1). The teenage mothers were 5-times more likely to have hypomagnesemia than women 20 years or older (100% vs. 20.75%, $P = 0.001$; Table 2). The risk of having hypomagnesemia in women of parity four was almost twice that of the nulliparas, but this did not reach statistical significance (30% vs. 16.7%, $P = 0.381$; Table 2). Social Class 4 was almost 5-times more likely to be associated with hypomagnesemia than Social Class 1 (100% vs. 23%, $P = 0.000$; Table 2).

The development of pre-eclampsia was 24% higher in the hypomagnesemic group than in the normomagnesemic group (38.5% vs. 14.9%, $P = 0.011$; Table 3). There were no cases of glucose intolerance in this study. Intrauterine fetal death was not encountered in this study. Symphysiofundal height smaller than date found at the time of delivery was associated with low serum magnesium levels in 5.3% of the subjects compared with 94.7% in the normomagnesemic group. The incidence of pre-term birth was generally low in this study. All the subjects in this study delivered after 34 weeks of gestation. However, pre-term birth was 19% more likely in women with low serum magnesium than in normomagnesemic subjects (30.8% vs. 11.9%, $P = 0.030$; Table 3). Similarly, the occurrence of leg cramps was 44% higher in the hypomagnesemic group than in patients who had normal serum magnesium levels (69% vs. 25%, $P = 0.000$; Table 3). Post-partum uterine cramps were reported

Table 1: Frequency of maternal hypomagnesemia at enrollment and delivery

Time of assay	Gp A (n=26) frequency (%)	Gp B (n=134) frequency (%)	P value
Enrollment	26 (16.25)	134 (83.75)	0.072
Delivery	40 (25)	120 (75)	

Values are given as number (percent), Gp= Group

Table 2: Maternal socio-demographic characteristics in relation to hypomagnesaemia

Characteristic	Frequency (%)		P value
	Gp A (n=26)	Gp B (n=134)	
Age (years)			
<20	4 (15.38)	0 (0)	0.000
20-35	8 (30.77)	82 (61.19)	
>35	14 (53.85)	52 (38.81)	
Parity			
0	8 (30.77)	40 (29.85)	0.455
1-3	15 (57.69)	87 (64.93)	
≥4	3 (11.54)	7 (5.22)	
Body mass index kg/m ²			
Normal	10 (38.47)	36 (26.87)	0.015
Overweight	16 (61.53)	64 (47.76)	
Obese	0 (0)	34 (25.37)	
Social class			
1	18 (69.23)	60 (44.78)	0.000
2	0 (0)	42 (31.34)	
3	0 (0)	32 (23.88)	
4	8 (30.77)	0 (0)	

Gp= Group

Table 3: Adverse maternal outcome

Variable	Gp A (n=26) frequency (%)	Gp B (n=134) frequency (%)	P value
Preeclampsia	10 (38.46)	20 (14.93)	0.011
Leg cramps	18 (69.23)	34 (25.37)	0.000
Preterm birth	8 (30.77)	16 (11.94)	0.030
Postpartum cramps	2 (7.69)	32 (23.88)	0.071

Values are given as number (percent), Gp= Group

by 16% more patients with normal magnesium levels than the hypomagnesemic group (24% vs. 8%, $P = 0.071$; Table 3). There was no maternal mortality in the study population.

A logistic regression analysis was conducted to predict the roles of age, parity, social class and body mass index (BMI) as confounding variables in the determination of pre-eclampsia, pre-term birth and leg cramps by hypomagnesemia. A test of the full model was statistically significant for all three dependent variables (Chi square 43.478, $P = 0.000$, with $df = 5$; Chi square 51.419, $P = 0.000$, with $df = 5$; and Chi square 30.407, $P = 0.000$, with $df = 5$, respectively). Prediction success overall for pre-eclampsia, pre-term birth and leg cramps was 87.8%, 87.1% and 74.8%, respectively. A test of age, parity, social class and BMI to predict

Table 4: Logistic regression tables for preeclampsia, preterm birth and leg cramps

Variable	P value		
	Preeclampsia	Preterm birth	Leg cramps
Age	0.003	0.132	0.000
Parity	0.227	0.006	0.692
BMI	0.001	0.034	0.812
Social class	0.999	0.999	0.998
Hypomagnesaemia	0.000	0.000	0.268
Constant	0.763	0.147	0.000

BMI=Body mass index

Table 5: Adverse perinatal outcome

Characteristic	Gp A (n=26) frequency (%)	Gp B (n=134) frequency (%)	P value
Low birth weight	2 (7.69)	10 (7.46)	1.000
Birth asphyxia	4 (15.38)	16 (11.94)	0.745
SCBU admission	0 (0)	8 (5.97)	0.356

Values are given as number (percent), SCBU=Special care baby unit, Gp=Group

hypomagnesemia showed that only age was statistically significant ($P = 0.042$).

The Wald criterion demonstrated that age, BMI and hypomagnesemia made significant contributions to prediction of pre-eclampsia; age, parity and hypomagnesemia to pre-term birth; and only age contributed significantly to leg cramps, although hypomagnesemia and social class were significant in the “variables not in equation” table ($P = 0.046$ and $P = 0.000$, respectively). Hypomagnesemia was 22-times more likely to contribute to the occurrence of pre-eclampsia than age [Table 4].

Adverse perinatal events were generally few in this study. There were 12 cases of low birth weight babies, with 2 (7.7%) of them born to mothers who had low magnesium levels, but this did not reach statistical significance ($P = 1.000$). Birth asphyxia occurred 3% higher in the 26 babies born to women with hypomagnesemia than 134 babies of normomagnesemic mothers (15% vs. 12%, $P = 0.745$; Table 5). All eight babies admitted to the SCBU for moderate birth asphyxia were born to women in the normomagnesemic group ($P = 0.356$), and were transferred to their mothers within 96 h of admission. There was no early neonatal death; all the babies were either discharged or were alive at the termination of the study 7th day post-partum.

Discussion

This study revealed that 16.25% of our pregnant women had deficiency of magnesium. Young age was associated with magnesium deficiency. Magnesium deficiency was also observed to increase the likelihood of pre-eclampsia and pre-term birth.

The previous pilot study and the prospective design of this study were essential in the validity of our results. The sample size of 160 pregnant women was adequate, although it was smaller than some previous study populations.^[5,7] This was a tertiary hospital-based study in an urban setting; even so, its results may be representative of the general patient population because of the referral status of the hospital. The direct (Calmigite) measurement of serum magnesium used in this study has been shown to have acceptable precision and coefficient of variation.^[17]

Our study confirmed the finding of previous workers that serum magnesium values are reduced during pregnancy.^[10,11] Suggested reasons for the low levels of magnesium in pregnancy include inadequate intake, increased metabolic demand of pregnancy, especially as gestation advance, physiological hemodilution in pregnancy, and increasing parity.^[11,7] Our observed hypomagnesemia prevalence of 16.25% is lower than the figures reported by some investigators working in different populations. Pathak *et al.*^[7] reported an incidence of 43.6% among rural Indian women in a community-based cross-sectional study, and showed that higher parity was associated with higher rates of lack of magnesium. Kumar and co-authors^[8] found a prevalence of 48% in their study, but failed to show any difference between urban and rural participants, nor did they find any association between hypomagnesemia and social class. However, Kapil *et al.*^[6] studied urban Indian dwellers and reported magnesium deficiency in only 4.6% of all pregnant women included in the study. Our finding that teenagers had a higher prevalence of hypomagnesemia has also been reflected in a previous study.^[7] This is likely a result of higher demands of pregnancy at an age characteristic for poor nutrition.

Similar to this study, several investigators in the past have also reported a link between magnesium depletion and hypertension in pregnancy from both animal and human studies.^[20-23] This link is attributed to vascular muscle spasm in the uterus, which is thought to be produced by magnesium deficiency.^[11] Standley *et al.*^[24] in their study demonstrated that all subjects who eventually developed pre-eclampsia showed a decrease in ionized magnesium concentration with increasing gestational age. In this study, there were 10 patients with hypomagnesemia at recruitment who developed pre-eclampsia. Another 10 patients who had normal magnesium levels at recruitment and eventually developed pre-eclampsia were found to have low serum magnesium levels at delivery. The remaining 10 pre-eclamptics had normal serum magnesium levels at delivery; however, their sub-group analysis revealed a decrease from a mean of 1.41 ± 0.41 mEq/L at recruitment to 1.22 ± 0.08 mEq/L at delivery, and this was in agreement with the report of Standley *et al.*^[24] In our study, further logistic regression also showed that hypomagnesemia was 22- and 47-times more likely to result in pre-eclampsia than age or BMI, respectively.

The association of leg cramps with low serum magnesium in this study supports the finding by Dahle *et al.*^[25] in a prospective double-blind, randomized trial that oral magnesium substitution was associated with a significant decrease in leg cramps distress. Similarly, a Cochrane review by Young and Jewell^[26] provided evidence for magnesium lactate or citrate in the treatment of muscle cramps in pregnancy.

The role of magnesium lack in pre-term birth has been documented previously by Shahid *et al.*,^[27] who concluded that this observation can be useful as a marker for pre-term delivery. Our study also found a significant association of low serum magnesium and pre-term birth. A possible mechanism of action of magnesium in pre-term labor attenuation is by competing with intracellular calcium at its binding sites, thereby decreasing muscle contractility and stabilizing the membrane potential. Other authors have reported improved outcome in patients given magnesium supplements, with evidence of reduced pre-term births.^[10,11]

Symphysiofundal height discrepancy during pregnancy, which may be suggestive of intrauterine growth restriction, was not associated with magnesium deficiency in this study. A few researchers have, however, linked poor fetal growth with gestational magnesium deficiency.^[12,14] It is possible that ultrasound diagnosis of intrauterine growth restriction may be a better parameter to analyze with respect to magnesium deficiency than symphysiofundal height measurement.

The literature suggests a possible role for magnesium deficiency in the causation of post-partum uterine cramps.^[11] In contrast, our findings in the present study did not show any correlation between the lack of magnesium and the occurrence of post-partum uterine cramps. This may be so because those studies reporting an association were interventional and involved the use of supplemental magnesium salts without a documentation of deficiency. This makes it difficult to determine what level of deficiency is critical for uterine cramps to be significant. It is also possible that other factors may be involved in the determination of what the patient considers to be significant uterine cramps necessitating reporting, such as previous experience during breastfeeding, parity, age, mode of delivery, and emotional state.

With respect to perinatal outcome, the findings of this study did not show any relationship between the lack of magnesium and the rates of low birth weight, birth asphyxia, or SCBU admission, contrary to the reports of some other workers.^[9,12-14] However, the findings in the present study are not surprising considering the fact that most babies were delivered after the 34th week of gestation and therefore, perinatal outcome was expected to be favorable.

A factor in the pregnant woman that may suggest lack of magnesium was shown in this study to be young age.

The relationship of a negative magnesium balance to the risk of pre-eclampsia and pre-term delivery was confirmed in this study. It is noteworthy that the toll on maternal health and perinatal indices from a combination of pre-eclampsia and pre-term delivery remains significant in our environment.

To reduce the high prevalence of magnesium deficiency in pregnancy, magnesium balance needs to be improved. This can be attained through nutritional counseling. We recommend that the average diet in this environment be evaluated in a nutritional survey to determine the content of magnesium. The diet with the highest amounts of magnesium can be advised for women who are at risk of magnesium deficiency. We also recommend interventional studies to prove the efficacy or otherwise of dietary counseling or magnesium substitution in pregnancy involving these high-risk groups in a case-control study.

In conclusion, discouraging teenage pregnancy and improving the socio-economic status of every woman through education and social emancipation will directly translate to giving them the means to better their magnesium balance in or out of pregnancy. Magnesium supplementation or consumption of a magnesium-rich diet should be recommended in pregnancy.

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