SERUM MAGNESIUM LEVELS IN PREECLAMPSIA AND IN NORMAL PREGNANCY IN A TERTIARY HOSPITAL

A RESEARCH DISSERTATION SUBMITTED TO THE NATIONAL POSTGRADUATE MEDICAL COLLEGE OF NIGERIA IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE PART II FELLOWSHIP EXAMINATION OF THE FACULTY OF OBSTETRICS AND GYNAECOLOGY

BY

DR. MONDAY UKWEDUAN IKHILE

(MBBS)

2018

Error! Objects cannot be created from editing field codes.

Error! Objects cannot be created from editing field codes.

Error! Objects cannot be created from editing field codes.

Error! Objects cannot be created from editing field codes.

DEDICATION

This book is dedicated to Almighty God, my wife Fehintola who showed immense understanding during the period of study and my children David and Emmanuella for their love and to all women everywhere in the world.

ACKNOWLEDGEMENT

I wish to express my profound gratitude to my supervisors Prof. A.O.Sule-Odu, Dr. T.O. Shorunmu and Dr. O.O. Olawale for their enormous encouragement, guidance and support during the period of this study.

I also appreciate the support of Prof. O.L.Odusoga, the Head of Department of Obstetrics and Gynaecology OOUTH, Sagamu who provided invaluable fatherly advice and direction.

Thanks to other consultants for their support and constructive criticism, fellow residents and house officers who worked tirelessly in ensuring completion of data collection.

ABBREVIATIONS AND SYMBOLS

LMP	Last menstrual Period
EDD	Expected Date of Delivery
EGA	Estimated Gestational Age
BMI	Body Mass Index
ATP	Adenosine Triphosphate
LBW	Low Birth Weight
SGA	Small for Gestational Age
OOUTH	Olabisi Onabanjo University Teaching Hospital
WHO	World Health Organization
ISSHP	International Society for Study of Hypertension in Pregnancy
Mg	Magnesium
Ca	Calcium
SPSS	Statistical Package for the Social Sciences
L	Litre

ml	Millilitre
mg	Milligramme
mEq	Milliequivalent
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
μL	Microlitre

TABLE OF CONTENTS

ABSTRACT

BACKGROUND OF STUDY: Hypertensive disorders of pregnancy is a significant cause of maternal and fetal morbidity and mortality across the world and especially in developing countries.

Several theories have been proposed for the aetiopathogenesis of preeclampsia with the central pathology being defective trophoblastic invasion of the spiral arterioles. While some studies show that hypomagnesaemia is associated with the aetiopathogenesis of preeclampsia and adverse fetal outcome including preterm birth, other studies however, refute this.

AIM AND OBJECTIVES: The study was aimed at comparing serum magnesium levels in preeclamptic pregnancies and normal pregnancies with evaluation of fetal outcome at the Olabisi Onabanjo University Teaching Hospital

SUBJECTS AND METHODS: This was a comparative cross-sectional analytical study involving women with preeclampsia and normotensive pregnant women. One hundred women with clinically diagnosed preeclampsia were recruited as the study group while same number of

normotensive pregnant women, matched for age, parity and gestational age were recruited consecutively to serve as the control group. Blood samples were collected at delivery and assayed for serum magnesium and comparison made. Socioeconomic differences between women with hypomagnesemia and normal magnesium was assessed. The relationship between fetal outcome and serum magnesium level was determined by assessing the birth weight and need for neonatal admission in women with low and normal magnesium. Data was analyzed using SPSS version 23.

RESULTS: Mean serum magnesium level was 0.63±0.07mmol/L and 0.89±0.14mmol/L (p=0.001) in preclamptic and normotensive women respectively. Socioeconomic status did not significantly correlate with low or normal magnesium in the study population (p=0.0685). Women with hypomagnesemia had more babies with low birth weight 16.9% vs 2.7% (p=0.001) and more need for neonatal intensive care unit admission (p=0.004).

CONCLUSION: The statistical difference in serum magnesium between normotensive and preeclamptic women shows that magnesium may play a role in the aetiology of preeclampsia and its severity and thus a recommendation for magnesium supplementation for pregnant women may be made.

STRENGHTS AND LIMITATIONS: The number of variables matched and the sample size increased the power of the study, however generalization of result to the general pregnant population may have been affected due to it being a single centre study in a tertiary hospital.

KEY WORDS:

Preeclampsia, Normal Pregnancy, Serum magnesium, Fetal outcome

INTRODUCTION

Hypertension is a common medical problem encountered in pregnancy and it is an important leading cause of maternal and fetal morbidity and mortality accounting for a quarter of all antenatal admissions[1]. The fetus and neonate are also at an increased risk of preterm delivery, intrauterine growth restriction, placenta abruption, still birth and early neonatal death[2].

Hypertension during pregnancy can be viewed as a continuum. On one end is chronic hypertension and on the other end is preeclampsia with gestational hypertension between these two extremes[1,3,4]. Preeclampsia is noted to account for up to 70% of hypertensive disorders of pregnancy while all other hypertensive disorders of pregnancy account for just 30%[5]. Preeclampsia is defined as the onset of hypertension, proteinuria after 20 weeks in a previously normotensive woman[6]. It is specific to human pregnancy. Preeclampsia is known to affect 5-7% of pregnancies in the United States[7], while globally, the incidence rate stands at 3-10%[8]. In a Nigerian study, hypertensive disorder of pregnancy was known to complicate 3.7% of all deliveries[9]. A systolic and diastolic blood pressure of $\geq$ 140 and 90 mmHg respectively, on two

occasions, (at least 4 hours apart) and proteinuria (protein excretion of ≥ 300mg in a 24hr urine collection, or a dipstick of ≥ 2+) characterizes preeclampsia[10]. Prevention has so far been disappointing while treatment remains a daunting task[11].

Studies have shown that there is a relationship between worsening of hypertensive complications and the change in concentration of various chemicals in the serum of the mother[12].

With pregnancy there is a depletion of nutritional reserves of essential nutrients such as vitamin B complexes, calcium and magnesium as a result of increased utilization[13,14]. The recommended dietary allowance of magnesium in an adult is 300-360mg/day with daily requirement increased during pregnancy and lactation to 360-400mg daily. Despite increased utilization, magnesium intake during pregnancy has been reported to be below the recommended dietary allowance[12]. Magnesium is a major intracellular divalent cation and plays an essential physiologic role in many bodily functions. It is essential for the synthesis of proteins and nucleic acids and also serves as an important co-factor in many enzyme systems and transporters such as guanosine triphosphate, phospholipase C, adenylate cyclase and guanylate cyclase including 300 other enzyme systems[15]. Magnesium exerts a significant effect on the cardiovascular system. It forms a key complex with adenosine triphosphate which is an important membrane stabilizing agent that is required for the structural integrity of numerous intracellular proteins and nucleic acids[15,16]. Also subserves, are other biologic processes such as protein synthesis, cell replication and energy metabolism[15,16,17]. Magnesium, a cofactor for many enzyme systems (e.g sodium potassium ATPase) and involved in peripheral vasodilatation[15,16,17], has been shown to be significantly reduced in the serum of preeclamptic patients[18,19,20,21] with most of these data emanating from outside Sub-saha ran Africa. This has led to several conclusions that

hypomagnesemia is implicated in the aetiopathogenesis of preeclampsia[20,21]. Some of these studies were however not adequately matched to further improve the significance of the association between hypomagnesaemia and preeclampsia[18,19]. Some studies have shown just a marginal difference while some showed no such difference in the level of magnesium balance between preeclamptic and normal pregnancy[22,23]. There is a gradual decrease in mean serum magnesium levels with increasing period of gestation which has led some researchers to postulate that checking the levels of magnesium should be considered as a predictive factor for preeclampsia during the first evaluation of pregnancy[24]. In a recent study, maternal hypomagnesaemia was associated with the development of adverse fetal outcome in pregnant Nigerian women such as preterm birth[25] with its attendant complications. This observation suggests that preeclampsia in the presence of hypomagnesaemia is a disease with increased fetal risks[26].

Magnesium supplementation has been studied on the relationship between serum magnesium and preeclampsia and the success of magnesium sulphate administration in the treatment and prophylaxis of eclampsia and preeclampsia[14,16]. Some authors have reported improved outcome in patients given magnesium supplements, with evidence of reduced preterm births[16].

The possible role of magnesium deficiency in the genesis of preeclampsia and preterm labour therefore begs the question; is the data we have, sufficient enough to change routine management plan and totally accept magnesium supplementation? Seeing that the complications of preeclampsia are highly prevalent in Sub-saharan Africa where poverty, social deprivation and

lack of access to essential health care services are more compared to that seen in developed nations[8].

AIM AND OBJECTIVES

AIM

Assess serum levels of magnesium in preeclamptic pregnancies compared to normal pregnancies and associated fetal outcome in a tertiary hospital in Southwestern Nigeria.

OBJECTIVES

1. Compare mean serum magnesium levels in women with preeclampsia and in normal pregnancy.

2. Assess influence of sociodemographic characteristics on serum magnesium levels in both sets of patients.
3. Evaluate the relationship between magnesium levels and fetal outcome in both sets of patients.

STUDY HYPOTHESIS

Null hypothesis:

There is no statistically significant difference in the level of serum magnesium between normal pregnant women and women with preeclampsia.

LITERATURE REVIEW

SEARCH STRATEGY

Objective of the literature search was to identify and critically analyze articles that addressed the relationship of hypomagnesaemia to the aetiopathogenesis of preeclampsia and the corresponding fetal outcome.

The literature search was carried out using MEDLINE, PUBMED, PUBMED CENTRAL, GOOGLE SCHOLAR and the reference list of relevant and eligible studies. Search words included hypomagnesaemia in pregnancy, magnesium levels in preeclampsia, relationship between magnesium levels and pathogenesis of preeclampsia with key words being magnesium, preeclampsia, prevention and aetiopathogenesis.

Eighty nine articles were identified and seventy two selected for review that matched the criteria for inclusion. Studies were included; if they reported on magnesium alone or in combination with other trace elements and preeclamptic women.

BACKGROUND

Preeclampsia, which is a syndrome that is characterized by the onset of hypertension and proteinuria in the second half of pregnancy has been and still is a major cause of maternal and perinatal morbidity and mortality especially in low and middle income countries with an estimated fifty thousand maternal deaths annually[27]. Maternal mortality estimates, suggests that about 10-15% of maternal deaths in developing countries are associated with hypertension in pregnancy while in Latin America and the Caribbeans it is about 25% of maternal deaths[27,28]. The economic impact of hypertensive disorders in pregnancy is clearly evident such that in high income countries such as the United States, hospital admission has risen from 67.2% to 81.4% between 1998 and 2006[29]. A Brazilian multicentre study showed that there was an increase in the risk of severe complications to as much as 3-25 times in women with hypertensive disorder of pregnancy compared to women without hypertension[30].

Despite lack of complete understanding of preeclampsia, it had been recognized and described many centuries ago by Hippocrates that headaches, convulsion and drowsiness were ominous signs associated with pregnancy. Ancient civilizations of China, Egypt and

India had all recognized and described this disease as well as the bleak maternal and fetal prognosis it portends[31].

The placenta is central to the occurrence of preeclampsia[32]. It is associated with defective trophoblastic invasion of the maternal uterine spiral arteries which leads to reduced oxygenation at the uteroplacental bed. Two waves of normal trophoblastic invasion occur in the first and second trimesters respectively. In the first trimester, the proliferating trophoblast invades the decidual segment of maternal spiral arteries while early in the second trimester the second wave occurs with further extension into the myometrial segments of the spiral arteries. This converts the uterine spiral arteries from a low capacitance high resistance vessels to high capacitance low resistance vessels with subsequent increased uteroplacental blood flow[1,33]. In preeclampsia, this normal trophoblastic invasion does not happen leading to decreased placenta perfusion with release of toxic substances from the hypoperfused placenta which becomes responsible for the wide spread endothelial damage.

Some other theories implicated in the aetiology of preeclampsia include immunologic theory, prostacycline/thromboxane A2 ratio imbalance, oxidative theory and abnormal maternal serum concentration of certain metals[1,2,12,19].

Alteration in the maternal serum level of magnesium has been implicated in the aetiology and possibly severity of preeclampsia[16]. This has led several authors in various studies done to suggest a role for supplemental magnesium in the prevention of hypertensive disorder of pregnancy[34]. This assertion however, was not supported by Adewolu in a pilot study carried out in Nigeria which indicated that apart from the

elevation of the electrolyte sodium in preeclamptic women, the levels of both serum calcium and magnesium were within normal reference values[35].

MAGNESIUM METABOLISM

Magnesium is the major intracellular divalent cation and plays an essential physiologic role in many bodily functions. It is essential for the synthesis of proteins and nucleic acids and also serves as an important co-factor in many enzyme systems and transporters such as guanosine triphosphate, phospholipase C, adenylate cyclase and guanylate cyclase including 300 other enzyme systems. Magnesium exerts a significant effect on the cardiovascular system. It forms a key complex with adenosine triphosphate which is an important membrane stabilizing agent that is required for the structural integrity of numerous intracellular proteins and nucleic acids. It also subserves other biologic processes such as protein synthesis, cell replication and energy metabolism[36,37]. Magnesium is intimately involved in nerve conduction, muscle contraction, potassium transport and calcium channels[38]. Magnesium turnover in the bone is so low such that short-term requirements are met by a balance of gastrointestinal absorption and renal excretion. As a result, the kidney plays a central role in magnesium homeostasis[39]. Factors that regulate and modulate renal excretion of magnesium can have profound effects on magnesium balance.

The normal adult body contains approximately 1000 mmol of magnesium (22-26g) in a 70kg adult. It is predominantly distributed in the bone with 60% while 30% of this is

exchangeable and functioning as a reservoir to maintain serum concentration. About 20% is found in skeletal muscles and 19% in other soft tissues. Only about 1% is found in the serum and interstitial compartments[40]. Approximately 30% of serum magnesium is protein bound; 15% is complexed and the major portion of 55% is in the ionized form and this is maintained within narrow limits. Normal serum magnesium is within the range of 0.75-1.0mmol/L[41].

The recommended daily allowance for magnesium in adults is about 300 to 360 mg/day but with daily requirements increasing during pregnancy, lactation and debilitating illnesses. The average intake of magnesium in developed countries has been found to be less than the recommended daily average[42]. The intake of magnesium is directly related to its concentration in food sources and drinking water. Food rich in magnesium include green leafy vegetables, cereal, grains, nuts, banana and legumes. Intermediate sources of magnesium include fruits, meat, fish and chocolates while poor sources of magnesium intake include dairy products[42].

Magnesium from food sources are majorly absorbed in the jejunum and ileum. About 30-40% of intake is absorbed on the average with the degree of absorption inversely related to the level of intake. Eleven percent (11%) absorbed at high intake and about 65% absorbed at low intake[43]. The factors that control absorption are not well understood however, studies suggest a role for parathyroid hormone and vitamin D[37]. 1,25-dihydroxy-vitamin D3 may mildly increase the intestinal absorption of magnesium.

The kidney plays a major role in magnesium homeostasis and the maintenance of serum magnesium concentrations. The urinary excretion of magnesium, normally matches intestinal absorption. Approximately 95% of ultrafiltrable magnesium is absorbed with

majority of absorption taking place in the cortical thick ascending limb of the loop of Henle. Hypomagnesaemia is associated with an increase in magnesium excretion due to an increase in the filtered load and reduced absorption in the thick ascending limb[44].

Assaying for magnesium commonly uses serum magnesium concentrations because as at present, there is no simple, rapid and accurate laboratory test to indicate the total body magnesium status. However, total serum magnesium estimation may be influenced by changes in serum protein concentrations without necessarily affecting the ionized fraction or total body stores[42,45].

Magnesium is believed to play a role in the regulation of blood pressure by modulating vascular tone reactivity and total peripheral resistance. Increased extracellular magnesium concentration results in vasodilatation and decreased concentration of vasoconstrictive agonists. However, lower magnesium concentration results in vasoconstriction, increased concentration of vasoconstrictive agonists and subsequently increased peripheral resistance[46].

Hypomagnesemia or magnesium deficiency are words used interchangeably to depict reduced levels of magnesium. Magnesium depletion has been noted to increase atherogenesis by increasing total cholesterol and triglyceride levels and by decreasing high density lipoprotein levels. Hypomagnesemia also increase hypertensive tendencies[39].

MAGNESIUM IN PREGNANCY AND PREECLAPMSIA

Normally, the body tends to maintain magnesium balance within narrow limits, however in pregnant women, magnesium levels tend to be lower than in the non-pregnant population even when there is no disease condition with a further lowering with preeclampsia[19,20,47]. This has led to numerous suggestions that magnesium may play a role in the aetiology of preeclampsia thus the need for magnesium supplementation for the prevention of preeclampsia[48]. On the other hand, some studies have found no difference in the serum magnesium of normal pregnant women and women with preeclampsia[49] and thus have no causative role to play in the genesis of preeclampsia[50]. Other studies have also shown that though there may be a difference, it was a non-significant difference between preeclamptics and normotensives[51].

The earliest reports of serum magnesium levels in pregnancy were by Krebs and Briggs in the 1920s where they reported a range of 1.7-2.2mEq/L among seventeen women in their eight to fortieth weeks of pregnancy[52]. A study done by Bogart and Plass noted that the average magnesium value of 2.0mEq/L at the beginning of pregnancy fell to an average of 1.7mEq/L at the end of pregnancy. This was not so in non-pregnant women[47]. Stanton and Lowenstein also found out that there was a significant reduction in blood magnesium as pregnancy advanced in pregnant women[53]. Olatunbosun et al reported a non-pregnancy average of 1.47mg/dl that dropped to an average of 1.03mg/dl at about the eight month of normal pregnancy. Attributable reasons include the relative haemodilution of pregnancy, increased utilization of magnesium by the growing fetus, deficient dietary intake, poor intestinal absorption and excessive urinary loss[54].

The possibility therefore arises that a negative magnesium balance may be responsible for some of the pathophysiologic changes seen during pregnancy especially cardiovascular abnormality. There is mounting evidence that compromised magnesium balance may be involved in several pregnancy associated disorders including preeclampsia and preterm delivery[55,56].

Proposed explanations for the pathophysiologic effect of magnesium in hypertensive disease have been espoused to include intracellular imbalance between calcium and magnesium due to relatively low magnesium which thus, results in increased vascular tone in the smooth muscles of the arteries and therefore increased blood pressure. Also magnesium deficiency causes a dysregulation of the Na-Mg exchanger, resulting in higher intracellular sodium and higher blood pressure. Thirdly magnesium deficiency causes insulin resistance which leads to hyperinsulinaemia, thereby resulting in hypertension[57].

Studies in sheep with pregnancy induced hypertension revealed that there was a demonstrable higher arterial pressure and lower fetal weight in sheep that has been fed on magnesium deficient diet[58.]

Kanchapan S et al compared the serum levels of magnesium in preeclamptic and in normal pregnancy. The serum magnesium concentration in preeclamptic was significantly lower than in normal pregnant women (0.77±0.8mmol/L vs. 0.85±0.09mmol/L, $P < 0.001$). They therefore asserted that this finding supported the hypothesis that hypomagnesemia is a possible aetiology of preeclampsia[59].

Standley and associates in a study on serum ionized magnesium levels in normal and preeclamptic gestation noted that in 22 normal pregnant women, both serum ionized and total magnesium levels decreased significantly with increasing gestational age. Nine of the thirty-one subjects developed preeclampsia by term and serum total magnesium levels decreased significantly by the second trimester in these women compared to those of normal pregnant women[60].

Borecki and associates in investigating the relationship between preeclampsia and iodine levels and magnesium concentration, obtained blood from 24 preeclamptic and 16 healthy pregnant women. Serum magnesium concentration in maternal blood was lower in patients with severe preeclampsia compared to normal pregnant women[61].

Vahidrosari F et al in Iran compared serum magnesium and calcium between preeclamptic and normal pregnant women. Results showed that serum magnesium levels in the preeclamptic women were significantly lower than those in women with normal pregnancy. They concluded that serum magnesium levels in preeclampsia is lower than that in normal pregnant women and thus supporting the hypothesis of the role of magnesium deficiency in the pathophysiology of preeclampsia and suggests the usefulness of its assessment in the early diagnosis of the disorder[62].

Al-Rubaye and associates in Iraq sought to demonstrate the pattern of minerals during preeclampsia with respect to normal pregnancy. A case control study of 60 patients per group was carried out. Results showed that corrected serum calcium and magnesium were significantly reduced in preeclamptics with a significantly high elevation of the ratio between ionized calcium to ionized magnesium. They therefore concluded that preeclamptics have

altered mineral status when compared with healthy pregnant women that are matched for chronological age and gestational age[63].

Jafrin and associates in a study in Mymensingh medical college in Bangladesh divided 108 women into normal pregnancy, mild preeclampsia and severe preeclampsia. The mean serum magnesium level in women with mild as well as severe preeclampsia was significantly decreased in comparison to that of normal pregnant women. Also a significant difference was seen in serum magnesium between severe preeclamptics and mild preeclamptics. They concluded that serum levels of magnesium during pregnancy might be a possible contributor in the aetiology of preeclampsia and supplementation of this element as diet or drugs may be of value to prevent preeclampsia[21].

Tavana Z et al in Iran followed up women from early pregnancy. They found out that the initial level of magnesium in women with preeclampsia was not only significantly less than the control group, but also that the secondary level was low when the diagnosis was confirmed. They concluded that there was a gradual decline in mean serum magnesium levels with increasing period of gestation in women with preeclampsia and therefore suggested that checking the level of magnesium should be considered as a predictive factor for preeclampsia in the first evaluation of pregnancy[24.]

A critical review of the above studies notes its Caucasian leanings with questions as to its applicability in the context of sub-Saharan Africa. The number of cases and controls included in the studies also raises questions on the generalization of results in the general obstetric population. Of note however, is the knowledge that serum magnesium assay may be of help in predicting if a pregnant woman would go on to have preeclampsia[24], therefore

adding to the armamentarium of screening tools available to the clinician in predicting this disease. That being the case, at what cut-off point of low magnesium levels would define patients that would be at risk of preeclampsia and thus, benefit from intervention such as dietary supplementation?

Majority of studies on magnesium balance in pregnancy has been outside of Africa. However a study was conducted in Sudan, with the assessment of serum mineral amongst Sudanese pregnant women. In this study, it was noted that mean serum magnesium and calcium were significantly lower in preeclamptic pregnant women, thus concluding that serum magnesium might be a possible contributor in the aetiology of preeclampsia[19].

In Ghana, West Africa, a case control study of 380 pregnant women was carried out by Ephraim and associates. They found out that serum magnesium was significantly lower in women with hypertensive disorders in pregnancy compared with normal pregnant women and also suggested that mineral supplementation during the antenatal period may significantly influence the occurrence of hypertensive disorders in pregnancy[34].

In Nigeria, Enaruna and associates in a study on the clinical significance of low serum magnesium in pregnant women attending the University of Benin Teaching hospital found out that hypomagnesemia was significantly correlated with the occurrence of preeclampsia and preterm birth with a logistic regression analysis showing that hypomagnesemia had an Odds ratio of 22 for preeclampsia. They concluded that magnesium supplementation or magnesium-rich diet consisting of green leafy vegetables, nuts, soy milk and legumes may improve pregnancy outcome[25].

Adekanle et al in a study in Southwestern Nigerian carried out a multicenter prospective case-control study comparing serum magnesium levels in preeclampsia and in normal pregnancy in tertiary hospitals. Their result showed that, preeclamptic women had lower serum magnesium levels compared to the normal pregnant women[18].

Igberase and associates in a study in Benin-City Nigeria, noted there to be a statistically significant difference in serum magnesium between normal and preeclamptic pregnancies and also found out that serum magnesium decreases with increasing gestational age, thus concluding that magnesium may be a marker for preeclampsia[64].

These African and Nigerian studies highlighted the association between magnesium levels and preeclampsia which is applicable to the proposed study however; the controls were not stringently matched with cases with the knowledge that parity and age are independent risk factors for preeclampsia. Questions on the level of decline in serum magnesium associated with preeclampsia and the transition to severe preeclampsia needs to be answered.

Despite the multiplicity of studies showing a significant reduction in serum magnesium in preclamptics, some studies however have a contrary view. Kanagal and associates in coastal India in a study of 60 preeclamptics and same number of controls found out that the serum levels of magnesium only showed a marginal difference between both groups (1.43±0.55mg/dl vs. 1.57±0.72mg/dl P=0.257)[22].

Golmohammad and associates in Iran measured serum magnesium and other mineral in 52 preeclamptics and same number of controls. Results showed that there was no

significant difference in magnesium levels between the two groups and thus concluded that it has no role in the pathogenesis of preeclampsia[51].

Kumru S et al compared trace elements including magnesium in preeclamptic and healthy pregnant women. Subjects and controls were 30 apiece. Results revealed that magnesium concentration showed non-significant difference between the two groups[65].

Puthumapol C et al also noted that there was no difference in the serum magnesium between normal pregnant women and both mild and severe preeclampsia[66]. Magri et al. did not find a relationship between serum levels of calcium, magnesium, zinc and gestational hypertension and therefore proposed that these elements might not clinically participate in the pathogenesis of gestational hypertension[67].

In Nigeria, Idogun et al. found that there was no significant difference between the plasma magnesium in preeclamptic and normal pregnancy (1.5±0.28 vs. 1.55±0.32mg/dl, P = 0.28)[68].

Thus there is a contrast of opinion in the literature on the role of hypomagnesaemia in the aetiopathogenesis of preeclampsia, thus casting doubt on the utilization of magnesium supplementation in preventing this disease. Would the methodology, such as the study done by Idogun et al that utilized only 11 cases to reach this conclusion have a role to play in this contrasting opinion? Could poor dietary consumption of magnesium rich diet as seen in the study from southern India have a bearing on the failure to elicit a significant difference?

Systemically, magnesium lowers blood pressure and alters peripheral vascular resistance. Magnesium sulphate is being used for the treatment of seizure and prophylaxis in

women with eclampsia and preeclampsia worldwide. Magnesium may act by opposing calcium-dependent arterial constriction and may also antagonize the increase in intracellular calcium concentration[34,69].

Magnesium supplementation has been studied following conclusions from several studies on the relationship between serum magnesium and preeclampsia and the success of magnesium sulphate in the treatment and prophylaxis of eclampsia and preeclampsia. Some authors have reported improved outcome in patients given magnesium supplements, with evidence of reduced preterm births[70,71].

A meta-analysis of randomized clinical trials on the effect of magnesium sulphate supplementation on blood pressure concluded that there was a detectable dose dependent blood pressure reduction from magnesium supplementation[72].

The World Health Organization in its recommendation for the prevention and treatment of preeclampsia and eclampsia submitted that magnesium supplementation is not recommended for the prevention of preeclampsia but for the prevention of eclampsia in women with severe preeclampsia in preference to other anticonvulsants[73,74].

A Cochrane review selected randomized and quasi-randomized trials of dietary magnesium supplementation during pregnancy. The objective of the review was to assess the effects of magnesium supplementation during pregnancy on maternal, neonatal and paediatric outcomes. Seven trials were included involving 2689 women. There was no apparent effect of magnesium supplementation on maternal systolic or diastolic blood pressure during pregnancy. There was no difference in the risk of preeclampsia or pregnancy induced

hypertension between the magnesium and placebo groups. However, there was a reduced risk of low birth weight and of smaller than gestational age babies compared with placebo. The review thus concluded that there was need for more high quality evidence for the benefit of magnesium supplementation in pregnancy[48].

JUSTIFICATION

Fetal and maternal risks are increased with hypertensive disorders in pregnancy. Preeclamptic pregnancies are a significant contributor to maternal and fetal mortality and morbidity here in Nigeria and the world at large[3]. Seventeen point four percent (17.4%) of babies born to women with preeclampsia die with a perinatal mortality rate (PMR) of 174/1000 births[26] and this was noted to worsen with increasing blood pressure.

Hypomagnesaemia has been observed in preeclamptic pregnancies and magnesium levels have been noted to have been significantly reduced in early pregnancy even before the clinical diagnosis of preeclampsia is made[24]. This has led to the postulation that hypomagnesaemia could be an aetiology of preeclampsia[15]. Preeclampsia with hypomagnesaemia has been associated with adverse fetal outcome including preterm birth[25].

Most of the data implicating hypomagnesemia in the aetiopathogenesis of adverse maternal and perinatal outcome have come from outside Sub-Saharan Africa. Furthermore, there is paucity of studies that refute this claim in Nigeria and this served as an attraction. Not many studies focus on the role of magnesium in the genesis of preeclampsia.

Studies that have supported the association between hypomagnesaemia and preeclampsia have not matched cases and controls or were inadequately matched[18,19,34]. This study matched cases and controls for both chronological age and parity which on their own are risk factors for preeclampsia. Participants were also matched for gestational age as magnesium levels even outside of preeclampsia reduces with increasing gestational age.

Furthermore, the sample size of this study, was calculated to adequately power this study to detect or disprove significant association between hypomagnesaemia and preeclampsia as against the low sample sizes used in studies that showed no significant association[35,67].

There has been no study in Sagamu to validate or refute these findings, therefore this study on magnesium levels in preeclamptic women and in normal pregnancy was undertaken to further support other researches going on in various centres of the world on the possible association between variations in serum magnesium and aetiology of preeclampsia. This would

contribute to a better understanding and improvement in the prevention of this condition especially so in Sub-Saharan Africa where late diagnosis, inadequate clinical management and poor health seeking behaviour of the populace increase the morbidity and mortality associated with this disease. This study would further stimulate interventional research into magnesium supplementation for the prevention of preeclampsia especially in high risk population such as primigravid women. This study will add to the body of knowledge of this subject matter and may inform professional decision making.

With preventive medicine being advocated as the key to improving the health status of our women, this study would further inspire work in the assay of magnesium levels in early pregnancy to serve as a predictor and prognosticator of preeclampsia.

METHODOLOGY

STUDY SETTING

The study was carried out in the antenatal and labour wards of the department of Obstetrics and Gynaecology of the Olabisi Onabanjo University Teaching Hospital (OOUTH). This hospital is located in Sagamu, Ogun State Southwestern Nigeria. It is the only government teaching hospital in the state and is the main referral center for private, primary and secondary

health care facilities in Ogun State. Due to its close proximity to Lagos State, OOUTH also receives patients from parts of Lagos State, the commercial capital of Nigeria. Sagamu, Ogun state, Nigeria is in the South-West geopolitical region of Nigeria with a land mass of 614km^2 and a population of 253,412 according to the 2006 census. The southwestern part of Nigeria is populated mainly by people of the Yoruba ethnic group and they account for majority of the patient population of OOUTH. Attendance in the hospital is unrestricted and hence the patients are of mixed socioeconomic and religious background. Obstetric services are provided for both high and low risk pregnant women by nurses/midwives, resident doctors undergoing specialist obstetric training and consultant obstetricians.

STUDY POPULATION

Women whose pregnancies were complicated by proteinuric hypertension and who have been admitted into the obstetric ward for vaginal or abdominal delivery during the study period and also normotensive pregnant women.

STUDY DESIGN

This was a comparative cross-sectional analytical study that involved women with normal pregnancy and those with preeclampsia. It determined the serum magnesium levels at delivery and fetal outcome in preeclamptic women, and then compared this with normotensive pregnant controls. Selection of cases was by non-probability purposive selection of all pregnant women diagnosed with preeclampsia within the time frame for the study until the sample size was met. The controls were selected by purposively matching them to the selected cases as they

presented to the antenatal and labour ward. This was done by selecting every first woman who presented for delivery after a case had been selected and who matched for chronological age (±2 years), parity and gestational age. Limitation to this study design was the time interval to adequately recruit matched controls that satisfied in fine details the three variables needed to match.

SAMPLE SIZE DETERMINATION

The minimum sample size required for the study was estimated using the formula for the comparison of two independent means.

$N = (Z1-\alpha/2 + Z1-\beta)^2 \, 2\sigma^2 / d^2$

N = Minimum sample size for each study group.

$Z1-\alpha/2$ = Standard normal deviate corresponding to the probability of type 1 error (α) at 5% - 1.96

$Z1-\beta$ = Standard normal deviate corresponding to the probability of making a type 2 error (β) of 10% power at 90% - 1.28

σ = Standard deviation of the outcome variable

d = Effect size (the smallest difference in means that it would be clinically meaningful to detect)

Using the mean value for serum magnesium amongst preeclamptic pregnancies in a study done in SouthWest Nigeria at 0.58±0.17 mmol/L[18]. Also allowing the effect size to be 0.1mmol/L.

Therefore;

$N= (1.96 + 1.28)^2 \times 2 \times (0.17)^2 / 0.1^2$

$= 61.$

However to increase the power of the study and allow for attrition, a sample size of 100 patients per group was used.

INCLUSION CRITERIA

Pregnant women with clinically diagnosed preeclampsia and admitted into the antenatal ward or the labour ward for vaginal or abdominal delivery with a singleton gestation greater or equaling 28 weeks were approached, counselled and recruited following an informed consent. Normal healthy pregnant women with gestational age greater or equaling 28 weeks were recruited also.

EXCLUSION CRITERIA

Women with essential hypertension, chronic renal disease, liver disease, sickle cell anaemia, diabetes mellitus, peptic ulcer disease patients on magnesium containing antacids, retroviral disease patients were excluded. In addition women with multiple gestation, on dietary magnesium supplementation found in some prenatal multivitamin combinations, who smoke cigarette or consume alcohol were also excluded. Also patients who refuse to participate in the study were excluded though this did not in any way affect their subsequent management.

STUDY PROCEDURE

When the patient who is preeclamptic was admitted into the ward, and planned for abdominal delivery or presented in labour, the researcher was informed of such admission by the

personnel in the antenatal ward or labour ward. I then made myself available for the study procedure.

Following an informed consent (Appendix II), subjects who fulfilled the inclusion criteria were recruited. A detailed history and physical examination was conducted. Under aseptic conditions, five milliliters (5mls) of venous blood was drawn from the ante-cubital vein by the investigator or any of the research assistants before the commencement of any intravenous therapy or intervention. Therefore for women for vaginal delivery, blood samples were collected in the advanced first stage of labour either booked or unbooked prior to any intravenous therapy. Those planned for abdominal delivery had samples taken just prior to institution of anaesthesia. The collected samples were dispensed into a plain non-anticoagulated bottle. Blood samples were allowed to clot and within thirty minutes (30mins), the samples were centrifuged at 3000 revolutions per minute for 10 minutes and the serum stored at -20ºC until analysis. Data collection was done by the use of a data capture sheet (Appendix III). A total of twenty-five items were requested including open and close ended items divided into five sections for ease of analysis. Data obtained included sociodemographic data, gestational age at delivery, and blood pressure at delivery. Other data included clinical examination information, level of proteinuria, serum magnesium level at delivery and fetal outcome assessment. Fetal outcome variables included the gestational age at delivery, the birth weight, the APGAR scores at 1 and 5 minutes and need for neonatal admission. The investigator administered the data sheet and was assisted by trained research assistants. The research assistants were selected from the resident doctors in the department of obstetrics and gynaecology. The data sheet was not pretested as it was not a de-novo questionnaire.

A diagnosis of hypertension was considered when the blood pressure was ≥140/90mmHg taken on two occasions 4-6 hours apart or a single reading of 160/110mmHg. The blood pressure was measured after five minutes of rest to eliminate anxiety. It was measured while the subject was sitting with the feet on the floor and the arm to be used at the level of the heart and free of any constricting clothing. The Accoson branded mercury sphygmomanometer with appropriately sized cuffs was used. Korotkoff phase I sound was used to identify the systolic blood pressure while Korotkoff phase V sound was used to identify the diastolic blood pressure.

The diagnosis of significant proteinuria was made when there was a total protein excretion of 300mg or more in a 24-hour urinary protein estimation or presence of 2+ or more of protein on dipstick or 1+ when the pH is less than 8.0 and the specific gravity is less than 1.030 in two random clean catch or catheter urine specimen.

DURATION OF STUDY

The study ran for nine months to allow sufficient time for the collection of samples for both cases and controls. The review of summary of Obstetric admission and discharges over the past two years in the department showed an average of 15-20 preeclamptic patients presented per month for delivery.

ESTIMATION OF SERUM MAGNESIUM LEVELS

PRINCIPLE

Magnesium levels in the samples and standards were determined using the enzymatic colorimetric method. Magnesium concentration was determined by a coupled enzyme that takes advantage of the specific requirement of glycerol kinase for magnesium resulting in a colorimetric (450nm) product that is proportional to the magnesium present. The assay gives a linear range of 2-15 nmoles with detection sensitivity of approximately 40µM and exhibits no detectable interference with Fe^{2+}, Cu^{2+}, Ni^{2+}, Zn^{2+}, Co^{2+},Ca^{2+} and Mn^{2+}.

PROCEDURE FOR SERUIM MAGNESIUM ANALYSIS

The serum magnesium analysis was performed in conjunction with the Medical Laboratory Scientist under the supervision of the Chemical Pathologist at OOUTH Sagamu. The assay was done using commercially manufactured ready to use kits by Biovision Incorporated, 155 S, Milpitas Boulevard, San Francisco Bay area, California, United States of America. The magnesium assay kit contents included magnesium assay buffer, magnesium developer, magnesium enzyme mix and a 150nmol/µl magnesium standard.

The kit components were reconstituted before use. The magnesium developer was reconstituted with 1.1ml of sterile water and mixed well by pipetting. It was then protected from light and stored at 2-8ºC and was used within two months. The magnesium enzyme mix was reconstituted with 550µl of magnesium assay buffer. This was mixed well by pipetting and also

protected from light. It was also used within two months of reconstitution. All samples and standards were run in duplicate. 10µL of the 150nmole/µL magnesium standard was diluted with 990µl of water to prepare a 1.5nmole/µL standard solution. 0, 2, 4, 6, 8 and 10µL of the magnesium standard was now added to a series of wells in a 96 well flat-bottom plate. Volume in each well was made up to 50µL/well with distilled water to generate 0, 3, 6, 9, 12 and 15nmole/well of magnesium standard. Five microlitre (5µL) of serum samples was put in a series of wells and made up to a volume of 50µL with distilled water. A 50µL of magnesium reaction mix (35µL of magnesium assay buffer, 10µL of developer, 5µL of magnesium enzyme mix) was added to each well that has magnesium standards and test samples. The mixture was incubated for ten minutes at 37ºC and the flat bottomed plate read at OD450nm to get the initial absorbance. Incubation was continued for an additional ten to thirty minutes until the final absorbance was read. All readings did not exceed 1.5 OD. The values obtained from the appropriate magnesium standards will be used to plot a standard curve. The initial absorbance value of the test samples was subtracted from the final absorbance value and the result applied to the standard curve to determine the amount of magnesium present in nanomole (nmol) from which the magnesium concentration was calculated using the formula:

$$C = Sa / Sv$$

Sa = Amount of magnesium in test sample (nmol)

Sv = Sample volume (µL) added to reaction well

C = Concentration of magnesium in sample

QUALITY CONTROL

Measures were taken to ensure that results obtained from this study were accurate. Commercial control samples of known concentration were procured and included with every analytic run. Analytic runs in which the control samples fall out of the required range were repeated.

DETERMINATION OF FETAL OUTCOME

The fetal outcome of both cases and control was determined following delivery. The gestational age at birth, the 1 and 5 minute APGAR scores, the birth outcome (live birth or still birth), birth weight and the need for neonatal admission was collated. Within thirty minutes to one hour of delivery the weight of the neonate was taken by the investigator, the assistants or the midwife on duty. The baby was measured while completely exposed and without diapers. Two measurements were taken during the time frame to the nearest fifty grammes. If the obtained weights were different, the average was used and taken as the absolute birth weight of the baby. This was done so as to reduce error as much as possible.

DATA MANAGEMENT AND ANALYSIS

The statistical package for the social sciences (SPSS) version 23 was used to analyze the data collected. Sociodemographic and obstetric variables were expressed as numbers and percentages with frequency tables generated and comparison made between cases and controls and Chi-Square used to determine level of significance. Continuous variables were expressed as means with standard deviation and comparison made between cases and controls and the student t-test used to determine level of significance. In all variables, a p-value of < 0.05 was considered as statistically significant. Endeavour was made to determine the Odds ratio between hypomagnesaemia and preeclampsia with confidence interval determined.

STRENGTH OF THE STUDY

The strength of this comparative cross-sectional analytical study, was in the number of variables used to match the cases. This increased the power of the study. Cofounders such as the use of dietary magnesium supplementation which is present in some over- the- counter pregnancy multivitamins was mitigated by particularly asking for the use and thus restricted these group of women from participation in the study as this may have interfered with serum magnesium levels.

ETHICAL CONSIDERATION

Ethical approval for the study was obtained from the Health Research Ethics committee of the Olabisi Onabanjo University Teaching Hospital, Sagamu in November 2015.

INFORMED CONSENT

Detailed information about the study was given to the selected subjects and in cases of language barrier such information was translated into the local language. Women who consented to the study indicated such by appending their signature to the informed consent form. If uneducated, they were required to thumb print the consent form.

CONFIDENTIALITY OF DATA

An assurance on the confidentiality of the obtained data was communicated to the subjects. Data collected was stored as both hard copy and electronic copy that was carefully handled by me in utmost confidentiality.

BENEFICIENCE TO PATIENTS

The participants were informed that findings from the research may eventually lead to the better management of women with hypertensive pregnancies. No additional financial burden was incurred by the participants for being part of the study.

NON-MALEFICENCE TO PARTICIPANTS

Assurances were given to the study participants that, no harm will come to them for participating in the study and neither were they denied any beneficial treatment.

RIGHT TO DECLINE

Participants were reassured that they had the right to refuse to participate in the study. If they had initially agreed to participate and thereafter become uninterested in the study, they were assured that they had the right to back out of the study also.

RESULTS

The study enrolled 200 subjects consisting of 100 preeclamptics and 100 controls. Table I shows the sociodemographic characteristics or both group of patients. The mean age of preeclamptics was 26.50±5.08 while the mean age in normotensive women was 26.10±4.72. (p=0.565). The majority of subjects are civil servants (34% and 40% for cases and controls

respectively). The husbands' are mainly traders (45%) for the study group and artisans (38%) for the control group. Fifty five percent (55%) of cases had primary level of education while forty five percent (45%) of controls had .tertiary level of education. The table also shows that women with low socioeconomic status made up more of the subjects (62 and 49 women for cases and controls respectively p= 0.179). Unbooked patients were more in the preeclamptic group as compared with the normotensive group (p=0.001).

Table II shows the maternal clinical characteristics of the study population. The mean body mass index (BMI) for cases was 29.65±4.56 while it was 27.31±2.96 for controls (p=0.001). The mean systolic blood pressure was 168.62±17.97 and 117.14±8.32 respectively for cases and controls (p= 0.001) while mean diastolic blood pressure was 110.82±13.25 and 70.80±5.11 for preeclamptics and normotensive patients respectively (p= 0.001). Most women whether in cases or control had more vaginal births than caesarean deliveries (65% and 70% VS 28% and 30% respectively). Seven percent (7%) of cases and zero percent (0%) of controls had instrumental delivery (p= 0.007).

Table III shows the perinatal clinical characteristics of the study population. The mean birth weight of babies born to normotensive patients was 3.12±0.24 while it was 3.0±0.29 in preeclamptic patients (p=0.001). Fifty-eight (58%) of babies born to women with preeclampsia were asphyxiated at one minute compared to 10% of babies born to normotensive women (p= 0.001) while at 5 minutes, 8% of babies of preeclamptic women and none of normotensive women had some form of birth asphyxia (p= 0.003). Neonatal intensive care unit (NICU) admissions were highest among babies of preeclamptic women with 30% admissions compared to 9% for babies of normotensive women (p= 0.001).

Table IV shows the magnesium concentration in preeclampsia and in normal pregnancy. The mean serum magnesium was 0.63±0.07mmol/L in cases and 0.89±0.14mmol/L in controls (p= 0.001).

Table V shows the magnesium concentration in mild and severe preeclampsia in relation to that of normotensive women. The mean magnesium in mild preeclampsia was 0.69±0.07mmol/L and in severe preeclampsia it was 0.59±0.05mmol/L (p= 0.001).

Table VI shows association of some maternal clinical characteristics with magnesium levels. Thirty five (39.3%) of women with reduced magnesium levels were in the obese range (BMI $\geq$ 30) compared to 21 (20.2%) with normal magnesium levels (p= 0.021). Seventy six (76) women with hypomagnesaemia had preeclampsia compared with 24 women with normal magnesium levels (p= 0.001).

Table VII shows association of perinatal clinical characteristics with magnesium levels. Babies with low birth weight (<2.5kg) were more in women who had low serum magnesium levels with 15 babies as against 3 in women with normal magnesium level (p=0.001). Twenty seven (27) babies were admitted in the neonatal intensive care unit from the hypomagnesaemic group with only 12 babies in women with normal magnesium (p=0.004). Fifty three (55.2%) of babies from women with low serum magnesium had low APGAR score at one minute as against 15 (14.4%) in women with normal magnesium levels (p=0.001). Low APGAR score at five minutes also was seen more in babies born to women with low serum magnesium levels compared with women with normal magnesium levels 7.4% versus 1% (p=0.001).

Table VIII shows association of some sociodemographic characteristics with serum magnesium. There was no significant difference in serum magnesium level in association with the patient's educational status. Thirty seven (37) women with tertiary level of education had low serum magnesium level as against 46 women with same level of education but had normal serum magnesium level (p=0.081). Fifty one (57.3%) of women with low serum magnesium were in the low socioeconomic class, while women with normal serum magnesium were 60 (54.1%) (p=0.685).

Table IX shows serum magnesium as a predictor of preeclampsia. Hypomagnesemia was 21-times more likely to contribute to the occurrence of preeclampsia (OR= 21.192, CI=10.09 – 44.50).

RESULTS

Table 1: Socio-demographic characteristics of the participants.

Characteristics	Cases (%) N=100	Control (%) N=100	Statistical test	p-value
Mean age±SD	26.50±5.08	26.10±4.72	-0.577	0.565
Age				
<20	8(8.0)	4(4.0)		
20-29	67(67.0)	74(74.0)	2.777	0.427
30-39	22(22.0)	21(21.0)		
40-49	3(3.0)	1(1.0)		
Occupation				
Trading	32(32.0)	27(27.0)		
Civil Service	34(34.0)	40(40.0)		
House wife	18(18.0)	18(18.0)	1.220	0.875
Artisan	13(13.0)	11(11.0)		
Student	3(3.0)	4(4.0)		
Religion				
Christianity	65(65.0)	70(70.0)	0.570	0.450
Islam	35(35.0)	30(30.0)		
Husband's Occupation				
Trading	45(45.0)	30(30.0)		
Civil Service	31(31.0)	31(31.0)	7.679	0.053
Artisan	22(22.0)	38(38.0)		
Farming	2(2.0)	1(1.0)		
Educational Level				
Primary				

Secondary	55(55.0)	43(43.0)	3.376	0.185
Tertiary	7(7.0)	12(12.0)		
	38(38.0)	45(45.0)		
Type of Marriage				
Monogamous	96(96.0)	94(94.0)	0.421	0.748
Polygamous	4(4.0)	6(6.0)		
Tribe				
Yoruba	76(76.0)	73(73.0)		
Igbo	13(13.0)	15(15.0)	12.213	0.007
Hausa	11(11.0)	5(5.0)		
Others	0(0.0)	7(7.0)		
Presumed social status				
Low	62(62.0)	49(49.0)	3.444	0.179
Medium	24(24.0)	33(33.0)		
High	14(14.0)	18(18.0)		
Booking Status				
Booked	41(41.0)	75(75.0)	23.727	0.001
Unbooked	59(59.0)	25(25.0)		

Table 2: Maternal clinical characteristics of the study population

Variable	Cases	Control	Statistical test	p-value
BMI(Kg/m2)±SD	29.65±4.56	27.31±2.96	-4.309	0.001
Systolic Blood Pressure(mmHg)±SD	168.62±17.97	117.14±8,32	-26.012	0.001
Diastolic Blood Pressure(mmHg)±SD	110.82±13.25	70.80±5.11	28.177	0.001
Mode of Delivery				
Instrumental	7(7.0)	0(0.0)	9.958	0.007
Vaginal	65(65.0)	70(70.0)		
CS	28(28.0)	30(30.0)		

Table 3: Perinatal clinical characteristics of the study population

Variable	Cases	Control	Statistical test value	p-value
Birth Weight±SD	3.0±0.29	3.12±0.24	3.39	0.001
APGAR score at 1 minute±SD	6.02±1.31	7.20±0.82	7.58	0.001
APGAR score at 5 minutes±SD	7.95±0.90	8.58±0.54	6.00	0.001
Neonatal Admission(%)				
Yes	30(30.0)	9(9.0)	14.047	0.001
No	70(70.0)	91(91.0)		
APGAR score at 1 minute (%)				
</=3	4(4.0)	0(0.0)		
4-5	26(26.0)	5(5.0)	56.67	0.001
6	28(28.0)	5(5.0)		
>/=7	42(42.0)	90(90.0)		
APGAR score at 5 minutes(%)				
4-5	2(2.0)	0(0.0)	11.424	0.003
6	6(6.0)	0(0.0)		
>/=7	92(92.0)	100(100.0)		

Table 4: Mean serum concentration of magnesium in preeclamptics and controls

Variable	Cases	Control	Statistical test value	p-value
Serum Magnesium (mmolL)±SD	0.626±0.07	0.89±0.14	16.65	0.001

Table 5: Mean serum concentration of magnesium between mild and severe preeclampsia

Variable	Control	Mild Preeclampsia	Severe Preeclampsia	Statistical test value	p-value
Serum Magnesium (mmol/L)±SD	0.89±0.14	0.69±0.07	0.59±0.05	158.224	0.001

Table 6: Association between maternal clinical characteristics and serum magnesium levels

Maternal Characteristics	Serum Magnesium <7mmol/L(%)	Serum Magnesium ≥7mmol/L(%)	Statistical test value	p-value
BMI				
18.5-24.9	19(21.3)	23(20.7)		
25-29.9	34(38.2)	63(56.2)	9.745	0.021
30-39.9	35(39.3)	21(20.0)		
>/=40	1(1.1)	1(1.0)		
SBP				
Controls	13(14,6)	87(78.4)		
Mild Preeclampsia	15(16.9)	18(16.2)	98.959	0.001
Severe Preeclampsia	61(68.5)	6(5.4)		
DBP				
Controls	13(14.6)	87(78.4)		
Mild Preeclampsia	17(19.1)	18(16.2)	96.755	0.001
Severe Preeclampsia	59(66.3)	6(5.4)		

SBP – Systolic Blood Pressure

DBP- Diastolic Blood Pressure

Table 7: Association between perinatal clinical characteristics and serum magnesium levels

Fetal Outcome	Serum Magnesium <7mmol/L(%)	Serum Magnesium ≥7mmol/L(%)	Statistical test value	p-value
APGAR score at 1 mins				
</=3	4(4.2)	0(0.0)	39.133	0.001
4-5	24(25.3)	7(6.7)		
6	25(26.3)	8(7.6)		
>/=7	42(44.2)	90(85.7)		
APGAR score at 5 mins				
4-5	2(2.1)	0(0.0)	6.518	0.038
6	5(5.3)	1(1.0)		
>/=7	88(92.6)	104(99.0)		
Birth weight				
<2.5	15(16.9)	3(2.7)		
>/=2.5	74(83.9)	108(97.3)	2.716	0.001
Neonatal Admission				
Yes	27(28.4)	12(11.4)	8.124	0.004
No	68(71.6)	93(88.6)		

Table 8: Association between Socio-demographic characteristics and magnesium level

Characterist	Magnesium Level	Magnesium Level	Statistic al test	p-

ics	<0.7mmol/L(%)	≥0.7mmol/L(%)	value	value
Age				
<20	8(9.0)	4(3.6)		
20-29	59(66.3)	82(73.9)	2.910	0.406
30-39	20(22.5)	23(20.7)		
40-49	2(2.2)	2(1.8)		
Occupation				
Trading	21(23.6)	38(34.2)		
Civil Service	35(39.3)	39(35.1)	2.903	0.574
House wife	18(20.2)	18(16.2)		
Artisan	12(13.5)	12(10.8)		
Student	3(3.4)	4(3.6)		
Religion				
Christianity	60(67.4)	75(67.6)	0.001	0.982
Islam	29(32.6)	36(32.4)		
Husband's Occupation				
Trading	35(39.3)	40(36.0)	5.303	0.151
Civil Service	33(37.1)	29(26.1)		
Artisan	20(22.5)	40(36.0)		
Farming	1(1.1)	2(1.8)		
Educational Level	48(53.9)	50(45.0)	5.026	0.081

Primary	4(4.5)	15(13.5)		
Secondary	37(41.6)	46(41.4)		
Tertiary				
Type of Marriage				
Monogamous	86(96.6)	104(93.7)	0.896	0.344
Polygamous	3(3.4)	7(6.3)		
Presumed social status				
Low	51(57.3)	60(54.1)	0.757	0.685
Medium	26(29.2)	31(27.9)		
High	12(13.5)	20(18.0)		

Table 9: Serum magnesium as predictor of preeclampsia

DEPENDENT VARIABLE	B	OR	p-Value	CI
Preeclamptic	3.054	21.192	0.001	10.09-44.50
Control	Constant			

OR – Odds Ratio, CI – Confidence Interval

DISCUSSION

Preeclampsia, which is a syndrome that is characterized by the onset of hypertension and proteinuria in the second half of pregnancy has been and still is a major cause of maternal and perinatal morbidity and mortality especially in low and middle income countries with an estimated fifty thousand maternal deaths annually[27]. Pregnant women in these developing countries have been reported to consume diets with lesser amounts of essential minerals and vitamins[75].

The precise aetiology of preeclampsia is still not known with certainty despite intensive research worldwide[18]. The pathogenesis of placenta dysfunction, the initiation of systemic vasospasm, ischaemia and thrombosis that ultimately progresses to fetal and or maternal morbidity and mortality is still not fully understood[3,11].

Although several screening tests have been proposed over time for preeclampsia, no test has so far been able to appropriately screen for preeclampsia and no well established measurement for initial prevention has been designed[24].

The major finding in this study is that of a significantly lower level of serum magnesium in preeclamptic patients (0.63±0.07mmol/L) as compared to normotensive pregnant women (0.89±0.12mmol/L). This is also a similar observation in other studies[18,19,24,34,62,63,64]. The aetiology of reduced levels of serum magnesium in women with preeclampsia is not yet fully understood. Is this a cause or effect of preeclampsia? The findings in this study however revealed that, low serum magnesium in preeclampsia is more than just a coincidental finding and that magnesium assay may be a marker for preeclampsia, therefore adding to the

armamentarium of screening tools available to the clinician in predicting this disease. In this study, further analysis also showed that hypomagnesemia was 21-times more likely to contribute to the occurrence of preeclampsia. This is in keeping with the study by Enaruna[25] and colleagues in Nigeria where it was espoused that, hypomagnesemia was 22 and 47 times more likely to contribute to preeclampsia than age and body mass index respectively.

Proposed explanations for the pathophysiologic effect of magnesium in hypertensive disease have been espoused to include intracellular imbalance between calcium and magnesium due to relatively low magnesium which thus, results in increased vascular tone in the smooth muscles of the arteries and therefore increased blood pressure. Also magnesium deficiency causes a dysregulation of the Na-Mg exchanger, resulting in higher intracellular sodium and higher blood pressure[57].

Lending credence to the strong association between hypomagnesemia and preeclampsia as found in this study is the success of magnesium sulphate in the treatment and prophylaxis of eclampsia and preeclampsia[34] and also a detectable dose dependent blood pressure reduction from magnesium supplementation[72].

Furthermore this study also reveals that serum magnesium level was statistically lower in women with severe preeclampsia when compared with those with mild preeclampsia (0.59±0.05mmol/L VS 0.69±0.07mmol/L). This shows that, there is a further dip in serum magnesium level as the patient's clinical condition worsens. This was also found in a study by Jafrin and associates in Bangladesh[21]. Seeing that preeclampsia is a progressively worsening disease and that serum magnesium reduces concomitantly, a case may then be made for the

use of serum magnesium in the array of tests necessary for monitoring the severity of this disease of theories.

Despite the multiplicity of studies showing a significant reduction in serum magnesium in preclamptics, some studies however have a contrary view[22,51,65,68]. Golmohammed et al[51] in India and Idogun[68] in Nigeria reported no significant difference in the magnesium levels among normal pregnant women, pregnancy-induced hypertension and preeclampsia. Same conclusion was also reached by Adewolu[35] also in Nigeria who carried out a pilot study of 20 patients apiece. Would the methodology, such as the study done by Idogun et al that utilized only 11 cases to reach this conclusion have a role to play in this contrasting opinion? Could poor dietary consumption of magnesium rich diet as seen in the study from southern India have a bearing on the failure to elicit a significant difference? This contrasting finding may however be slightly contentious as magnesium use during prevention and treatment of eclampsia has been shown to oppose calcium-dependent arterial constriction leading to vasodilatation and blood pressure reduction. This is supported by a meta-analysis of randomized clinical trials on the effect of magnesium sulphate supplementation on blood pressure which concluded that, there was a detectable dose dependent blood pressure reduction from magnesium supplementation[72].

Magnesium deficiency may contribute towards uterine artery vasospasm and ultimately placental insufficiency and then release of antiangiogenic substances leading to the clinical picture of preeclampsia. In Nigeria, where morbidity and mortality from this disease is unacceptably high[27], further wide multicentre research over a reasonable duration may not be out of place.

In this study, the booking status of patient's revealed that the unbooked patients with preeclampsia was 59% which shows that the health seeking behavior of women in developing countries is generally poor which further contributes to adverse effects for mother and the baby. This finding is similar with other studies[76] where most pregnancy complications are seen in women who are unbooked.

This study reveals that, there were more women with low socioeconomic status who had hypomagnesemia but this was not statistically significant when compared with women with normal serum magnesium levels (p= 0.685) thus showing that there is no association between hypomagnesemia and socioeconomic status. This is supported by studies by Okunade[77] and colleagues in Nigeria and Kumar[78] in Mauritius. This is not surprising in this study because most of the food items available to our pregnant women are rich in magnesium and are affordable to those with low, medium and high socioeconomic status in the society. Food rich in magnesium include green leafy vegetables, cereal, grains, nuts, banana and legumes. Intermediate sources of magnesium include fruits, meat, fish and chocolates while poor sources of magnesium intake include dairy products[42]. That being said, dietary patterns of parturients may need to be further elucidated in further studies to assess the role of food consumption on serum magnesium levels. Some reports however, differ in this submission and assert that there is a significant difference in serum magnesium between women of different socioeconomic status[79,80]. Of note however, is the observation that these studies were carried out in a clime where there may have been a wide gulf in diet as compared to Nigeria and thus comparison cannot be justifiably made.

The association of birth weight and serum magnesium is evident in this study. There was a significant difference in serum magnesium levels between women who delivered low birth weight babies and women who delivered normal weight babies (p=0.001). This is consistent with findings from other studies[81,82] where it was found that maternal hypomagnesemia led to fetal loss and caused fetal and postnatal growth restriction. The probable reason for this may be the change in placental morphology with decreased spongiotrophoblast area and increasing glycogen cell area[82] thus impairing placental development and function thereby leading to low birth weight babies. Parizadeh et al[83] in India and Enaruna[25] in Nigeria reached a different conclusion and did not find any relationship between a lack of magnesium and rates of low birth weight. The provision of multivitamins and mineral supplements to all pregnant women in the study from India as a mandate from the ministry of health may have led to this conclusion.

Magnesium supplementation during pregnancy has been associated with a reduction in preterm delivery and less frequent referral of the newborn to the neonatal intensive care unit[83]. The results of this study may suggest a role for magnesium supplementation in view of the significant number of women with hypomagnesemia who had babies admitted into the neonatal intensive care unit (p=0.004).

This present study indicates a need for further longitudinal studies with larger sample sizes to be undertaken in different parts of the country to further assess the enormity of mineral deficiencies amongst pregnant women.

CONCLUSION

This study found levels of serum magnesium to be significantly lower in women with preeclampsia and much more with increasing severity of the disease. Negative magnesium balance was also found to be associated with low birth weight babies with increasing need for admission in the neonatal intensive care unit. This may suggest a cause and effect relationship between magnesium and preeclampsia. It is worthy to note that, the maternal and or perinatal morbidity and mortality associated with preeclampsia and low birth weight babies remains significant in our environment.

This therefore, suggests a role for improved magnesium balance for pregnant women. Should this be via diet or magnesium supplementation? A case may be made for the latter, seeing nutritional survey has not characterized the exact magnesium content of our staple food and ascertaining the true magnesium content of our diet may be difficult due to the diversity of our diet across the country which relies strongly on socio-cultural backgrounds. The literature further supports a role for the use of magnesium supplementation in women who are found to be magnesium deficient with some results.

RECOMMENDATION

Correcting negative magnesium balance in pregnancy should be considered via magnesium supplementation for the prevention of preeclampsia.

More awareness and incentives for women to attend antenatal care services should be created as more women with preeclampsia in this study were unbooked. This will facilitate early recognition of women at risk and who will readily benefit from increased surveillance and prophylaxis.

Furthermore, population-level data to eliminate the bias of hospital studies may need to be carried out to further strengthen this study. Interventional studies can also be embarked upon to prove the efficacy of magnesium supplementation in our environment.

LIMITATIONS

Limitations included the fact that the study was conducted in only one centre (Olabisi Onabanjo University Teaching Hospital, Sagamu) which is a tertiary centre where referral of complicated cases are made and this may therefore not have been a reflection of the general obstetric population and therefore a multicentre study may have been more appropriate or the use of multiple control groups from both the community and the hospital setting.

Being also a referral centre some patients who have had care at peripheral centres for the prevention of eclamptic fits may have been given magnesium sulphate without their knowledge prior to referral to this centre and this would have given a falsely elevated serum magnesium result.

Furthermore, some patients with chronic hypertension who were meant to be excluded may have been inadvertedly recruited because they may have not been booked and thus unaware of their blood pressure.

REFERENCES:

1. Bansal S. Hypertension in pregnancy. In: Desai P, Malhotra N, Shah D (Eds). Principles and Practice of Obstetrics and Gynecology for Postgraduates. 3rd edition. Jaypee Brothers Medical Publishers Ltd. 2008;100-107.
2. Miller DA. Hypertension in pregnancy. In: Decherney AH, Nathan L, Laufer N, Roman AS (Eds). Current Diagnosis and Treatment: Obstetrics and Gynaecology, 11th edition. McGraw-Hill Companies, Inc. 2013;454-464.
3. Duley L. The global impact of preeclampsia and eclampsia. Seminars in Perinatology. 2009;33:130-137.
4. Uzan J, Carbonne M, Piccone O, Arman R, Ayoubi JM. Preeclampsia: Diagnosis and management. Vasc Health Risk Manag. 2011;7:467-74.
5. Hernandez-Diaz S, Toh S, Cnattingius S. Risk of preeclampsia in first and subsequent pregnancies: Prospective cohort study. BMJ. 2009;338:b2255.
6. Lamina MA, Akisanya AF, Ogunsowo KM. Maternal and perinatal outcome of patients with severe preeclampsia in a tertiary health centre in south-western Nigeria: a cohort study. Res J Health Sci. 2015;3(1):53-61.
7. Lindheimer MD, Taler SJ, Cunningham FG. Hypertension in pregnancy. ASH Position Article. J Am Soc Hypertens 2008;2(6):484-494.
8. Osungbade KO, Ige OK. Public health perspectives of preeclampasia in developing countries: implication for health system strengthening. J Pregnancy 2011, 2011:481095.

9. Mbachu II, Udigwe GO, Okafor CI, Umeonunihu OS, Ezeama C, Eleje GU. The pattern and obstetric outcome of hypertensive disorders of pregnancy in Nnewi, Nigeria. Niger J Med. 2013 Apr-Jun; 22(2):117-22.

10. NICE. Hypertension in pregnancy. National institute of health and clinical excellence (NICE), CG107, London. 2010:3-22.

11. Urato AC, Norwitz ER. A guide towards pre-pregnancy management of defective implantation and placentation. Best Pract Res Clin Obstet Gynaecol. 2011 Jun 25(3):367-87.

12. Akinloye O, Oyewale OJ, Oguntibeju OO. Evaluation of trace elements in pregnant women with preeclampsia. Afr J Biotechnol. 2010;9(32):5196-5202.

13. Hofmeyr GJ, Duley L, Atallah A. Dietary calcium supplementation for prevention of preeclampsia and related problems: A systematic review and commentary. BJOG. 2007;114:933-943.

14. Catov JM, Nohr EA, Bodnar LM, Knudson VK, Olsen SF, Olsen J. Association of preconceptional multivitamin use with reduced risk of preeclampsia among normal weight women in the Danish national birth cohort. American Journal of Epidemiology. 2009;169:1304-1311.

15. Chaurasia PP, Jadav PA, Jasani JH. Changes in serum calcium and magnesium level in preeclampsia vs. normal pregnancy. Int J Biomed Adv Res. 2012;3(6):511-3.

16. Chanvitya P, Boonsri K. Serum calcium, magnesium and uric acid in preeclampsia and in normal pregnancy. J. Med Assoc Thailand 2008;91(7):968-73.

17. Indumatti K, Kodliwadmath MV, Sheela MK. The role of serum electrolytes in pregnancy induced hypertension. J Clin Diagn Res.2011;5(1):66-9.

18. Adekanle DA, Adeyemo OT, Adeniyi AA, Okere RA, Jimoh AK, Adebara IO, Bakare A, Atiba AS, Adelekan A, Olofinbiyi BA. Serum Magnesium levels in healthy pregnant and Pre-Eclamptic Patients- A Cross-Section Study. Open Journal of Obstetrics and Gynaecology. 2014;4:561-568.

19. Abdellah A, Abdrabo AA. Assessment of serum calcium, magnesium, copper and zicc levels in Sudanese pregnant women with preeclampsia. Glo. Adv. Res. J. Med. Med. Sci. 2014;3(2):33-36.

20. Sandip S, Asha K, Paulin G, Hiren S, Gagandeep S, Amit V. A comparative study of serum uric acid, calcium and magnesium in preeclampsia and normal pregnancy. JARBS. 2013;5(1):55-58.

21. Jafrin W, et al. An evaluation of serum magnesium status in preeclampsia compared to normal pregnancy. Mymensingh med J. 2014;23(4):649-53.

22. Kanagal DV, et al. Levels of serum calcium and magnesium in preeclamptic and normal pregnancy: A study from coastal india. Journal of Clin and Diag Research. 2014;87(4):0001-0004.

23. Pairu J, GS T, Manohar A. The study of serum calcium and serum magnesium in pregnancy induced hypertension and normal pregnancy. Int J Reprod Contracept Obstet Gynecol. 2015;4(1):30-34.

24. Tavana Z, Hosseinmirzaei S. Comparison of maternal serum magnesium levels in preeclampsia and normal pregnant women. Iran Red Crescent Med J. 2013;15(12):e10394.

25. Enaruma NO, Ande ABA, Okpere EE. Clinical significance of low serum magnesium in pregnant women attending the University of Benin Teaching Hospital. Niger J Clin Pract. 2013;16:448-53.

26. Doddamani GB, Doddamani UG. Perinatal outcome in preeclampsia: A prospective study. Sch. J. App. Med. Sci. 2014;2(1):291-293.

27. Firoz T, Sanghvi H, Merialdi M, von Dadelszen P. Preeclampsia in low and middle income countries. Best Pract Res Clin Obstet Gynaecol. 2011;25(4):537-48.

28. Khan KS, Wojdyla D, Say L, Gulmezoglu AM, Van Look PF: WHO analysis of causes of maternal death: a systematic review. Lancet 2006;367:1066-1074.

29. Kuklina EV, Ayala C, Callaghan WM: Hypertensive disorders and severe obstetric morbidity in the United States. Obstet Gynaecol 2009;113: 1299-1306.

30. Zanette E, Parpinelli MA, Surita FG, Costa ML, Haddad SM, Sousa MH et al. Maternal near miss and death among women with severe hypertensive disorders: a Brazilian multicentre surveillance study. Reproductive Health 2014; 11;4

31. Jido TA, Yakasai IA. Preeclampsia: A review of the evidence. Ann Afr Med 2013;12:75-85.

32. Gu Y, Lewis DF, Wang Y. Placental productions and expressions of soluble endoglin, soluble fms-like tyrosine kinase receptor-1, and placental growth factor in normal and preeclamptic pregnancies. The Journal of Clinical Endocrinology and Metabolism. 2008;93(1):260-266.

33. Courtrey R, William C, Baha M, Sibai BM. Hypertensive states of pregnancy. In: Alan H, Murry G, Lauren N, eds. Current Obstetrics and Gynaecology. !0th edition Mc Graw-Hill press 2007; 318-327.

34. Ephraim RKD, Osakunor DNM, Denkyira SW, Eshun SA, Amoah S, Anto EO. Serum calcium and magnesium levels in women presenting with preeclampsia and pregnancy induced hypertension: a case-control study in the cape coast metropolis, Ghana. BMC Pregnancy and Childbirth 2014;14:390-397.

35. Adewolu OF. Serum sodium, potassium, calcium and magnesium in women with pregnancy induced hypertension and preeclampsia in Oredo local government, Benin metropolis: A pilot study. Afr J Med Health Sci. 2014;12(1):1-5.

36. Drueke TB, Lacour B. Magnesium homeostasis and disorders of magnesium metabolism. Feehally J, Floege J, Johnson RJ, eds. Comprehensive Clinical Nephrology. 3rd ed. Philadelphia, PA: Mosby; 2007:136-8.

37. Konrad M. Disorders of magnesium metabolism. Geary D, Shaefer F. Comprehensive Pediatric Nephrology. Philadelphia PA. Mosby Elsevier; 2008:461-475.

38. Rude RK. Magnesium. In: Ross AC, Caballero B, Cousins RJ, Tucker KL, Ziegler TR, eds. Modern Nutrition in Health and Disease. 11th ed. Baltimore, Mass: Lippincott Williams & Wilkins; 2012:159-75.

39. Xi Q, Hoenderop JG, Bindels RJ. Regulation of magnesium reabsorption in DCT. Pflugers Arch. 2009;458(1):89-98.

40. Wagner CA. Disorders of renal magnesium handling explain renal magnesium transport. J Nephrol. 2007;20(5):507-10.

41. Elin RJ. Assessment of magnesium status for diagnosis and therapy. Magnes Res 2010;23:1-5.

42. Lima Mde L, Cruz T, Rodrigues LE, Bomfim O, Melo J, Correia R, et al. Serum and intracellular magnesium deficiency in patients with metabolic syndrome--evidences for its relation to insulin resistance. Diabetes Res Clin Pract. 2009; 83(2):257-62.

43. Rude RK. Magnesium. In: Coates PM, Betz JM, Blackman MR, Cragg GM, Levine M, Moss J, White JD, eds. Encyclopedia of Dietary Supplements. 2nd ed. New York, NY: Informa Healthcare; 2010:527-37.

44. Seo JW, Park TJ. Magnesium metabolism. Electrolyte & Blood Pressure. 2008;6:86-95.

45. Witkowski M, Hubert J, Mazur A. Methods of assessment of magnesium status in humans: a systematic review. Magnesium Res 2011;24:163-80.

46. Dennie R, Mario C, Cecilia G. Effect of magnesium on central arterial compliance in preeclampsia. Am J Obstet Gynaecol. 2009;201(6):526.

47. Takaya J, Yamatu F, Kaneko K. Possible relationship between lowbirth weight and magnesium status: from the stand point of 'fetal origin' hypoyhesis. Magnes Res. 2006;19(1):63-69.

48. Makrides M, Crowther CA. Magnesium supplementation in pregnancy (Review) Cochrane Database Syst Rev. 2012;10:CD000937.

49. Punthumapol C, kittichotpanich B. Serum calcium, magnesium and uric acid in preeclampsia and normal pregnancy. J Med Assoc Thai. 2008;91(7):968-72.

50. Barbagallo M, Domingues LJ, Resnick LM. Magnesium metabolism in hypertension and type 2 diabetes mellitus. Am J Ther. 2007;14:375-385.

51. Golmohammad lou S, Yazdian M, Pashapour N. Evaluation of serum calcium, magnesium, copper, and zinc levels in women with preeclampsia. IJMS. 2008;33(4):231-234

52. Takaya J, Kaneko K. Fetus and magnesium. Clin Calcium 2005;15(11):105-110.

53. Stanton MF, Lowenstein FW. Serum magnesium in women during pregnancy, while taking contraceptives and after menopause. Journal of the American College of Nutrition. 1987;6(4):313-9.

54. Olatunbosun DA, Adeniyi FA, Adadevoh BK. Serum calcium, phosphorus and magnesium levels in pregnant and non-pregnant Nigerians. Br J Obstet Gynaecol. 1975;82:568-571.

55. Del Gobbo LC, Imamura F, Wu JHY, Otto MCdO, Chiuve SE, Mozaffarian D. Circulating and dietary magnesium and risk of cardiovascular disease: a systematic review and meta-analysis of prospective studies. Am J Clin Nutr 2013;98:160-73.

56. Kassu A, Yabutani T, Mulu A, Tessema B, Ota F. Serum zinc, copper, selenium, calcium and magnesium levels in pregnant and non-pregnant women in Gondar, Northwest Ethiopia. Bio Trace Elem Res. 2008;122(2):97-106.

57. Barbagallo M, Dominguez LJ, Galioto A, Pineo A, Belvedere M. Oral magnesium supplementation improves vascular function in elderly diabetic patients. Magnesium Research. 2010;23(3):131-137.

58. Seydoux J, Girardin E, Paunier L, Beguin F. Serum and intracellular magnesium during normal pregnancy and in patients with preeclampsia. Br J Obstet Gynaecol. 1992;99:207-211.

59. Kanchapan S, Vorapong P. Serum calcium and serum magnesium in normal and preeclamptic pregnancy. Arch Gynaecol Obstet. 2005;273(1):892-96.

60. Standley CA, Whitty JE, Mason BA, Cotton DB. Serum ionized magnesium levels in normal and preeclamptic gestation. Obstet Gynaecol. 1997;89(1):24-27.

61. Borecki B, Gulaboglu M, Gul M. Iodine and magnesium levels in maternal and umbilical blood of preeclamptic and normal pregnant women. Biol Trace Elem Res. 2009;129(1-3):1-8.

62. Vahidrosari F, et al. Serum calcium and magnesium in preeclamptic and normal pregnancy: A comparative study. J Reprod Infert. 2008;9(3):36-38.

63. Al-Rubaye FG, Al-Bayati MM, Al-Khayat TH. Mineral homeostasis in preeclampsia. Iraqi J Med Sci. 2009;7(2):4-11.

64. Igberase GO, Ebeigbe PN, Okonta PI, Okpere EE, Gharoro EP. Serum magnesium levels in normal and preeclamptic gestation in Benin-City. Niger. Med J. 2007;48(1):21-23.

65. Kumru S, Aydin S, Simsek M, Sahin K, Yaman M, Ay G. Comparison of serum copper, zinc, calcium and magnesium levels in preeclamptic and healthy pregnant women. Biol Trace Elem Res. 2003;94:105-12.

66. Punthumapol C, Kittichotpanich B. Serum calcium, magnesium and uric acid in preeclampsia and normal pregnancy. J Med Assoc Thai. 2008;91(7):968-72.

67. Magri S, Sammut M, Savon C. Lead and other metals in gestational hypertension. Int J Gynaecol. 2003;83:29-36.

68. Idogun ES, Imarengiaye CO, Momoh SM. Extracellular calcium and magnesium in preeclampsia and eclampsia. Afr J Reprod Health. 2007;11(2):89-94.

69. Van Laecke S, Maréchal C, Verbeke F, Peeters P, Van Biesen W, Devuyst O. The relation between hypomagnesaemia and vascular stiffness in renal transplant recipients. Nephrol Dial Transplant. 2011;26(7):2362-9.

70. Hantoushzadeh S, Jafarabadi M, Khazardoust S. Serum magnesium levels, muscle cramps and preterm labour. Int J Gynaecol Obstet. 2007;98:153-4.

71. Piso B, Koss-Zechmeister I, Winkler R. Antenatal interventions to reduce preterm birth: an overview of Cochrane systematic reviews. BMC Research Notes. 2014;7:265-275.

72. Kass L, Weekes J, Carpenter L. Effect of magnesium supplementation on blood pressure: a meta-analysis. Eur J Clin Nutr. 2012;66(4):411-8.

73. WHO (2010). WHO handbook for guideline development. World Health Organization , Geneva.

74. Khong Y, Brosens I. Defective deep placentation. Best Practice and Research Clinical Obstetrics & Gynaecology. 2011;25:301-311.

75. Jain S, Sharma P, Kulshreshtha S, Mohan G, Singh S. The role of calcium, magnesium and zinc in preeclampsia. Biol Trace Res. 2010;133:162-170.

76. Tucker A, Ogutu D, Yoong W, Nauta M, Fakokunde A. The unbooked mother: A cohort study of maternal and fetal outcome in a North London hospital. Arch Gynecol Obstet. 2009;281:613-616.

77. Okunade KS, Oluwole AA, Adegbesan-Omilabu MA. A study on the association between low maternal serum magnesium level and preterm labour. Adv Med. 2014;2014:704875.doi:10.1155/2014/704875.

78. Kumar AN, Kumar R. Correlation of serum magnesium level with increase in parity and comparison among rural and urban pregnant women. Int J Cur Bio Med Sci. 2012;2(1):185-187.

79. Pathak P, Kapoor SK, Kapil U, Dwivedi SN. Serum magnesium level among pregnant women in a rural community in Hayarna state, India. Eur J Clin Nutri. 2003;57:1504-1506.

80. Kamal S, Sharan A, Kumar U, Shahi SK. Serum magnesium level in preterm labour. Ind J Path Micro. 2003;46(2):271-273.

81. Gupta M, Solanki MH, Chatterjee PK, Xue X, Roman A et al. Maternal magnesium deficiency in mice leads to maternal metabolic dysfunction and altered lipid metabolism with fetal growth restriction. Mol Med. 2014;20:332-340.

82. Schlegel RN, Cuffe JSM, Moritz KM, Paravicini TM. Maternal hypomagnesemia causes placental abnormalities and fetal and postnatal mortality. Placenta. 2015;36:750-758.

83. Parizadeh SM, Mohammadzadeh A, Farhat A, Valaee L, Khajedaluee M et al. Maternal serum magnesium level and low birth weight neonate. Int J Prev Med. 2103;4(12):1476-1479.

APPENDIX I: PARTICIPANTS INFORMATION SLIP

MAGNESIUM LEVELS IN PREECLAMPTIC WOMEN AND IN NORMAL PREGNANCY IN A TERTIARY HOSPITAL

Dear Respondent,

This study is aimed at assessing the relationship of serum magnesium levels in preeclamptic women admitted for delivery and comparing that with normal pregnancies including fetal outcome. Preeclampsia is a medical condition in pregnancy that is characterized by elevated blood pressure of ≥ 140/90mmHg taken on two separate occasions at least six hours apart, after the 20^{th} week of pregnancy with associated significant proteinuria (>300mg in 24 hrs) in a previously normotensive and non-proteinuric woman. Decreased levels of serum magnesium have been noted in women with preeclampsia and have been associated with preterm deliveries. This study is therefore designed to better manage pregnant hypertensive women and their fetuses as it may help in identifying women who may have a poor fetal outcome and thus help in making timely intervention.

Participation in this study is voluntary and it will involve the signing of a consent form and the filling of a data sheet. The information provided will be treated with strict confidentiality. The study will involve the collection of five milliliters (5mls) of blood from any of your forearm veins following delivery. Necessary precaution will be put in place to ensure that this procedure does not endanger you. If you wish to participate in this study kindly fill the consent form that is attached.

APPENDIX II: CONSENT FORM

I have been duly informed by Dr. Ikhile M.U. of the department of obstetrics and gynaecology, OOUTH, Sagamu about this study. I have had the opportunity to ask questions which have all been answered satisfactorily.

I hereby agree to participate in this study and I know that my participation is voluntary and that my refusal will not affect my treatment in any way. I consent to being examined clinically and my blood sample taken for serum magnesium analysis.

I agree that the findings may be made public provided my identity is not revealed.

Name of participant…….. Phone number……..

Signature and Date……..

I confirm that I have given an explanation on the purpose and benefits of this study to the above named participant who has agreed to participate.

Name of Researcher……..

Signature/Date……..

CONTACT INFORMATION

If you have any questions about your participation in this study or need further information, you may contact the investigator at the address stated below.

DR. IKHILE M.U.

Department of Obstetrics and Gynaecology, OOUTH, Sagamu, Ogun State. Nigeria

Mobile phone number: 08034976376

APPENDIX III: DATA CAPTURE SHEET

MAGNESIUM LEVELS IN PREECLAMPSIA AND IN NORMAL PREGNANCY IN A TERTIARY HOSPITAL.

Serial Number…… Date……

SOCIODEMOGRAPHIC INFORMATION:

1) Age…… 2) Marital status……..

3) Occupation……. 4) Husband's occupation……..

5) Presumed socioeconomic status: Low ( ) Medium ( ) High ( )

6) Type of marriage: monogamous ( ) polygamous ( )

7) Tribe …….. 8) Residence……..

9) Religion: Christianity ( ) Islam ( ) Traditionalist( ) Others ( )

10) Educational Level: Primary ( ) Secondary ( ) Tertiary ( )

OBSTETRIC INFORMATION:

1) Parity ……..

2) History of hypertension in previous pregnancy? Yes [ ] No [ ]

3) Booking Status Booked [ ] Unbooked [ ]

4) Estimated gestational age at delivery [……weeks]

5) Mode of delivery: Vaginal Delivery Yes [ ] No [ ]

Caesarean Delivery Yes [ ] No [ ]

Instrumental delivery Yes [ ] No [ ]

CLINICAL EXAMINATION:

1) Height……. 2) Weight…….. 3) BMI……

3) Blood pressure at delivery [……mmHg]

LABORATORY EVALUATION:

1) Proteinuria at delivery: None[ ] 1+[ ] 2+[ ] 3+[ ]

2) Serum Magnesium level at delivery …….mg/dl

FETAL OUTCOME:

1) Gestational age at birth …….

2) Birth weight …….Kg

3) APGAR scores 1st minute [ ] 5th minute [ ]

4) Birth Outcome Live birth [ ] Still birth [ ]

5) Neonatal Admission Yes [ ] No [ ]