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Association of serum calcium and serum magnesium in gestational hypertension and pre-eclampsia

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Abstract
In India, the prevalence of hypertensive disorders of pregnancy was found to be 7.8% and incidence of preeclampsia was 5.4% [1]. The exact cause of hypertension in pregnancy still remains unknown, even after years of extensive research and hence this disorder has come to be dubbed as the "disease of theories". Epidemiologic data from many surveys and studies supports the fact that specific nutritional deficiencies may contribute to maternal and fetal morbidity [2]. Among all, there exists an alteration in calcium and magnesium metabolism during pregnancy which could be a potential factor causing pre-eclampsia.
Materials and Methods: This was a prospective case control observational study done over a period of one year in the Department of Obstetrics & Gynaecology at Sri Balaji Action Medical Institute, New Delhi. A total of 60 patients with a singleton pregnancy in the third trimester between the age group of 18-35 years were enrolled in the study, out of which 30 who had a BP reading of ≥140/90 mmHg were classified as cases and 30 normal, normotensive pregnant patients were classified as controls. Comparison of levels of serum calcium and magnesium of both the groups was done.
Results: This study was undertaken to analyse the serum concentration of calcium and magnesium in women with gestational hypertension and pre-eclampsia and compare these levels with normotensive pregnant women. We found that serum calcium and serum magnesium was significantly decreased amongst the cases when compared with the control group (p value <0.001).
Conclusion: Though calcium and magnesium deficiencies cannot be pin pointed as the sole factors in the etiology of pregnancy induced hypertension (PIH), these findings do support the hypothesis that hypocalcaemia and hypomagnesaemia could be possible modifiable factors in the causation of hypertension in pregnancy and their relationship cannot be denied.

Keywords: Pre-eclampsia, gestational hypertension, magnesium, calcium

Introduction
Haemorrhage, hypertensive disorders and sepsis are responsible for more than half of all maternal deaths worldwide [1, 3]. The impact of pre-eclampsia is greatest in developing countries where it accounts for 20 – 80% of the striking increase in maternal morbidity and mortality [3].
There are many similarities between the management of gestational hypertension and that of preeclampsia. Adverse pregnancy outcomes can occur as a result of gestational hypertension as well as pre-eclampsia and thus the former may not be a separate entity from preeclampsia. A rapid rise in blood pressure poses a danger to both, the mother and the foetus and as such should not be ignored only because proteinuria has not yet developed [4, 5].
Dietary deficiency of calcium consequently reduces serum calcium levels and has been implicated as a cause of pre-eclampsia in some studies. This theory can be explained by the vasoconstrictive effect that is caused by reduced serum calcium levels [6]. Stimulation of 1.25-dihydroxycholecalciferol has been implicated in this vasoconstrictive mechanism. Furthermore, Low serum calcium stimulates parathyroid hormone (PTH) production, which increases the intracellular calcium levels, this forms the physiological basis behind the hypothesis that hypocalcemia may lead to vasoconstriction and consequently a rise in BP. This leads to contraction of vascular smooth-muscle resulting in hypertension [7]. Magnesium is "nature's physiological calcium blocker" and the effects of hypocalcemia are further augmented with decreased levels of serum magnesium. Hypomagnesemia opens the L type Ca^{2+} channel and blocks the Ca^{2+}-ATPase present in sarcoplasmic reticulum and leads to increased intracellular calcium [8]. Low serum magnesium decreases prostacyclin production which in itself leads to vasoconstriction.

Nutritional interventions to prevent pregnancy induced hypertension, if successful, would have considerable clinical and public health implications, especially in resource poor countries where dietary deficiencies are prevalent and access to optimal obstetric care is limited.

Materials and Methods

Ours was a hospital based case control study conducted over a period of one year after the ethical approval. The study was conducted at Department of Obstetrics and Gynaecology, Sri Balaji Action Medical Institute, New Delhi.

Based on an article by Chaudhari R *et al*. mean serum calcium and magnesium was reported in the gestational hypertension/pre-eclamptic group was 8.69±1.59 mg/dL and 1.91±0.36 mg/dL versus 10.13±0.66 mg/dL and 2.08±0.12 mg/dL in the normotensive group. Taking this article as a reference the sample size was calculated by considering Serum calcium level as a variable [9].

Formula for sample size calculation

$$n = 2\frac{S^2(Z1 + Z2)^2}{(M1 - M2)^2}$$

Minimal samples size by above calculation is 15 in each group, however in this study we enrolled a total of 60 patients with 30 participants in each group.

The inclusion and exclusion criteria was as follows:

a) Inclusion criteria

ACOG 2013 Guidelines were applied for recruitment of cases.

Study group

- Age: 18-35 years
- Singleton pregnancy
- Gestational age >28weeks
- BP >/= 140/90 mmHg on two separate occasions 4 hours apart with or without proteinuria of more than >/= 1+ on dipstick.

Control group

- Age: 18-35 years
- Singleton pregnancy
- Gestational age >28 weeks
- BP < 140/90 mmHg

b) Exclusion criteria

- Known case of chronic hypertension
- Known case of renal disease (acute kidney injury, chronic kidney disease)
- Known case of liver disease (hepatitis, cirrhosis, liver failure)
- Known case of cardiac disease (valvular heart lesions, cardiomyopathies, congenital heart disease, coronary artery disease)
- Known case of diabetes.
- Known case of seizure disorder

Biochemical analysis

Estimation of serum calcium was done by the NM-BAPTA method and reference range was 8.6-10.3 mg/dl.

Principle and method of the procedure used for estimation of serum magnesium was Colorimetric end point method (Xylidyl blue) and the reference range was 1.6-2.6 mg/dl

Statistical analysis

Data was collected by using a structured pre-format. Data was entered in MS excel sheet and analyzed by using SPSS 24.0 version IBM USA. Qualitative data was expressed in terms of percentages. Quantitative data was expressed in terms of mean and standard deviation (SD). Comparison of mean and SD between two groups was done by using unpaired t test to assess whether the mean difference between groups was significant or not. Descriptive statistics of each variable was presented in terms of mean, standard deviation and standard error of mean. Comparison of mean and SD between all groups was done by using one way ANOVA test. Logistic regression test was applied in order to assess the effect of independent risk factors on outcome. A p value of <0.05 was considered as statistically significant whereas a p value <0.001 was considered as highly significant.

Results

We conducted a prospective observational case control study. We enrolled 60 pregnant women in their third trimester in the age group of 18-35 years. 30 women were classified as cases based on the development of hypertension for the first time during pregnancy and 30 were taken as normotensive controls. The serum calcium and magnesium level was estimated in each patient.

The mean serum calcium level in the cases was 8.33±0.58 mg/dl and 8.93±0.45 mg/dl in the controls. Comparison of the serum calcium (mg/dL) between the two groups shows that serum calcium (mg/dL) is higher in control group with a t value of 4.491and is statistically significant with a p value of <0.001.

The mean serum magnesium level in the cases was 1.63±0.24 and in the controls was 1.84±0.12. Comparison of the serum magnesium(mg/dL) between the two groups shows that serum magnesium(mg/dL) is higher in Control group with a t value of 4.249 and is statistically significant with a p value of <0.001. (Table 1)

The correlation between the systolic blood pressure (mmHg) & serum calcium (mg/dL) shows a negative correlation, and is not significant with a t value -0.343 and with a p value of 0.064. The correlation between the systolic blood pressure (mmHg) & serum magnesium (mg/dL) shows a strong negative correlation, and is significant with a p value of 0.014. (Table 2)

The correlation between the diastolic blood pressure (mmHg) & serum calcium (mg/dL) shows a negative correlation, with a p value of 0.013 which is statistically significant. The correlation between diastolic blood pressure (mmHg) & serum magnesium (mg/dL) with a t value -0.358 and a p value of 0.052 which is not statistically significant. (Table 3)

Table 1: Mean Serum calcium and mean serum magnesium value (mg/dl) in cases and controls and their p value

Parameter	Control(n=30)	Cases(n=30)	t value	P Value
	Mean ± SD	Mean ± SD		
Serum Calcium (mg/dL)	8.93±0.45	8.33±0.58	4.491	<0.001
Serum Magnesium (mg/dL)	1.84±0.12	1.63±0.24	4.249	<0.001

Table 2: Correlation between SBP and mean serum calcium and magnesium:

Systolic BP (mmHg)	140-149mmHg	150-159mmHg	≥160mmHg	P value
Mean serum calcium (mg/dl)	8.7	8.3	8.1	0.064
Mean serum magnesium (mg/dl)	1.7	1.7	1.5	0.014

Table 3: Correlation between DBP and mean serum calcium and magnesium

Diastolic BP (mmHg)	90-99mmHg	100-109mmHg	≥110 mmHg	p value
Mean serum calcium (mg/dl)	8.6	8.3	7.9	0.013
Mean serum magnesium (mg/dl)	1.7	1.6	1.5	0.052

Discussion

In India, the prevalence of hypertensive disorders of pregnancy was found to be 7.8% and incidence of preeclampsia was 5.4%. (1) It is known that the impact of pre-eclampsia is greatest in developing countries and more so within the low socio-economic group. Thus we can say that nutritional deficiencies could play a major role in the causation of hypertension in pregnancy.

Ours was a prospective observational case control study. We enrolled 60 pregnant women in their third trimester between the age group of 18-35 years. 30 women were classified as cases based on the development of hypertension for the first time during pregnancy and 30 were taken as normotensive controls. The serum calcium and magnesium level was estimated in each patient.

In this study, we observed a lower level of mean serum calcium among the cases as compared to the normotensive group (8.33±0.58 mg/dl versus 8.93±0.45 mg/dl). It is a known fact that calcium homeostasis is altered during pregnancy to meet the needs of the growing foetus [10]. Previous reports such as that by Belizan JM *et al*. in 1988 have suggested that a decrease in serum calcium may be associated with hypertension in pregnancy [11]. Our findings are similar to the studies conducted by Sukonpan K *et al*. (2004), Punthumapol *et al*. (2008), Jain S *et al*. (2009), Hofmeyr GJ *et al*. (2010), Bera S *et al*.(2011), Kanagal DV *et al*. (2014) [6, 12-16].

Furthermore, we found a negative correlation between serum calcium and systolic BP with a p value of 0.064 and though we cannot conclude that it was statistically significant we can say that it is somewhat significant. We also found a statistically significant negative correlation between serum calcium and diastolic BP with a p value of 0.013. It simply means that the level of serum calcium decreased with an increase in systolic and diastolic BP among the subjects studied. This finding further corroborates the hypothesis that calcium may play an important role in the causation of hypertension in pregnancy. Our findings were similar to the studies conducted by Ephraim *et al*. (2014), Onyegbule O *et al*. (2014), Aghade S *et al*. (2017) [17-19].

This concept of a reduced serum calcium level in the causation of pregnancy induced hypertension, however, is not accepted universally and Salari Z *et al*. (2005), Bera S *et al*. (2011) [20, 14], found no significant change in the serum levels of calcium among the hypertensive group when compared to the normotensive subjects which is contrasting to this study. This could be due to differences in the method of assay, dietary patterns of the subjects and geographical variation.

Magnesium sulphate is the drug of choice and is highly effective for the treatment of severe pre-eclampsia and eclampsia. Magnesium plays an important role in the neurochemical transmission and has an important role in peripheral vasodilation. It is also an essential cofactor for many enzyme systems [21, 23].

In our study, the mean serum magnesium level among the controls was 1.84±0.12 mg/dl and 1.63±0.24 (mg/dl) among the cases. Comparison of the serum magnesium (mg/dL) between the two groups shows that serum magnesium (mg/dL) is significantly lower in the cases. We also observed a strong negative correlation of serum magnesium with systolic BP with a p value of 0.014 which was statistically significant and a negative correlation of magnesium with diastolic BP. Since the p value of this comparison was 0.052 we cannot call it statiscally significant. However an association of serum level of magnesium, or more importantly, hypomagnesemia with hypertensive disorders of pregnancy cannot be denied.

Our finding is similar to that of Sukonpan K *et al*. (2004), Jain S *et al*. (2009), Chaurasia P *et al*. (2012), Omotayo O *et al*. (2015), Al-Jameil N *et al*. (2015), Bharti A *et al*. (2018) [6, 13, 24-27]. These results support the hypothesis that a reduction in the serum levels of magnesium during pregnancy may play a role in the causation of hypertensive disorders of pregnancy. Thus supplementation of these elements to the diet may be of value to prevent pregnancy induced hypertension.

This was in contrast to the studies conducted by Punthumapol *et al*. (2008), Golmohammad *et al*. (2015), Dwarka E *et al*. (2017) [12, 28, 29] who have disputed the role of trace elements in hypertensive disorders of pregnancy. This is debatable because magnesium therapy during eclamptic seizures has been shown to oppose arterial constriction by blockage of calcium entry via voltage-gated channels [20]. The causal relationship between hypomagnesaemia and hypertensive disorders of pregnancy can also be explained by the hypothesis that magnesium deficiency may be responsible for spasm of umbilical and placental vasculature [30]. Thus hypomagnesaemia may be one of the important factors for the pathophysiological changes of pregnancy induced hypertension.

The National Nutrition Monitoring Bureau (NNMB) - 2012 data from 10 Indian states shows that the daily calcium intake during pregnancy and lactation for Indian women is less than 30% of RDA. This shows that most pregnant and lactating women in India have low dietary calcium intake [31]. In populations with low dietary calcium intake, the WHO recommends a daily calcium supplementation (1.5 g–2.0 g oral elemental calcium) for pregnant women to reduce the risk of pre-eclampsia [32]. No such guidelines for magnesium supplementation exist as yet.

We conducted this study to find out the serum levels of calcium and magnesium and to evaluate the association between these elements and gestational hypertension and pre-eclampsia. There was a significant reduction in the levels of both these elements in our study.

Conclusion

Our study shows that both serum calcium and serum magnesium were significantly lower in pregnant women with hypertension when compared with normal pregnant women. Thus, intake of supplements of these trace elements may help in the reduction of incidence of hypertension in pregnancy especially in a

population of a developing countries where the nutrition of the average woman is poor.

Though calcium and magnesium deficiencies cannot be pin pointed as the sole factors in the etiology of PIH, these findings do support the hypothesis that hypocalcaemia and hypomagnesaemia could be possible modifiable factors in the causation of hypertension in pregnancy and their relationship cannot be denied.

The results of this study may help us better understand the pathophysiological process behind the development of hypertension in pregnancy, more so its association with trace elements, and assist us to establish and boost existing preventive strategies for the condition. Adequate dietary mineral supplementation during the antenatal period, at least in susceptible women, may influence significantly, the occurrence of hypertensive disorders in pregnancy and could provide us with a simple and cost-effective preventive measure.

Not many studies have been done in developing countries to assess the role of these elements in hypertensive disorders of pregnancy. The actual role of calcium and magnesium supplementation needs to be further investigated by larger multicentric studies.

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