



Original Research Article

Association of vitamin D deficiency during pregnancy with pre-eclampsia and eclampsia- A Case control study

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Abstract

Background: *The etiology of pre-eclampsia (PE) is not yet fully known, although current literature indicates an inflammatory mediators produced by the placenta as a potential causal mechanism. Vitamin D is emerging as a promising agent for pre-eclampsia prevention. This study was done to determine whether vitamin D deficiency is an independent risk factor for pre-eclampsia/eclampsia.*

Methods: *A prospective case-control study was conducted on 60 cases and 60 controls (with same age and sex matched without risk of pre-eclampsia) groups pregnant women admitted to our tertiary care hospital between July 2016 and august 2017. Detailed history and complete physical examination was done in all patients. It was recorded on a pre planned record sheet. All the Investigations carried out at were recorded in this record sheet throughout the duration of the study. Hypertension is diagnosed when 2 B.P. (Blood pressure) readings of 140/90 mm Hg or greater are noted 6 hours apart within a 1-week period.*

Results: *This study showed a very high prevalence of vitamin D deficiency in pregnant women, 90% women with preeclampsia and eclampsia had Vitamin D deficiency (vit D<20ng/ml) as compared to 3.33% in the control group, which was statistically significant (p value < 0.05). Mean serum vit. D concentration was lower in women who subsequently developed preeclampsia and eclampsia (12.65±5.112) compared with controls (51.15±16.357), statistically significant (p<0.05). Mean S.calcium level was lower in pre eclampsia and eclampsia (7.65±0.732) as compared to control (8.87±1.186) which was also statistically significant (p<0.05).*

Conclusion: *Maternal vitamin D deficiency may be an independent risk factor for preeclampsia. Vitamin D and calcium supplementation in early pregnancy should be given for preventing pre-eclampsia /eclampsia and to promote neonatal well-being.*

Keywords: *Pre eclampsia , Eclampsia, Vitamin D, Pregnancy.*

Introduction

Pre-eclampsia, formerly called toxemia, is when pregnant women have high blood pressure, protein in their urine, and swelling in their legs, feet, and

hands. It can range from mild to severe. It usually happens late in pregnancy, though it can come earlier or just after delivery.

The incidence of preeclampsia in the United States is estimated to range from 2% to 6% in healthy, nulliparous women.^[1,2,3] Among all cases of the preeclampsia, 10% occur in pregnancies of less than 34 weeks' gestation. The global incidence of preeclampsia has been estimated at 5-14% of all pregnancies. In developing nations, the incidence of the disease is reported to be 4-18%,^[4,5] with hypertensive disorders being the second most common obstetric cause of stillbirths and early neonatal deaths in these countries.^[6]

Medical consensus is lacking regarding the values that define preeclampsia, but reasonable criteria in a woman who was normotensive before 20 weeks' gestation include a systolic blood pressure (SBP) greater than 140 mm Hg and a diastolic blood pressure (DBP) greater than 90 mm Hg on 2 successive measurements, 4-6 hours apart. Preeclampsia in a patient with preexisting essential hypertension is diagnosed if SBP has increased by 30 mm Hg or if DBP has increased by 15 mm Hg.

Researchers have previously reported lower maternal serum vitamin D concentrations in women after diagnosis of preeclampsia^[7,8], and a single study has demonstrated lower levels before clinical diagnosis of preeclampsia at term^[9]. However, the clinically significant morbidity associated with preeclampsia occurs when the diagnosis is made preterm. There is some evidence now that low levels of Vitamin D are associated with the risk of preeclampsia but more studies are needed to prove the same. This study was done to determine whether vitamin D deficiency is an independent risk factor for preeclampsia/ eclampsia.

Patients and Methods: Prospective study was done between July 2016 to August 2017. Cases are selected from the patients who are attending Obstetrics and gynaecology OPD (out-patient department) or admitted in Dept. of Medicine and Dept. of Obstetrics and gynaecology in Tertiary care hospital, Prayagraj, as a case of pre-eclampsia and eclampsia.

60 cases and 60 age and sex matched healthy controls were selected.

The controls were screened for eclampsic risk factors and assessed for serum vitamin D level.

Inclusion criteria for control -All the non hypertensive, non proteinuric pregnant women between 18-34 years of age will be included in the study.

Exclusion Criteria

1. Pregnant women less than 18 years of age and more than 34 years of age.
2. Patients with pre-existing renal disease.
3. Patients with pre-existing hypertension.
4. Patients with pre-existing diabetes mellitus.
5. Patient with pre-existing cardiovascular disease

Detailed history was taken and data gathered on demographic characteristics, age, gestational age (>20 weeks), underlying disease, presenting signs and symptoms, blood pressure on admission and complete physical examination was done in all patients. It was recorded on a pre planned record sheet. All the Investigations carried out at were recorded in this record sheet throughout the duration of the study.

The laboratory investigations including CBC, S. Urea and Creatinine, S.Calcium, S.Vit. D, USG abdomen, EEG, Urine Routine Microscopy, 24hrs Urine protein, PTH, Fundus and ECG were done.

All patients with a diagnosis of pre-eclampsia /eclampsia based on the criteria of The American College of Obstetrics and Gynecology were included in the study consecutively.

Pre-eclampsia was defined as the onset of hypertension and proteinuria after 20 weeks of gestation in previously normotensive and non-proteinuric pregnant women. Mild preeclampsia was defined as Blood pressure >140/90 mm Hg but < 160/110 mm Hg and proteinuria ranged between 300mg to < 5 gms/24hrs. Severe preeclampsia was defined as presence of any of these (Blood pressure \geq 160/110 mm of Hg, urinary protein excretion of > 5gm in 24hrs,

oliguria or < 500 ml in 24 hours, visual disturbances, pulmonary edema or cyanosis, Right upper quadrant tenderness, fetal growth restriction, thrombocytopenia, and impaired liver function) features in a preeclamptic women.

Eclampsia was defined as occurrence of new onset grand mal seizure in a patient of preeclampsia.

Hypertension was defined as blood pressure \geq 140/90 mm of Hg on two occasions at least 6 hours apart, in women not known to have hypertension in pre-pregnancy phase.

Vitamin D deficiency was defined as low serum vitamin D <20 ng/ml.

Measurement of Blood pressure- Hypertension is diagnosed when 2 BP readings of 140/90 mm Hg or greater are noted 6 hours apart within a 1-week period. Measuring BP with an appropriate-sized cuff placed on the right arm at the same level as the heart is important. The patient must be sitting and, ideally, have had a chance to rest for at least 10 minutes before the BP measurement. She should not be lying down in a lateral decubitus

position, as the arm often used to measure the pressure in this position will be above the right atrium.

Vitamin -D estimation- Serum Vitamin D level was estimated in the central pathology laboratory of the Tertiary care hospital (using CLIA method-chemiluminescent immunoassay)

Statistical Analysis

The data was analysed for statistical significance wherever possible. Student's t test was used to compare continuous variable. The chi-square test was used for categorical variables. P -values less than 0.05 were considered statistically significant.

Observations and Results

The participants were divided into two groups, group I cases (60 women presenting with preeclampsia/eclampsia) group II controls (60 healthy normotensive pregnant women with matched age and sex). Following observations were made:

Table 1 Demographic parameters

Variables	Cases	Control	P value
Number	60	60	
Mean age (years)	26.9 \pm 3.4	26.04 \pm 3.17	0.154
Back-Ground	Rural	51(85%)	32(53.33%) 28(46.66%)
	Urban	9(15%)	
Gestational hypertension	Pre eclampsia	48 (80%)	0 0
	Eclampsia	12 (20%)	
Mean gestational age at presentation(weeks)	26.71 \pm 3.3	26.52 \pm 3.27	0.7520
Mean S.vit.D (ng/ml)	12.65 \pm 5.112	51.15 \pm 16.357	<0.001
Mean S.calcium(mg/dl)	7.65 \pm 0.732	8.87 \pm 1.186	<0.001

Table 1. Shows the mean age of cases and control was 26.9 \pm 3.4 years and 26.04 \pm 3.17 years respectively. In cases 85% were rural and 15% were urban, and in control groups 53.33% were rural and 46.66% were urban. On the basis of gestational hypertension 80% were pre eclampsia and 20% were eclampsia. Mean gestational age at

presentation 26.71 \pm 3.3 weeks in cases and 26.52 \pm 3.27 weeks in control group. Mean serum vitamin D level in cases 12.65 \pm 5.112ng/ml and control 51.15 \pm 16.357ng/ml. Mean serum calcium level of cases and control was 7.65 \pm 0.732mg/dl and 8.87 \pm 1.186mg/dl respectively.

Table 2: Age wise distribution of the patients

Age class(years)	Case	Control	Total
20—24	10	10	20
25—29	37	37	74
30—34	13	13	26
Total	60	60	120

Most of the patients were in the age group of 25-29 years both in cases and controls. In both groups least number of patients were of 20-24 years age.

Table 3: Patients according to gestational age

Gest. age(week)	Case	Control	Total
20	0	4	2
21—25	20	23	40
26—30	29	26	58
31-34	11	7	20
Total	60	60	120

Majority of the patients were in the gestational age of 26-30 week, followed by 21-25 week.

Table 4: Cases according to parity

PARITY	No of Cases	Percentage (%)
0	14	23.3
1	9	15.0
2	24	40.0
3	13	21.7
Total	60	100.0

Majority of the cases were of parity 2, 40% followed by parity 0, 23.3% and parity 3 were 21.7%.

Table 5: Mean serum vit. D in gestational hypertensives-

Eclampsia status	Mean S.Vit. D (ng/ml)	± SD	No of patients	P- Value
Eclampsia	9.67	1.435	12	<0.05
Pre eclampsia	13.40	5.429	48	

The mean s. vitamin D level was lower in eclamptic patients (9.67 ± 1.435) than pre -eclamptic patients (13.40 ± 5.429). Which was statistically significant (P value is <0.05).

Table 6: Age wise distribution of mean S. Vit. D-

Age (years)	Case		Control		P value
	Mean S.VIT D	± SD	Mean S.VIT D	± SD	
20—24	11.20	4.780	40.60	9.180	<0.001
25—29	12.68	5.442	56.68	17.456	<0.001
30—34	13.69	4.423	43.54	9.404	<0.001

The mean S.vit. D of cases was significantly lower than controls at every age group, which was statistically significant.

Table 7: Gestational age correlation with hypertension.

Gest age (week)	Eclampsia	Pre eclampsia	Total
21—25	0	20	20
26—30	2	27	29
31-35	10	1	11
Total	12	48	60

Majority of the patients of Eclampsia were in gestational age, 31-35 week while most of the pre eclamptics were in gestational age of 26-30 weeks.

Table 8: Vit. D deficiency in study population-

S.VIT. D level (ng/ml)	Case(n=60)	Control(n=60)	P-value
< 20	54(90%)	2(3.33%)	<0.001
> 20	6(10%)	58(96.66%)	

S.Vit .D deficiency was more common in cases (90%) than controls (3.33%) and it was statistically significant (p-value <0.05).

Discussion

The present study was conducted with the aim to study the association of low serum vit. D level as a risk factor for pre eclampsia and eclampsia in Pregnant women. The study was conducted in Tertiary care hospital, Prayagraj U.P, on pregnant patients attending to hospital for their routine antenatal visit or some other complaints, were evaluated for preeclampsia and Eclampsia. Study conducted during a period of July 2016 to august 2017.

In the present study, the mean age of patients in cases was 26.9±3.4years and in control group was 26.06±3.17years which was comparable to the studies done by Abedi, et al.^[12] and Mohaghegh, et al.^[14].

Our study revealed significant risk factor for severe preeclampsia and eclampsia in patients of rural background, 85% of cases were rural population as compared to 53.3% were in control groups (statistically significant).

Recent studies worldwide have demonstrated a high prevalence of pregnant women at or near term are vitamin D-deficient.^[20,21] The optimum level of vitamin D and maternal vitamin D requirements during pregnancy has been poorly studied.

The value used to define vitamin D deficiency in different studies are different; therefore, levels of 'vitamin D deficiency' in various populations

cannot be directly compared.^[18,19] According to American College of Obstetrics and Gynecology (ACOG), serum 25(OH)D concentration below 20ng/ml used as a cut off for deficiency and below 32ng/ml as a cut off for insufficiency^[19].

This study showed a very high prevalence of vitamin D deficiency in pregnant women, 90% women with preeclampsia and eclampsia had Vitamin D deficiency (vit. D <20ng/ml) as compared to 3.33% in the control group (statistically significant). Lowered Vitamin D < 20 ng/ml were found in 54 patients (90.0%), and all patients were in <35wks of gestational age. Low vitamin D was also found in a study by Bodnar et al.^[9], where vitamin D deficiency early in pregnancy was associated with preeclampsia.

In our study mean serum 25 (OH) D levels were significantly less in women who developed preeclampsia and eclampsia as compared to controls. The mean vitamin D levels in the cases was 12.65 ± 5.112 ng/ml (vitamin D deficiency) and in the control group was 51.15 ± 16.357ng/ml and the difference was statistically significant and is comparable to studies by Mohaghegh, et al.^[14] and Bakacak, et al.^[13].

Whereas in the study conducted by Dhillon, et al.^[17], Sadin, et al.^[11], Sahu, et al.^[16] and Mehmood, et al.^[15] there was a universal prevalence of vitamin D deficiency among the pregnant females, but the level of serum vitamin

D was significantly lower in the preeclamptic group as compared to the normotensive. The above findings in different studies may indirectly suggest that vitamin D deficiency could increase the risk of pre-eclampsia

In the present study, the mean maternal serum calcium levels in the pre-eclamptic /eclamptic women were 7.65 ± 0.732 mg/dl and in the normotensive women was 8.87 ± 1.186 mg/dl ($p = < 0.001$) similarly to the studies done by Sahu, et al.^[16] and Gupta, et al.^[10]

Conclusion

Maternal vitamin D deficiency was found in 90% of cases (pre-eclampsia/eclampsia) in our study. Mean serum vitamin D (12.65 ± 5.112 ng/ml) and mean serum calcium level 7.65 ± 0.732 mg/dl was also low in cases (pre-eclampsia/eclampsia) as compared to control, in our study. From this study, we conclude that, vit. D estimation should be done in early pregnancy along with routine checkup of BP to evaluate any risk of association of vit.D deficiency and preeclampsia/eclampsia. So that prior vit.D and calcium supplementation in early pregnancy should be given for preventing pre-eclampsia /eclampsia and to promote neonatal well-being.

Conflicts of Interest: None

Source of Funding: None

Ethical Issue: None

References

1. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. *Am J Obstet Gynecol* 2000;183:S1-S22.
2. Andersgaard AB, Herbst A, Johansen M, Ivarsson A, Ingemarsson I, Langhoff-Roos J, et al. Eclampsia in Scandinavia: incidence, substandard care, and potentially preventable cases. *Acta Obstet Gynecol Scand* 2006;85:929-36.
3. Douglas KA, Redman CW. Eclampsia in the United Kingdom. *BMJ* 1994;26; 309:1395-400.
4. Sibai BM, el-Nazer A, Gonzalez-Ruiz A. Severe preeclampsia-eclampsia in young primigravid women: subsequent pregnancy outcome and remote prognosis. *Am J Obstet Gynecol* 1986;155:1011-6
5. Maternal mortality in 2005: estimates developed by WHO, UNICEF, UNFPA, and the World Bank. Geneva: World Health Organization. 2007.
6. Hogan MC, Foreman KJ, Naghavi M, Ahn SY, Wang M, Makela SM, et al. Maternal mortality for 181 countries, 1980-2008: a systematic analysis of progress towards Millennium Development Goal 5. *Lancet* 2010;375:1609-23.
7. Cruikshank DP, Chan GM, Doerrfeld D 1993 Alterations in vitamin D and calcium metabolism with magnesium sulfate treatment of preeclampsia. *Am J Obstet Gynecol* 168:1170-1176; discussion 1176-1177.
8. Seely EW, Wood RJ, Brown EM, Graves SW 1992 Lower serum ionized calcium and abnormal calciotropic hormones levels in preeclampsia. *J Clin Endocrinol Metab* 74:1436-1440.
9. Bodnar LM, Catov JM, Simhan HN, Holick MF, Powers RW, Roberts JM 2007 Maternal vitamin D deficiency increases the risk of preeclampsia. *J Clin Endocrinol Metab* 92:3517-3522
10. Taru G, Sonika W, Nupur G, Sarika A, Sangeeta G, et al. Correlation of Vitamin D Levels in Term Normotensive and Preeclamptic Patients in Labor. *J Obstet Gynecol India*. 2016;66:154159. PubMed: <https://pubmed.ncbi.nlm.nih.gov/27298523/>
11. Sadin B, Gargari BP, Tabrizi FPF. Vitamin D Status in Preeclamptic and Non-preeclamptic Pregnant Women: A Case-Control Study in the North West of

- Iran. Health Promot Perspect. 2015;5: 183190.
12. Abedi P, Mohaghegh Z, Afshary P, Latifi M. The relationship of serum vitamin D with pre-eclampsia in the Iranian women. *Matern Child Nutr.* 2014; 10: 206–212.
 13. Bakacak M, Serin S, Ercan O, Köstü B, Avci F, et al. Comparison of Vitamin D levels in cases with preeclampsia, eclampsia and healthy pregnant women. *Int J Clin Exp Med.*2015;8:1628016286.
 14. Mohaghegh Z, Abedi P, Dilgouni T, Namvar F, Ruzafza S. The relation of preeclampsia and serum level of 25-hydroxyvitamin D in mothers and their neonates: a case control study in Iran. *Horm Metab Res.*2015; 47: 284-288.
 15. Mehmood S, Karim SA. Vitamin D Deficiency during Pregnancy and its Relationship with Pre-Eclampsia, Eclampsia and Gestational Hypertension. *Austin J Nutr Metab.* 2016; 3: 1040.
 16. Sahu M, Das V, Agarwal A, Rawat V, Saxena P, et al. Vitamin D replacement in pregnant women in rural north India: a pilot study. *Eur J Clin Nutr.*2009;63:1157–1159.
 17. Dhillon MK, Bedi GK, Kaur K. Significance of 25 hydroxy vitamin D and calcium in pregnancy induced hypertension. *Int J Health Sci Res.* 2017; 7: 80-85.
 18. Holick MF, Binkley NC, Bischoff-Ferrari HA. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2011;96:1911- 30.
 19. ACOG Committee. Vitamin D: screening and supplementation during pregnancy. *Obstet Gynecol.* 2011;118:197-8
 20. Al Kalbani M, Elshafie O, Rawahi M. Vitamin D status in pregnant Omanis: a disturbingly high proportion of patients with low vitamin D stores. *Sultan Qaboos Univ Med J.* 2011;11:52-5.
 21. Asemi Z, Taghizadeh M, Sarahroodi S. Assessment of the relationship of vitamin D with serum antioxidant vitamins E and A and their deficiencies in Iranian pregnant women. *Saudi Med J.* 2010;31:1119.