

## Comparative study of serum calcium and serum magnesium levels in patients of preeclampsia and normotensive patients

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### Abstract

**Introduction:** Hypertension disorders are major factors responsible for morbidity and mortality in pregnancy and preeclampsia is the leading cause. The etio-pathology of PE is not known even after significant research done on it. Only thing which we can do is try to reduce the incidence and severity by predicting its occurrence. In our study we are trying to know the effect of serum calcium and serum magnesium on pre-eclampsia.

**Materials and Methods:** Total 256 pregnant patients attending D.Y. Patil hospital were included in our study. They were divided into two groups namely normotensive and hypertensive. The diagnosis of Pre-eclampsia was made by standard protocol, inclusion and exclusion criteria were applied for selection of case after permission from ethical committee of the institution and consent of the patients. In them we estimated serum calcium and serum magnesium levels and the correlation of these levels was studied with the pre-eclampsia related factors.

**Results:** Both groups comparable in terms of age, gravida, parity, high risk factors, BMI. The data was analysed by application of statistical test of significance.

**Conclusion:** Our study shows that low levels of calcium and magnesium are found in serum of pre-eclampsia patients as compared to normotensive cases of the study population. Also since calcium deficiency plays role in aetiology of pre-eclampsia antenatal administration of Ca supplements was done and its effect was studied to find out whether it is useful in reducing the severity of PE.

**Keywords:** Hypertensive disorder in pregnancy, Pre-eclampsia, S. calcium, S. magnesium.

### Introduction

Hypertensive disorders of pregnancy are major cause of maternal morbidity and mortality.<sup>1</sup> It is also a major contributor to maternal mortality worldwide as pre-eclampsia along with other hypertensive disorders complicates around 2-8% of total pregnancy. The mortality graph has ascended so much that hypertension disorders are Fifth on the list of causes of maternal mortality but recent trend showed it has climbed up to two steps to take third place preceded by haemorrhage and infection.<sup>2</sup> Multiple hypothesis have been put forward to explain its occurrence so it is called as the "Disease of Theories". The pathophysiology is characterized by failure of trophoblastic invasion of the spiral arteries ultimately leading to increased vascular resistance of uterine artery and decreased perfusion.<sup>3</sup> Poor early placentation is associated with early onset. Predisposing cardiovascular or metabolic risk leading to endothelial dysfunction, as a part of exaggerated systemic inflammatory response might dominate in the origins of late onset of preeclampsia.<sup>4</sup>

There has never been a definite consensus on the classification and diagnostic criteria for the hypertensive disorders of pregnancy. The International Society for the Study of Hypertension in Pregnancy (ISSHP) has classified hypertensive disorders in pregnancy as:

1. Chronic hypertension
2. Gestational hypertension

3. Pre-eclampsia – de novo or superimposed on chronic hypertension
4. White coat hypertension

The incidence is about 6% in Primigravida<sup>5</sup> Preeclampsia is defined as triad of Hypertension, Proteinuria and Edema occurring after 20 weeks of gestation in previously normotensive women.<sup>6</sup> Recent guidelines has suggested to omit edema from this triad. It may be associated with complications like visual disturbances, oliguria, eclampsia, HELLP syndrome, pulmonary edema and IUGR.<sup>5</sup>

Annually about 40,000 maternal deaths are occurring due to these hypertensive disorders. Due to this methods to reduce the risk of these disorders have received considerable attention. Research is focussing on prevention rather than treatment. There is an evidence that indicates the role for micronutrient supplementation in these disorders. Among these, increase in calcium and Magnesium supplements has been found to reduce the risk of PIH disorders.<sup>5</sup>

Physiologically, calcium plays an important role in muscle contraction and regulation of water balance in cells. The lowering of Serum calcium and increase in intracellular calcium can cause hypertension.<sup>7</sup> The mechanism of action by which low S. calcium causes hypertension is attributed to stimulating parathyroid hormone, renin release and also by inducing vasoconstriction by increasing its level in vascular smooth muscles. It also has an indirect effect on the

smooth muscle function by increasing magnesium levels.<sup>5</sup>

Magnesium is the fourth most abundant cation of intracellular fluid. It is present in more than 300 enzymes and is crucial ATP metabolism. It also acts as calcium channel antagonist. The result of low magnesium may lead to reduction in cerebral fluid flow, cerebral vasospasm etc. Magnesium has been found to have vasoprotective effect. It has also been found that it correlates with the clinical manifestation and pathological findings in PIH particularly eclampsia. It acts as potent vasodilator and its depletion increases vasoconstrictor effect of AG-II and Nor-adrenaline leading to increased blood pressure.<sup>8</sup>

The levels of calcium and magnesium are related as the deficiency of one is invariably accompanied with deficiency of the other. In our study we are focussing on comparing levels of S calcium and magnesium in normotensive patients to that in patients with pre-eclampsia.

### Aims and Objectives

**Aim:** Primary outcome will be comparison of serum calcium and magnesium levels in normotensive patients and preeclamptic patients.

### Objectives

1. To assess whether antenatal calcium administration has any effect on outcome of pregnancy
2. To correlate levels of serum calcium and magnesium with the severity of preeclampsia

### Materials and Methods

**Material:** Data collected from Antenatal patients coming to the labour room.

**Methods:** Institute Ethics Committee Clearance will be obtained before the start of the study.

**Type of Study:** Case control study of 256 cases (calculated by Winpepi software)

**Period of Study:** April 2016 to May 2018 (Data collection)

June 2018 to October 2018 (Data analysis)

**Period Required for Data:** 2 years.

### Collection

**Period Required for Data:** 6 months.

Analysis and reporting

**Place of Study:** Department of Obstetrics & Gynaecology, Dr. D. Y. Patil Medical College, Pimpri, Pune

**Source of Data:** Labour Room of Dr. D. Y. Patil Medical College, Pimpri, Pune.

### Inclusion Criteria

1. All pre-eclampsia patients admitted in department of Obstetrics and Gynecology
2. Age groups from 20 to 35 years
3. Patients having singleton pregnancy

### Exclusion Criteria

1. Age group less than 18 years and above 35 years

2. Multiple pregnancy
3. Other medical disorders like diabetes, hypothyroidism, renal disorders
4. Patients with chronic hypertension
5. Patients not willing to participate in the study

### Procedure

Taking into consideration the study "A comparison of maternal calcium and magnesium levels in Pre-Eclamptic and Normotensive Pregnancies: an Observational Case-Control Study" conducted by Richards DGD et al, at 5% significance level and 80% power considering their SD of calcium in cases as 0.09 and in control as 0.08 to detect the difference of 0.03, the total sample size came out to be 256 (128 in each) using Winpepi software.<sup>9</sup>

A total of 128 antenatal patients coming to labour room, diagnosed with pre-eclampsia (either earlier or during examination) and 128 control antenatal patients in their third trimester were considered.

The patients were explained about the study and their willingness to participate in the study was determined.

The patients were categorized according to their age, parity, socio-economic status, literacy, geographical variation, rural or urban dwelling. Patients between 20-35 yrs of age who were not suffering from any other medical disorders like hypothyroidism, gestational diabetes mellitus, chronic hypertension, chronic renal disease, and haemoglobinopathies were considered. Most of the patients were from a low socio-economical status but in terms of urban versus rural dwelling, the numbers were almost equal.

The patients underwent thorough clinical examination and anthropometric evaluation.

The blood pressure- systolic as well as diastolic, of the patients was assessed carefully by measuring it with mercury sphygmomanometer in the right arm, sitting position. 2 readings were taken 6 hours apart and then the patients were divided into 2 groups- study group and control group.

The severity of proteinuria was assessed using the dipstick method and all the patients with reading of 1+ or more and blood pressure equal to or more than 140/90 were included in the study group.

The subjects in the study group were further divided into 3 groups based on their blood pressure according to the National Institute for Health and Care Excellence (NICE) guidelines<sup>10</sup> updated in June 2017 into:

**Mild:** Systolic blood pressure between 140-149 mmHg, diastolic blood pressure between 90-99 mmHg

**Moderate:** Systolic blood pressure between 150-159 mmHg, diastolic blood pressure between 100-109 mmHg

**Severe:** Systolic blood pressure 160 mmHg or greater, diastolic blood pressure 110 mmHg or greater

Proforma was filled by researcher on the basis of answers that were obtained.

Blood sample (venous blood) of about 5ml was drawn from the ante cubital vein of the patient under all aseptic precautions.

The sample was collected in plain bulbs and allowed to clot.

The following tests were used for each and then photometry was used to determine the levels in the sample.

Serum calcium was estimated by the O-Cresol phthalene complexone method.

Serum magnesium was estimated by Xylidyl Blue method.

The following values were taken to be as the reference range for each of the blood component that was being evaluated.<sup>11</sup>

**Serum Calcium:** 8.2 - 9.7 mg/dL

**Serum Magnesium:** 1.1 - 2.2 mg/dL

Data was analyzed to check the statistical significance and draw conclusions based on the findings.

## Observation and Results

Since pre-eclampsia causes significant complications antenatally and also affects the outcome in terms of mortality and morbidity of both, the mother and the baby, it is necessary to have a group of tests that can give a vague idea with respect to the existence and severity of the disease.

In this study a total number of 256 cases in the third trimester of pregnancy were selected and divided into study and control groups of 128 each after confirming their willingness to participate in the study and taking their informed consent.

We have studied and compared both the groups (study and control groups) with respect to Age, distribution of Age, Gravida status and with respect to gestational age and found that both the groups are comparable with each other by applying test of statistical significance.

Control and study groups were also compared with respect to presence of High risk factors in which it was observed that both the groups were comparable with each other by applying test of significance. The high risk factors taken into account were: IUGR, Previous LSCS, PROM, Anemia, Oligohydramnios, Breech, Low lying placenta.

**Table 1: Comparison of Body Mass Index in study and control group**

Parameter	Study (n=128)		Control (n=128)		Z Value	P Value
	Mean	SD	Mean	SD		
BMI	24.97	2.08	23.52	1.33	6.65	<0.0001

On an average, patients having greater BMI fell into the study group as compared to the ones in the control group.

**Table 2: Calcium supplements wise distribution of cases in study and control group**

Calcium supplements	Study	Control	Total
Yes	90	103	193
No	38	25	63
Total	128	128	256

Chi-square = 3.56, P=0.059

From this, we can see that, the total number of study cases as compared to control cases had not received antenatal calcium supplements.

**Table 3: Comparison of Sr. calcium and Sr. Magnesium in study and control group**

Parameter	Study (n=128)		Control (n=128)		Z Value	P Value
	Mean	SD	Mean	SD		
Sr. Calcium	8.17	0.15	8.71	0.34	16.13	<0.0001
Sr. Magnesium	1.24	0.16	1.63	0.20	16.98	<0.0001

The levels of serum calcium was significantly lower in the study group than the control group. Similar findings were observed for serum magnesium also in study and control groups.

**Table 4: Severity of pre-eclampsia wise distribution of cases in study group**

Severity of pre-eclampsia	No of cases	Percentage
Mild	8	6.3
Moderate	46	35.9
Severe	74	57.8
Total	128	100

**Table 5: Comparison of Sr. calcium and Sr. Magnesium according to severity of pre-eclampsia in study group**

Severity of pre-eclampsia	Sr. Calcium			F Value	P Value
	N	Mean	SD		
Mild	8	8.15	0.11	2.13	0.12
Moderate	46	8.21	0.13		
Severe	74	8.15	0.16		
	Sr. Magnesium			1.54	0.22
	N	Mean	SD		
Mild	8	1.22	0.23	1.54	0.22
Moderate	46	1.27	0.13		
Severe	74	1.22	0.16		

The level of serum calcium is lower in the study group than the control group, but even among the study group, the levels of calcium are lower in the severe cases

as compared to the other two. Similar findings are observed in case of Serum Magnesium as shown in this table.

**Table 6: Association between calcium supplement and severity of pre-eclampsia in study group**

Severity of pre-eclampsia	Calcium supplement		Total
	Yes	No	
Mild	5	3	8
Moderate	41	5	46
Severe	44	30	74
Total	90	38	128

Chi-square = 12.21, P=0.002

It can be very clearly seen that the severity of pre-eclampsia is inversely proportional to administration of antenatal calcium supplements.

### Discussion

The study consisted of 256 cases between the ages of 20-35 years. The mean of the study group was 24.41 and that of the control group was 23.94. The mean of both the groups was found to be in the same range and hence we can conclude that both the groups are comparable in terms of age.

If the distribution of study and control were to be assessed as per the age of cases, then a typical bimodal peak can be seen with respect to the study group. An increased number of study cases were seen in the age group of  $\leq 20$  years of age and 31-35yrs of age. It has been hypothesized that the incidence of pre-eclampsia is more common in very young patients<sup>15</sup> (teenage pregnancies) and in patients beyond the age of 30 year which was quite evident in the present study.

Another factor that plays a role in the occurrence of pre-eclampsia is the gravida of the patient. Pre-eclampsia is more common in very young primigravidas and also, its incidence increases as the gravida goes in increasing. A similar picture can be seen in the present study.

The incidence of IUGR was 32% in the study group as opposed to a mere 4.69 in the control group asserting that the existence of pre-eclampsia affects the growth and development of the fetus. Anemia is seen in 10.94% of the study group which is almost double of the control group. The higher number of anemia cases in the study

group can be explained by the fact that majority of the women enter pregnancy in an iron deficient state and continue to have dietary deficiencies of micro-nutrients throughout pregnancy. One more aspect that can explain the high number of anaemia cases in the study group is the non-compliance of the patients towards iron and calcium supplementation provided to them throughout pregnancy; each of them responsible for anaemia and pre-eclampsia respectively.

Higher Body Mass Index (BMI) has been known to be associated with increased incidence of pre-eclampsia. A study conducted by Jalal Poorolajal et al concluded the same.<sup>12</sup> The mean of BMI of the cases in the study group is 24.97 which is more than 23.52 of the control group. The P value of this comparison is  $<0.0001$ , which means that BMI is a significant factor in the incidence of pre-eclampsia. (Table 1).

Out of the 128 cases in each of the groups, 38 cases of the study group had not received calcium supplementation as compared to 25 cases of the control group. Since the P value of this comparison is 0.059, we can conclude that antenatal calcium supplementation is somewhat significant if not totally significant in determining the incidence of pre-eclampsia (Table 2).<sup>5</sup>

When the levels of serum calcium of both, the study group and the control group were compared, it was found that the mean of serum calcium in the study group was 8.17 and that of the control group was 8.71. Lower levels of serum calcium indicate a higher level of intra-cellular calcium which in turn causes vasoconstriction. Also, when the levels of calcium are lower in the serum, parathyroid hormone is stimulated which leads to renin

release, increases the intracellular calcium in smooth muscles and causes vasoconstriction, increased peripheral resistance and ultimately increases the blood pressure.<sup>1</sup> It can be seen in this study that the cases in the study group had comparatively lower levels of serum calcium than the control group which is a significant finding (Table 3).

Magnesium is another important micronutrient which is abundantly found in many co-enzymes of the body.<sup>14</sup> It also plays a role in neurotransmission and peripheral vasodilatation. Magnesium is a competitive inhibitor of calcium and because of this action, it can prevent smooth muscle contractions caused by calcium. Peripherally, magnesium induces prostacyclin release from the endothelial cells which is a potent vasodilator can leads to vasodilatation and fall in the blood pressure. In case of low levels of magnesium, there is arterial vasoconstriction due to increased vasoconstriction effects of angiotensin-II and nor-adrenaline.<sup>2</sup> The mean of levels serum magnesium in the study group was 1.24 and of control group was 1.63 indicating that cases of pre-eclampsia indeed have lower levels of serum magnesium than cases who are normotensive (Table 3). Ugwaja et al conducted a survey in Nigeria and have the same result.<sup>3</sup>

The 128 cases in the study group were further divided into 3 subgroups-mild, moderate and severe based on their blood pressure readings. 57.8% of cases were from the severe subgroup followed by 35.9% of the moderate subgroup. This can be because of improper antenatal follow up and missed identification or improper identification and management of the disorder in the earlier stages at lower levels of health care set ups. Hence it is essential that once the diagnosis or pre-eclampsia is made or there is confusion regarding the neo appearance of hypertension in previously normotensive patients beyond 20 weeks of gestation at the primary centre of health care, the patient should be referred to a tertiary centre for proper diagnosis and management. (Table 4).

When the levels of serum calcium in the subgroups of the study group were considered, there was no specific decreasing trend observed with increase in the intensity of the disorder but the mean of levels of serum calcium of all 3 subgroups was towards the lower side, more so in the subgroup of severe cases (Table 5).

The source of dietary magnesium has become low due the low stores of magnesium in food products secondary to relatively low magnesium in the ecosystem. The content of magnesium in food products is further reduced due to overcooking, processing and reprocessing food products. Findings similar to those of calcium were seen with respect to the levels of serum magnesium in the subgroups of the study group. Severe cases had lower mean value (Table 5).

It can be seen that as severity of pre-eclampsia went on increasing, the number of cases who had not received calcium supplementation also rose proportionally. The P

value is 0.002 proving that the data comparison is significant (Table 6). A study conducted by Win Khaing et al also concluded that calcium supplementation could reduce the risk of pre-eclampsia.<sup>13</sup> A study conducted Kanagal et al in the coastal areas of India also says that calcium supplements may play a role in prevention of pre-eclampsia.<sup>5</sup>

The study was performed on a total of 256 cases which were equally divided into 2 groups of study and control groups respectively. Both the groups were comparable in terms of age, gravida and gestational age so the results determined from this study can be considered to be genuine since comparison was being made between two similar groups.

### Conclusion

Pre-eclampsia complicates as many as 10% of the pregnancies worldwide with adverse maternofetal outcome. Apart from blood pressure, proteinuria and systemic changes used to diagnose pre-eclampsia, it would be helpful to have a few biochemical markers which can help with the diagnosis of pre-eclampsia.

It is concluded from this study that low levels of calcium and magnesium are found in the serum of pre-eclamptic cases as compared to normotensive cases of the study population.

### References

1. Ephraim RKD, Osakunor DNM, Denkyira SW, Eshun H, Amoah S, Anto EO. Serum Calcium and Magnesium Levels in Women Presenting with Pre-Eclampsia and Pregnancy Induced Hypertension: a Case-Control Study in the Cape Coast Metropolis, Ghana. *BioMed Central Pregnancy and Childbirth*. 2014;14:390.
2. Maternal Mortality, World Health Organization fact sheet November 2016
3. Sirajwala HB, Sharma D, Agravatt AM. A study of serum total calcium and uric acid levels in preeclampsia. *Indian Journal of Basic and Applied Medical Research*. 2013;1(3):50-56.
4. Steegers EAP, Daddelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. *Lancet*. 2010;376:631-44.
5. Kanagal D, Rajesh A, Rao K, Devi UH, Shetty H, Kumari S. Levels of Serum Calcium and Magnesium in Pre-eclamptic and Normal Pregnancy: A Study from Coastal India. *Journal of Clinical and Diagnostic Research*. 2014;8,7:OC01-04.
6. Idogun ES, Imarengiaye CO, Momoh SM. Extracellular Calcium and Magnesium in Preeclampsia and Eclampsia. *African Journal of Reproductive Health August*. 2007;11(2):89-94.
7. Sendhav S, Khubchandani A, Gandhi P, Sanghani H, Sidhu G, Vadhel A. A Comparative Study of Serum Uric Acid, Calcium and Magnesium in Pre-Eclampsia and Normal Pregnancy. *Journal of Advance Researches in Biological Sciences*. 2013;5(1):55-58.
8. Verma V, Sogani S, Sarkar PD. Comparative Study of Serum Calcium and Magnesium in Pre-eclamptic Pregnancies in Third Trimester and its Comparison with Healthy Normotensive Nonpregnant and Pregnant Women and to Evaluate their role in Pregnancy-induced Hypertension. *MGM Journal of Medical Sciences*. 2015;2(3):137-141.

9. Richards DGD, Lindow SW, Carrara H, Haswell SJ, Van der Spuy ZM. A Comparison of Maternal Calcium and Magnesium levels in Pre-Eclamptic and Normotensive Pregnancies: an Observational Case-Control Study. *International Journal of Obstetrics and Gynaecology*. 2014;121(3):327-36.
10. Hypertension in Pregnancy. National Institute for Health and Care Excellence Pathways June 2017.
11. Abbassi-Ghanavati M, Greer LG, Cunningham FG. Pregnancy and Laboratory Studies: a reference table for clinicians. *Obstetrics and Gynecology*. 2009;114(6):1326-31.
12. Jalal Poorolajal, Ensiyeh Jenabi. The association between body mass index and preeclampsia: a meta-analysis. *The Journal of Maternal-Fetal and Neonatal Medicine*. 2016;29(22).
13. Win Khaing, Sakda Arj-Ong Vallibhkara, Ammarin Thakkinstian. Calcium and Vitamin D supplementation for prevention of preeclampsia: A systematic review and network meta-analysis. *Nutrients*. 2017;9(10).
14. Uwe Grober, Joachim Schmidt, Klaus sisters. Magnesium in prevention and therapy. *Nutrients*. 2015;23;7(9):8199-226.
15. Baha M. Sibai, Adel El-Nazer MD, Antonio Gonzalez-Ruiz MD. Severe preeclampsia-eclampsia in young primigravida women: subsequent pregnancy outcome and prognosis. *Am J Obstet Gynecol*. 1986;155(5):1011-6.

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