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

1Vandana Varma, 2Sonal Sogani, 3Purnima Dey Sarkar

ABSTRACT

Background: Despite numerous studies, the etiology of pre-eclampsia has not been fully elucidated. The study of serum calcium and serum magnesium is gaining ground in the pathophysiology of hypertension.

Objective: A comparative study of serum calcium and serum magnesium in women with pre-eclamptic pregnancy and its comparison with healthy normotensive nonpregnant women and healthy normotensive pregnant women in third trimester.

Materials and methods: Serum calcium and serum magnesium were measured in 52 women with pre-eclampsia in their trimester of pregnancy as patients group, and in 73 healthy normotensive nonpregnant women and 65 healthy normotensive pregnant women as control groups with similar maternal and gestational ages. Pre-eclamptic group was further divided into two subgroups mild (n = 36) and severe pre-eclampsia (n = 16). This is the case-control hospital based study carried in the Department of Biochemistry, MGM Medical College and associated MY Hospital, Indore, Madhya Pradesh.

Results: There were no significant differences among the three groups in age and body mass index (BMI) (p > 0.05) but significantly higher differences in gestational age, systolic and diastolic blood pressure was observed (p < 0.001). When comparison of serum calcium and serum magnesium between healthy normotensive nonpregnant women (9.87 ± 0.6 mg/dl, 2.60 ± 0.3 mg/dl) and healthy normotensive pregnant women was done, the levels were lower in the healthy normotensive pregnant women (9.34 ± 0.49 mg/dl, 2.36 ± 0.13 mg/dl) with statistically higher significant difference (p < 0.001). Lower mean values of serum calcium and serum magnesium were found in pre-eclamptic women (8.82 ± 0.93 mg/dl, 1.74 ± 0.24 mg/dl) than those of healthy normotensive nonpregnant women (9.87 ± 0.6 mg/dl, 2.60 ± 0.3 mg/dl) and healthy normotensive pregnant women (9.34 ± 0.49 mg/dl, 2.36 ± 0.13 mg/dl) in third trimester with statistically higher significant differences (p < 0.001). As compare to mild pre-eclamptic pregnant women (9.07 ± 0.8 mg/dl, 1.77 ± 0.24 mg/dl), the levels of serum calcium and serum magnesium in severe pre-eclamptic pregnant women (8.25 ± 0.97 mg/dl 1.65 ± 0.24 mg/dl) was lower and the difference was significantly higher (p < 0.001).

Conclusion: These findings support the hypothesis that hypocalcemia and hypomagnesemia are possible etiologies of pre-eclampsia and levels of calcium may be more important than magnesium.

Keywords: Calcitonin gene related peptide, Parathyroid hormone related peptide, Pre-eclampsia, Pregnancy-induced hypertension, Serum calcium, Serum magnesium.

How to cite this article: Varma 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 J Med Sci 2015;2(3):137-141.

Source of support: Nil
Conflict of interest: None

INTRODUCTION

Hypertension, defined by a blood pressure (BP) of 140/90 mm Hg or more, is a universal problem affecting at least 10% of all pregnancies. Half of the pregnant women with hypertension have pre-eclampsia. Hypertensive disorders accounts for up to 40,000 maternal deaths annually. Pre-eclampsia (hypertension in pregnancy in association with the excretion of >300 mg of urinary protein per day after 20th weeks of gestation) is an important cause of both maternal and perinatal morbidity and mortality. It is a transient but potentially dangerous complication of pregnancy affecting 5 to 8% of pregnancies. Because of multiple hypothesis, it has been dubbed as the ‘disease of theories’. Although the etiology of pre-eclampsia has not been fully elucidated, the contributing factors are obesity, diabetes, calcium deficiency, older maternal age. Environmental and nutritional factors may, therefore, play a role in the etiology of pre-eclampsia.
Calcium, one of the intracellular ions, is the most prevalent cation and the abundant mineral found in the body. These are needed for transmission of nerve impulses, muscle contraction, blood vessel contraction and expansion, secretion of hormones and enzymes, act as a cofactor in certain enzyme reactions, water balance in the cells, sending messages through the nervous system and in the coagulation of the blood as it is factor IV in blood coagulation. It is known that the deficiency of calcium may lead to capillary hemorrhages, tetanic convulsions, tissue exudation, osteomalacia, etc. Regulation of intracellular calcium plays a key role in hypertension.

Magnesium is the 4th most abundant cation of intracellular fluids. It is present in more than 300 enzymatic systems where it is crucial for ATP metabolism. It also acts as a calcium channel antagonist. The results of low magnesium may lead to a reduction in cerebral blood flow, cerebral vasospasm, and neuronal burst. Magnesium has a vasoprotective effect. These features have gotten some resemblance to the clinical manifestations and pathological findings in pregnancy induced hypertension (PIH), particularly eclampsia. Magnesium acts as a potent vasodilator and its depletion increases the vasoconstrictor effect of angiotensin II and nor-adrenaline thus increases blood pressure.

Since the serum calcium and serum magnesium contribute significantly in the functioning of the vascular smooth muscles, the present study was designed to evaluate the role of the serum calcium and serum magnesium in PIH.

MATERIALS AND METHODS

This case control study was conducted in the Department of Biochemistry, MGM Medical College and associated MY Hospital, Indore. The subjects were pregnant women clinically diagnosed as pre-eclampsia during third trimester (28–40 weeks) with the age 18 to 35 years (group-C) visiting obstetrics OPD and wards of MY Hospital. The study group was further divided into two subgroups. It comprised of 36 mild pre-eclamptic pregnant women (Subgroup C1) and 16 severe pre-eclamptic pregnant women (Subgroup C2) on the basis of blood pressure, (both systolic and diastolic) proteinuria and pathological edema, which is the diagnostic criteria of pre-eclampsia. A control group-73 healthy normotensive nonpregnant women (Group A) and 65 healthy normotensive pregnant women (Group B) were taken. The healthy normotensive pregnant women were also in the third trimester (28–40 weeks) of their pregnancy with the age 18 to 35 years. Group A women were normotensive, nonproteinuric and in child bearing age of 20 to 40 years. Inclusion criteria for women included in the study were should not be using any kind of oral contraceptives, anticoagulant drugs, should be non-smokers and nonalcoholics and exclusion criteria were: past history of diabetes, systemic or endocrine disorder, chronic infection, chronic renal disease and hypertension (in groups A and B only), women in the labor pains, were excluded from the study. Institutional ethics committee’s approval was obtained prior to start of the study.

Pre-eclampsia was diagnosed according to American College of Obstetrics and Gynecology (ACOG) criteria: a blood pressure higher than 140/90 mm Hg and proteinuria more than 300 mg/24 hr were observed on at least two occasions more than 6 hours apart after the 20th weeks of pregnancy. Pre-eclampsia were classified as severe if diastolic blood pressure increased to at least 110 mm Hg, proteinuria >5000 mg per day and the presence of headache, visual disturbances, epigastric pain, oliguria, elevated liver function test (LFT), elevated renal function test (RFT), thrombocytopenia.

Sample Collection

Blood samples were collected in the morning in a plain bulb with aseptic conditions. In the pre-eclampsia group, blood samples were collected when the patients presented for evaluation and before initiation of medical therapy. Serum calcium levels were measured by kits using an Arsenazo III method and serum magnesium levels were measured by kits using a calmagite method. The results were expressed as mean ± SD and groups were compared using analysis of variance (ANOVA).

Statistical Analysis

It was carried out by using statistical package for social sciences (SPSS) software, version 20. The level of significance was set at < 0.05.

RESULTS

The anthropometric factors of the study groups are summarized in Table 1. Maternal age and body mass index (BMI) were not significantly different between the groups (p > 0.05, Table 1). Gestational age, systolic and diastolic blood pressures were significantly higher in pre-eclamptic groups as compared to healthy normotensive nonpregnant and healthy normotensive pregnant women (p < 0.001, Table 1). The same when compared between mild and severe pre-eclamptic groups, it was found to be significantly higher in severe pre-eclamptic group (p < 0.001, Table 1).

Serum calcium and serum magnesium in healthy normotensive pregnant women (9.34 ± 0.49 mg/dl, 2.36 ± 0.13 mg/dl) was reduced when compared with healthy normotensive nonpregnant women (9.87 ± 0.6 mg/dl,
Comparative Study of Serum Calcium and Magnesium in Pre-eclamptic Pregnancies in Third Trimester

Table 1: Comparison of mean and standard deviation of anthropometric factors of control and pre-eclamptic groups

<table>
<thead>
<tr>
<th>Anthropometric factors</th>
<th>Group A healthy non-pregnant women (n = 73)</th>
<th>Group B healthy normotensive pregnant women (n = 65)</th>
<th>Group C Pre-eclamptic pregnant women (n = 52)</th>
<th>Subgroup C1 mild pre-eclamptic pregnant women (n = 36)</th>
<th>Subgroup C2 severe pre-eclamptic pregnant women (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>22.73 ± 3.65</td>
<td>22.67 ± 2.53</td>
<td>23.57 ± 3.73</td>
<td>23.52 ± 3.8</td>
<td>23.68 ± 3.7</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.21 ± 1.31</td>
<td>23.82 ± 1.61</td>
<td>24.19 ± 1.94</td>
<td>24.38 ± 1.95</td>
<td>23.78 ± 1.90</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>—</td>
<td>38.81 ± 3</td>
<td>36.63 ± 1.68</td>
<td>36.94 ± 1.54</td>
<td>35.93 ± 1.8</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>114.10 ± 7.68</td>
<td>114.0 ± 7.02</td>
<td>146.92 ± 16.27</td>
<td>138.61 ± 5.92</td>
<td>165.62 ± 16.72</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>73.84 ± 7.64</td>
<td>75.07 ± 5.33</td>
<td>98.65 ± 13.10</td>
<td>92.5 ± 7.22</td>
<td>112.5 ± 12.9</td>
</tr>
</tbody>
</table>

Table 2: Comparison of mean and standard deviation of clinical parameters of control and pre-eclamptic groups

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>Group A healthy non-pregnant women (n = 73)</th>
<th>Group B healthy normotensive pregnant women (n = 65)</th>
<th>Group C Pre-eclamptic pregnant women (n = 52)</th>
<th>Subgroup C1 mild pre-eclamptic pregnant women (n = 36)</th>
<th>Subgroup C2 severe pre-eclamptic pregnant women (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum calcium (mg/dl)</td>
<td>9.87 ± 0.6</td>
<td>9.34 ± 0.49*</td>
<td>8.82 ± 0.93**</td>
<td>9.07 ± 0.8@</td>
<td>8.25 ± 0.97#</td>
</tr>
<tr>
<td>Serum magnesium (mg/dl)</td>
<td>2.60 ± 0.3</td>
<td>2.36 ± 0.13*</td>
<td>1.74 ± 0.24**</td>
<td>1.77 ± 0.24@</td>
<td>1.65 ± 0.24#</td>
</tr>
</tbody>
</table>

*p < 0.001—compared with healthy non-pregnant women, **p < 0.001—compared with healthy non-pregnant women and healthy normotensive pregnant women, @p < 0.001—compared with healthy non-pregnant women and healthy normotensive pregnant women and mild pre-eclamptic pregnant women

2.60 ± 0.3 mg/dl) with statistically higher significant difference (p < 0.001, Table 2) and was found to be lowest in pre-eclamptic pregnant women (8.82 ± 0.93 mg/dl, 1.74 ± 0.24 mg/dl) as compared to healthy normotensive nonpregnant women and healthy normotensive pregnant women with statistically higher significant difference (p < 0.001, Table 2). When serum calcium and serum magnesium in mild pre-eclamptic pregnant women (9.07 ± 0.8 mg/dl, 1.77 ± 0.24 mg/dl) was compared with severe pre-eclamptic pregnant women (8.25 ± 0.97 mg/dl, 1.65 ± 0.24 mg/dl), it was found to be reduced in the latter group and the difference was significantly higher (p < 0.001, Table 2).

DISCUSSION

The estimation of serum calcium and serum magnesium in PIH provides a very useful index for the study of physiological and pathological changes during pregnancy. In many studies, decrease in serum calcium levels13 and decrease in serum magnesium levels14 has been considered as the cause of pathogenesis of pre-eclampsia. On the basis of some studies claim that serum calcium and serum magnesium have a relaxant effect on the blood vessels of pregnant women.15 In the present study, a highly significant decrease in serum calcium was seen in the normal pregnant women as compared to the healthy nonpregnant women, with a further highly significant decrease in the pre-eclamptic pregnant women. This contention is amply supported by a few other studies.13,16 Calcium metabolism is under strain during pregnancy. Expected mothers need to store about 30 to 50 gm of calcium during the course of pregnancy, of which 25 gm are needed by the fetus for fetal bone formation. Eighty percent of the total fetal calcium is deposited during the third trimester. The transport of ionized calcium from the mother to the fetus increases from about 50 mg/day at 20 weeks of gestation to a maximum of about 350 mg/day at 35 weeks of gestation.17 As during pregnancy, there is a hemodilution and with the expansion of extracellular fluid volume, there is a dilution of the cation and also lead to normal hypercalciuria of pregnancy consequent to increased glomerular filtration.18 Our study concluded that the serum calcium in normal pregnant women was reduced
when compared with healthy nonpregnant women with the statistically highly significant difference (p < 0.001) as supported by Olatunbosun et al19 who earlier in their study observed a highly significant reduction in serum concentration of calcium during the third trimester of normal pregnancy.

According to one study, in normal pregnancy hemodilution effect of estrogen and increased demand of fetus decreases the serum magnesium level.20 In the present study, serum magnesium levels in normal pregnant women as compared to healthy nonpregnant women was low in accordance with that of the study shown by Kesteloot H.20 Our study reveals that serum calcium and serum magnesium levels in pre-eclamptic pregnant women as compared to normal pregnant women was lower and the difference was statistically higher (p < 0.001). When comparison between mild and severe preeclamptic groups was done, it was concluded that the levels of both the parameters were lower in the latter group with statistically highly significant difference (p < 0.001). These results match previous data which suggest that there was an inverse relationship between serum calcium and magnesium and incidence if pregnancy-induced hypertension.13,16,21 Decreased serum calcium levels lead to an increase in the parathyroid hormone levels, thereby increasing the intracellular calcium levels, which leads to an increase in vascular smooth muscle contraction and thus, an increase in blood pressure.8 Some researchers have also shown an increased intracellular ionized calcium concentration and an increased sensitivity of these cells to angiotensin II in women with pre-eclampsia.22 Magnesium acts peripherally to produce peripheral vasodilatation by increasing the prostacyclin release from the endothelial cells which acts as a potent vasodilator and a fall in blood pressure. Thus, low level of magnesium predisposes to an increase in the arterial pressure by increasing the vasoconstrictor effects of angiotensin II and nor-adrenaline.23

According to another study, calcitonin gene-related peptide (CGRP) and parathyroid hormone-related peptide (PTHrP) is a potent vasodilatory peptide which increases in maternal circulation during pregnancy. Both peptides may have a role in blood pressure regulation because of their vasorelaxant properties.24 CGRP and PTHrP is involved in uterine relaxation during pregnancy. Increased receptor number in pregnancy aids in the initiation of labor.25 But in preeclampsia both the circulating peptides are imbalanced, and thus its low level was found to be responsible for the increase of peripheral resistance and BP; thus, it may be important in pathogenesis of pre-eclampsia.26

CONCLUSION
It is concluded from the study that low levels of serum calcium and serum magnesium were found in pre-eclamptic pregnant women as compared to healthy nonpregnant and healthy normotensive pregnant women. As compared with mild pre-eclamptic group, the level of serum calcium and serum magnesium was significantly lower in severe pre-eclamptic group. These results may support the hypothesis on the role of calcium and magnesium deficiency in pre-eclampsia pathophysiology and suggest the usefulness of its assessment in the early diagnosis of the disorder. Thus, hypocalcemia and hypomagnesemia leads to smooth muscle contraction and an elevation in blood pressure causing PIH.

ACKNOWLEDGMENT
We are highly grateful to those patients of the hospital who volunteered to donate their blood when needed for this project. Our thanks are also to the paramedical staff of the hospital for their assistance in collecting and maintaining blood samples.

REFERENCES
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