Role of Macronutrients in the Prevention of Pre-Eclampsia - A Cross Sectional Study at a Tertiary Care Centre in North India

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ABSTRACT

BACKGROUND

Role for macronutrient supplementation in preventing pre-eclampsia is now backed with evidence which is evolving rapidly. We wanted to study and compare serum calcium and serum magnesium levels in pre-eclamptic women and women with normal pregnancy.

METHODS

30 women with normal pregnancy and 30 women with preeclampsia were included in the study. Their serum calcium and magnesium levels were estimated using colorimetry.

RESULTS

Serum calcium levels in normotensive patients was found to be 9.3 ± 0.95 mg / dL and in preeclamptic patients, it was 8.3 ± 0.85 mg / dL. Serum magnesium levels were found to be 1.94 ± 0.24 mg / dL and 1.57 ± 0.125 mg / dL in normal and pre-eclamptic women respectively. These values were affected by age, parity, BMI, socio-economic status, and nutrition before and during pregnancy.

CONCLUSIONS

Low values of maternal serum calcium along with magnesium are related to pre-eclampsia which might have an association in this disease. We also realised that evaluation of base-line levels of serum calcium and magnesium are necessary during early pregnancy. Constant monitoring of blood pressure is also essential. Adequate intake of macronutrients is essential for maintaining health of both mother and child. Hence, measurable and realistic efforts must be made along these lines. Nutrition is a key concern in pregnant women and is pivotal in ensuring health in this vulnerable group.

KEYWORDS

Pre-Eclampsia, Serum Calcium, Serum Magnesium, Pregnancy, Macronutrients

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BACKGROUND

Almost 5 - 10 % pregnancies are complicated as a result of hypertensive disorders.[1] The incidence in primigravid women is about 6 %.[2] Celsus described this disorder almost 2000 years ago wherein pregnant women with seizures improved after delivery and was called as 'Eclampsia'. Proteinuria and blood pressure association with eclampsia was seen in the late 1800s along with the fact that hypertension and urinary proteins preceded the seizures. Thus, the term 'Pre-Eclampsia' came into being.[3]

It is a condition which progresses rapidly characterized by hallmarks of elevated blood pressure, platelet aggregation, oedema and proteinuria. Commonly, elevated blood pressure in pre-eclamptic condition occurs towards the end of third trimester. Hypertension for the first time in mid pregnancy with a blood pressure of more than 140 / 90 with no significant proteinuria is the key requirements for a diagnosis of gestational hypertension.[1] One of the objective markers for pre-eclampsia syndrome is proteinuria that has constantly raised blood pressure with readings more than 140 / 90 mm Hg, along with proteinuria and oedema.[1] Some other associated complications are vision disorders, low urine output, eclampsia, haemolysis, increased enzymes of liver, thrombocytopenia, pulmonary oedema, bilateral renal cortical necrosis and restricted fetal growth.[4]

Pregnancy is a very crucial and important stage where along with a change in the woman's physiology as well as essential requirements of a growing fetus are met by increased metabolic demands. The effects of pre-eclampsia in developing countries is even more devastating with it being responsible for 20 - 80 % of the significantly increased maternal mortality.[5] Annually hypertensive disorders are responsible for 40,000 maternal deaths[6] and there has been a proportional awareness to address methods to curtail the risk of disorders such as elevated blood pressure in pregnancy. Research is more and more concentrating on prevention as a better modality than treatment. Aspect of role for macronutrients supplementation in preventing pre-eclampsia pregnancy disorders is now backed with evidence.

Risk of gestational hypertension including pre-eclampsia can be reduced by supplementing calcium and magnesium intake.[7] Stimulation of parathyroid hormone is the mechanism of action played by which decreased serum calcium leads to hypertension as well as renin release and consequent vasoconstriction.[5,8,9] Although not directly but calcium also affects smooth muscle function leading to increased magnesium levels.[6] Another significant role is played by magnesium in peripheral vasodilatation.[9] Hence, this study was planned in order to re-emphasize the importance of supplementing macronutrients in pregnancy for preventing pre-eclampsia.

METHODS

Study was undertaken at a tertiary care hospital in North India with approval from the Institutional Ethical Committee. An informed written consent was obtained from each participant after explaining the nature of the study, in English and local language (Hindi) depending on the comfort level of each patient.

Sample Size

Based on prevalence from literature review a sample size of 20 in each group would have 80 % power to estimate a mean difference of 1.1 mg / dL (assuming α to be 5 %). Therefore, conservatively 30 subjects in each group were selected and a total sample size of 60 was arrived at (sample size calculated using n Master Version 2.0).

A cross sectional comparative study was carried out over 04 months to study the levels of calcium and magnesium amongst pregnant women with and without pre-eclampsia. The population under study were the pregnant women who were reporting to the antenatal clinic and women admitted in the Obstetrics Ward of the hospital. Out of the 60 subjects 30 were with pre-eclampsia and the other 30 subjects were without pre-eclampsia.

Pre-eclampsia was defined by the criteria given by Sibai et al.[10] These are:

1. Onset of hypertension at > 20 weeks' gestational age
2. 24-hour proteinuria ≥ 30 mg / day or, a protein concentration of ≥ 30 mg (≥ 1 + on dipstick) in two random urine samples collected 4 - 6 hours apart with pedal oedema.
3. Systolic blood pressure > 140 mmHg or diastolic blood pressure ≥ 90 mmHg as measured twice, using an appropriate cuff, 4 – 6 hours apart.

Inclusion Criteria

1. Pregnant women in the age group 20 - 40 years with single intrauterine pregnancy.
2. Gestational age > 20 weeks.
3. All cases meeting the above defined criteria of pre-eclampsia.

Exclusion Criteria

1. Women with previous history of gestational hypertension.
2. Women with associated antecedent diseases like long standing hypertension, kidney disease, cardiac diseases, disorder of liver and endocrine disorders affecting the thyroid and pancreas.
3. Women revealing history of nicotine, alcohol and drug consumption.
4. Case of eclampsia.

Body Mass Index of all participants was calculated using the formula[11]

$$\frac{\text{Weight(Kg)}}{(\text{Height})^2(\text{m}^2)}$$

The age, gravida and other details were also charted. A thorough history of all women was taken including detailed family history. Clinical examination was also done. Blood

pressure monitoring was done by manual method using sphygmomanometer while confirming pre-eclampsia on inclusion into study. The proteinuria was also confirmed by laboratory methods. The pre pregnancy weight and height were noted. Comorbidities were ruled out in all the study participants.

Collection and Processing of Sample

5 mL of blood was taken in a red-capped plain vacutainer using all possible aseptic precautions from the ante cubital vein. After centrifugation the serum was analysed for levels of serum calcium and magnesium by colorimetric method. The analysis was done in the EM 360 fully automated biochemistry analyser in our hospital laboratory. Serum calcium was estimated by the Arsenazo III method and serum magnesium was estimated by the Xylidyl blue method.

Mean ± standard deviation was brought out in the results and statistical analysis was done using the software SPSS version 20. Comparison of serum levels of calcium and magnesium between the two groups was performed by independent t-test and p-value was calculated. The p-value of < 0.05 was considered as statistically significant.

RESULTS

The age group of participants in the study was between 20 - 40 years.

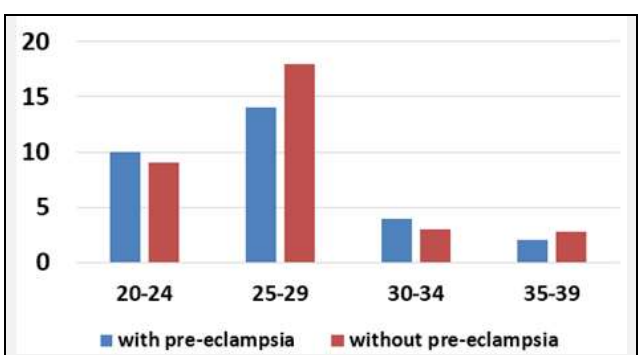

Figure 1. Distribution of Age among the Two Groups

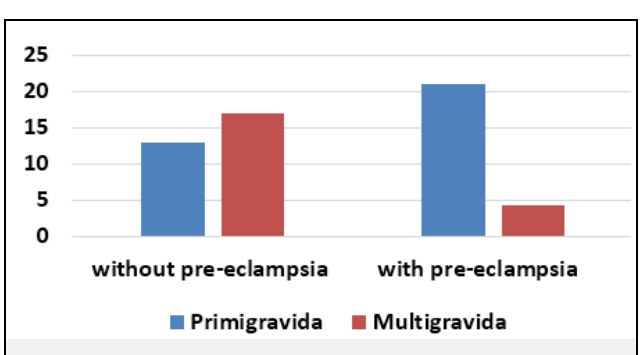

Figure 2. Distribution of Primi and Multi Gravida

It was found that in the normotensive control group 80 % women were below 30 years of age (n = 27) while in the pre-eclamptic group majority of the women were in the age group of 25 - 29 years. 20 % of women in this group were above 30 years of age. This age distribution is tabulated in Figure 1.

70 % women in the pre-eclampsia group were primigravida (n = 21) while only about 43 % (n = 13) in the normotensive group were pregnant for the first time. There were more multigravida in the control group. This is tabulated in Figure 2.

Mean BMI (Kg / m^2) in the pre-eclamptic group was 26.2 while that in the group without pre-eclampsia was 24.4. The BMI in the preeclamptic group was found to be slightly higher than that of women with normal pregnancies

The mean serum calcium levels in the normotensive pregnant women was 9.3 + / - 0.95 mg / dL and the values in the pre-eclamptic group of women was found to be 8.3 + / - 0.85 mg / dL. The difference between the two groups was found to be statistically significant with p value of < 0.01 (p < 0.05 is significant). This distribution is shown in Table 1.

Parameter	Subject	N	Mean	S.D.	Std. Error Mean	P Value
Calcium (mg / dL)	With pre-eclampsia	30	8.30	.85	.15	< 0.001
	Without pre-eclampsia	30	9.34	.95	.17	

Table 1. Comparison of Serum Calcium in the Two Groups

The serum magnesium levels in normotensive women were found to be 1.94 + / - 0.24 mg / dL and in pre-eclamptic pregnant women was 1.57 + / - 0.123 mg / dL. The p value was highly significant at < 0.01 revealing the significant difference in levels in the two groups. This is tabulated in Table 2.

Parameter	Subject	N	Mean	S.D.	Std. Error Mean	P Value
Magnesium (mg / dL)	With pre-eclampsia	30	1.57	.12	.022	< 0.001
	Without pre-eclampsia	30	1.94	.24	.044	

Table 2. Comparison of Serum Magnesium in the Two Groups

DISCUSSION

This study was conducted to measure the serum calcium and serum magnesium levels in pre-eclamptic pregnant women and compare it with levels in normal pregnant women. 30 subjects were taken in each group and all the inclusion and exclusion criteria were followed.

It was observed that out of the women in the age group 30 - 34 more cases were found in the pre-eclamptic group. This may be due to the fact that advancing maternal age is a risk factor for pregnancy induced hypertension. Women with age more than 35 years have an increased risk of pre-eclampsia and this increases further with age > 40 years.[12]

It was observed in our study that most of the women in the pre-eclamptic group were primigravida's. This has been observed in other studies as well [13,14,15,12] and may have an immunological basis due to which only the first pregnancy is

affected, wherein subsequent pregnancies are not affected. The paternal alloantigens in the fetus may be the cause of this immunological reaction.

The body mass index in the pre-eclamptic group was found to be slightly higher than that of the control group. Obesity as well as BMI in the range of overweight (BMI ranging between 26 - 29) are known risk factors for increased blood pressure and various food habits may contribute to this effect. This may be the reason that women with higher BMI are more prone to pregnancy induced hypertension.[15,16,17]

Our study observed statistically significant lower serum calcium and serum magnesium levels in patients with pre-eclampsia as compared to normal pregnancy. Our findings are consistent with various studies both international and Indian[18,19,20,21] but was inconsistent with some others which did not find a significant decline in these levels[22,23,24,25] This difference could be due to the different genetic pool and socio-demographic profile of the population. The baseline serum levels may also play a significant role, which maybe low in the population to begin with.

The mean value of calcium was slightly lower than the normal range of 8.4 - 10.2 mg / dL in the pre-eclamptic group in contrast to the non-pre-eclamptic group which was within normal range. Similarly, serum magnesium values, which are normally at 1.6 - 2.6 mg / dL according to our study, showed slightly lower mean among the pre-eclamptic group of patients. This probably points to the fact that lower baseline serum levels of calcium and magnesium may be of significance.

Calcium is the mineral which supplies the strength to bones that support locomotion, and also serves as a reservoir to maintain serum calcium levels.[26] Calcium is the nutrient that has been best studied in relationship to pre-eclampsia. Decrease in serum calcium levels cause intracellular calcium levels to increase which leads to constriction of smooth muscles in blood vessels and hence increased vascular resistance.[27,28,29] resulting in a raised systolic and diastolic blood pressure. The observation is further supported by the 2011 WHO recommendation, which found a higher risk of pre-eclampsia in pregnant women with low dietary intake of calcium and recommended supplementation for such women.[30] The richest dietary source of calcium is milk, milk products, tofu and fortified food. A cup of milk provides 300 mg of calcium. World Health Organisation [31] recommends 1200 mg / day of calcium in normal pregnancy and 1.5 to 2 gm elemental calcium in women with high risk of gestational hypertension from 20 weeks of gestation till termination of pregnancy. An upper limit of 3 gm calcium per day is also set by WHO. Pregnant women who have low-calcium diets will gain maximum benefit from a supplementary calcium since prior to their entry into a stage of calcium imbalance they already have a depleted store, which leads to depletion of calcium from maternal reserves in order to fulfil fetal developmental needs.[31]

Belizan et al,[32] as early as 1991, in his double blinded randomized controlled trial found that supplementation with 2 gm. calcium / day decreased the incidence of pregnancy induced hypertension. He also suggested that the urinary calcium to creatinine ratio was a good predictor of this effect. Levine et al,[33] in his study however did not find supplementation with calcium to help reduce pregnancy induced hypertension. It was although noted that calcium may be of value in women with lower intake of dietary calcium. Bucher HC et al[22] in a meta-analysis randomised controlled trial involving 2459 women found reduction in risk of pre-eclampsia in women who took calcium (odds ratio - 0.38). Another meta-analysis of 8 studies done in China by Xingmei Feng[34] found significant differences in serum calcium levels in hypertension as a result of pregnancy as compared to pregnant women without hypertension. Saila SB et al[20] showed a significant decline in the serum calcium levels in pregnancy induced hypertension so did Kanagal et al[21] and Pairu et al [18] from India. According to their results, intake of supplements, such as calcium will lead to decreased incidence of pre-eclampsia which is highly significant in a country like ours where the nutrition is poor.

Magnesium is an electrolyte found in the human body and is required by living organisms for their sustenance. According to the kit that we have used for measuring serum magnesium levels, the normal values are 1.6 - 2.6 mg / dL. Various chronic and inflammatory diseases are known to be associated with decreased levels of magnesium.[35]

The requirement for magnesium is about 400 mg / day for men & 300 mg / day for women, more is required during pregnancy and lactation. Magnesium has been established as successful therapy for eclamptic seizures and the in vitro effect of magnesium on vascular responses proves that magnesium in women with pre-eclampsia might have decreased magnesium levels.[36] It also plays an important role in neurochemical transmission and peripheral vasodilatation.[30]

Pairu et al[18] in his study depicts a moderate significance between the reduced values in hypertension as a result of pregnancy as compared to pregnant women without hypertension. Various studies[37,38,39,40] suggest association of pre-eclampsia with hypomagnesaemia.

Vafaei et al[23] showed that there is no clinical significance of magnesium levels in pre-eclampsia. But a relationship to severity of gestational hypertension was found in the study. Amirabi A[24] also showed no correlation between magnesium levels and pregnancy induced hypertension. Increased renal clearance during pregnancy, inadequate dietary intake, requirement of minerals by developing fetal skeletal system, haemodilution, all have a role in contributing hypomagnesaemia. Sanders et al[25] also refuted the role of reduced magnesium in pregnancy induced hypertension.

CONCLUSIONS

Serum calcium and serum magnesium levels in patients with pre-eclampsia were significantly lower as compared to normal pregnancy. The study emphasises the need to monitor these macronutrient values in antenatal period especially in high risk cases to reduce the incidence of gestational hypertension. The limitations of our study were the small sample size, lack of detailed socio-demographic picture, pre-pregnancy serum values of serum calcium and

magnesium and supplements given before and during pregnancy. Further larger studies needed to address these issues and establish causal association.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.

Financial or other competing interests: None.

Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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