

Research Article

Association of Deficiency of Maternal Vitamin D Levels with Severity of Preeclampsia

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A B S T R A C T

Introduction: Preeclampsia remains to be an important cause of maternal morbidity and mortality in both the developing and developed world. It is imperative to devise preventive strategies to reduce the burden of this disease. Vitamin D deficiency has emerged as an important inflammatory mediator in its pathogenesis.

Objective: To find an association between the severity of preeclampsia and vitamin D deficiency amongst women attending a tertiary hospital in northern India.

Material & Methods: this was a prospective comparative observational study. 125 women of preeclampsia and 125 controls were enrolled in the study after due written consent. The women of preeclampsia were further divided into preeclampsia with or without severe features. After history, examination and relevant routine investigations, both groups underwent testing for vitamin D. Statistical analysis was conducted with the statistical package for the social science software version SPSS 20.0. The comparison of normally distributed continuous variables between the two groups was performed using Student's t test and for more than two groups comparison done through ANOVA test. For all statistical tests, a p value less than 0.05 was taken to indicate a significant difference/ association.

Result: 80% subjects of study group were significantly more vitamin D deficient as compared to 68% of controls (p-value=0.03). Patients with preeclampsia with severe features had significantly lower levels of Vitamin D as compared to controls indicating that increased vitamin D deficiency was associated with increased severity of preeclampsia. None of the cases with severe preeclampsia had normal levels of Vitamin D. This was statistically significant (p-value=0.046).

Conclusion: Severe pre-eclampsia was significantly associated with Vit D deficiency. Prevention of Vitamin D deficiency could be beneficial to prevent pre-eclampsia but community intervention studies are required.

Keywords: Preeclampsia, Vit D Deficiency, Maternal Mortality

Introduction

According to WHO, mortality due to pregnancy or childbirth related complications are 830 women per day worldwide. Due to pregnancy and its complications, roughly 3,03,000 women died in year 2015 out of which 99% mortality occurred in developing countries.¹ Maternal mortality rate in India is 122 per 100,000 live births.² Preeclampsia is one of the major causes of perinatal mortality, accounting for approximately 25% of overall fetal and early neonatal deaths.³ According to WHO, the incidence of pre-eclampsia is 2.8% of live births in India and 0.4% of live births in developed countries like UK.⁴

Pre-eclampsia is a syndrome that chiefly includes the development of new onset hypertension in the second half of pregnancy and is considered to be a multifactorial disease whose cause remains unknown.⁵ Central to its pathogenesis is the occurrence of widespread endothelial dysfunction and vascular capillary leakage. There are many risk factors for pre-eclampsia like primigravida, multifetal pregnancy, advanced maternal age (>than 40 years), obesity, in vitro fertilization etc.⁵ There are multiple hypothesis regarding etiology of pre-eclampsia, one of which is hypovitaminosis D in pregnancy.⁶⁻⁸

Hypovitaminosis D is associated with various health problems like diabetes, cardiovascular diseases, neurological & neuropsychiatry disorders and several cancers in general population.⁹ In pregnancy, some studies have shown that its deficiency is associated with Pre-eclampsia, gestational diabetes mellitus, preterm birth, lower segment caesarian section, preterm labour and increased risk of bacterial vaginosis.¹⁰ As per Evans KN et al. (2004), vitamin D plays a role in implantation and placental function potentially due to its angiogenic, immunomodulatory and anti-inflammatory effects,¹¹ which may explain its role in preeclampsia.

Materials and Methods

Study Design

A hospital based prospective, comparative observational study.

Study Setting

The study was conducted in a tertiary care 980 bedded hospital which primarily caters to a population of about 18 lakh-largely from northern part of Delhi, though its services are also utilized by patients from rural areas, towns from neighbouring states of Uttar Pradesh, Haryana & Rajasthan. The annual attendance in the OPD of the department of obstetrics and gynaecology is around 34,000 patients per annum. The average delivery rate in the hospital is approximately 10,000 per year. This study was done in the Department of Obstetrics & Gynaecology in collaboration with the Department of Microbiology.

Period of Study

From September 2017- May 2019 (21 months).

Study Population

All antenatal cases with gestational age >20wks between 18-35years of age and singleton pregnancy attending antenatal clinic during the study period.

Study Tool

Study tool was a pre-structured proforma and it consisted of 3 parts: clinical evaluation, diagnostic and maternal & fetal outcome.

- Clinical evaluation part comprised of detailed history of the patient including age, demographic profile, history of present illness, menstrual history, obstetric history, past history, family history, general examination, obstetric examination and systemic examination.
- Diagnostic evaluation part comprised of investigations— Complete Blood Count with platelets, URINE PROTEIN, Renal Function Tests, Liver Function Tests, Serum Electrolytes, Random Blood Sugar, Total serum Vitamin D level, Prothrombin Time/ INR, Obstetric Ultrasound & Color Doppler, Fundus Examination.
- Outcome part comprised of maternal outcome in terms of mode & timing of delivery, maternal complications and neonatal outcome—Intrauterine Death, IUGR, Fetal distress, Low Birth Weight, Neonatal death, APGAR score & Neonatal ICU admission.

Operational Definitions

1. Diagnostic Criteria of Preeclampsia, classification of severity Definition Of Proteinuria were used as per ACOG CRITERIA 2013.
2. Definition of Vitamin D Deficiency:

In the present study, after consultation with microbiologist and review of literature (ritu g) the following levels were used to categorize the level of vitamin D as per the endocrinology society clinical guidelines.¹²

- <20ng/ml - Vitamin D Deficient
- 21-29ng/ml - Vitamin D Insufficient
- 30-100ng/ml - Sufficient Vitamin D Level

Additional operational definitions used in the study given as supplemental document.

Exclusion Criteria

Diagnosed cases of preexisting essential hypertension or hypertension diagnosed at <20 weeks of gestation, Preexisting diabetes mellitus, Renal disease, Liver disease, Thyroid disorder, Epilepsy, Multiple pregnancy, Placenta previa, morbidly adherent placenta (placenta accrete/ increta/ percreta), Previously diagnosed patients of

hypovitaminosis. Any other medical co morbidities are excluded.

Ethical Consideration

The study participants were explained about the objectives and purpose of the study. Informed written consent was taken from each participant prior to data collection. Privacy and confidentiality of each participant was assured. The study received ethical approval from the Institutional Ethics Committee.

Method of Collection of Data

Patients were enrolled only after fulfilling the inclusion criteria of the study, taking informed written consent and explaining the procedure to them. Pre structured Proforma as described above was used to record the details of the patient.

Equal numbers of normotensive pregnant females were taken as comparative control group.

This population was divided in to two groups.

Group 1: Healthy normotensive (normal) pregnant women

Group 2: Diagnosed cases of preeclampsia which was further divided according to severity into severe and non-severe groups.

These two groups were further divided according to total serum vitamin D levels into following groups:

- <20ng/ml
- 20-29ng/ml
- 30-100ng/ml

Detailed history of the patient including age, demographic profile, history of present illness, menstrual history, obstetric history, past history and family history was taken. After a detailed history, general examination, obstetric examination and systemic examination was done.

All the enrolled pregnant women underwent the following investigations-CBC with platelets, URINE PROTEIN, RFT, LFT, SE, RBS, Total Vitamin D level, PT/ INR, USG OBS.COLOUR DOPPLER, FUNDUS EXAMINATION.

For analysis of total vitamin D level, 2ml blood sample in plain vial on empty stomach was collected and then sample was centrifuged after formation of complete clot. After separation of serum, vitamin D estimation was done in fully automated cobas e411 analyzer based on electrochemiluminescence technology.

The groups were matched according to age, gravidity, parity, maternal weight & gestational age.

The study population were followed until delivery and early postpartum period and their babies till early neonatal period (0-6 days of age).

Statistical Methods

Sample Size

It was calculated by open epi online software using formula:

$$n = z^2_{1-\alpha/2} [(1-P_1)/P_1] + [(1-P_2)/P_2] / [\log(1-d)]^2$$

Here

$$z^2_{1-\alpha/2} = 1.96.$$

P_1 = Proportion of pre eclamptic women deficient in vitamin D [taking reference of Goel P et al (2016) [14] is 100%.

P_2 = Proportion of non preeclamptic women deficient in vitamin D, [Goel P et al. (2016) (48)] is 92%, Denominator is 5%.

By above formula, sample size was 121 in each group and total sample size was 242. For sake of convenience, sample size of 125 patients in each group (total 250) was taken.

Data was collected; compiled, and analyzed. Data collected during the study was tabulated in Microsoft Excel. Statistical analysis was conducted with the statistical package for the social science software version SPSS 20.0. Continuous variables were presented as mean±SD. Categorical variables were expressed as frequencies and percentages. Nominal categorical data between the groups were compared using Chi-square test. The comparison of normally distributed continuous variables between the two groups was performed using Student's t test and for more than two groups comparison done through ANOVA test. For all statistical tests, a p-value less than 0.05 was taken to indicate a significant difference/ association.

Result

Table 1. Distribution of age, BMI and gestational age at booking between study group and control group

	Study Group (n=125) Mean±SD	Controls (n=125) Mean±SD	p-value*
Age (years)	23.87±2.59	24.19±2.93	0.36
Body mass index (kg/ m ²)	23.63±1.89	23.27±1.85	0.13
Mean period of gestation at booking (wks.)	32.15±1.28	32.22±1.27	

As can be seen in table 1, women in both the study and control groups were of comparable age, BMI and gestational age.

Table 2. Gravity and booking status in controls and study group

Variable		Study Group N=125 (%)		Controls N=125 (%)	p-value*
		PE without severe feature N=89 (%)	PE with severe feature N=36 (%)		
Gravity	G1	62 (69.66)	20 (55.56)	68 (54.4)	0.19
	G2	25 (28.09)	14 (38.89)	49 (39.2)	
	G3	2 (2.25)	2 (5.56)	8 (6.4)	
Booking Status	Booked	57 (64.05)	16 (44.44)	98 (78.4)	<0.001
	Unbooked	32 (35.95)	20 (55.55)	27 (21.6)	

* χ^2 test, p-value < 0.05 significant.

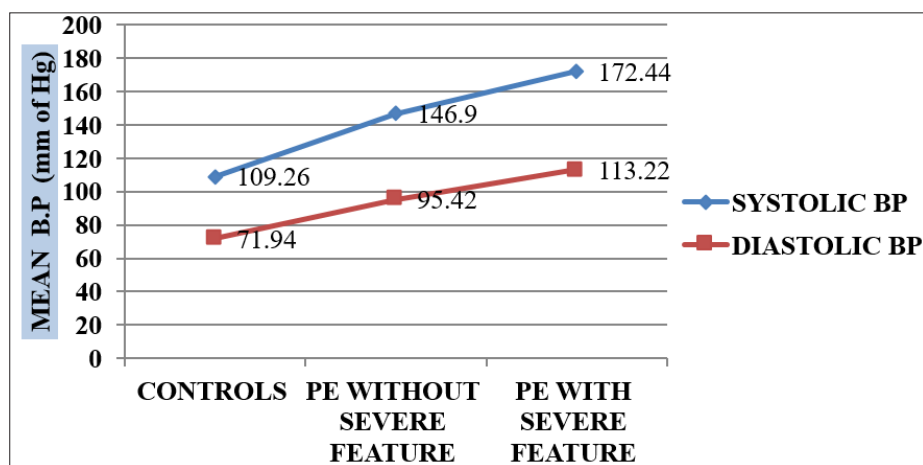


Figure 1. Line diagram showing distribution of systolic and diastolic BP in controls and study group

Looking at the distribution of severity in our study, 71.2 % were patients of preeclampsia without severe features and 28.8% were patients with preeclampsia with severe features.

As can be seen in Figure 1, our study also showed that there was a statistically significant increase in systolic and diastolic BP in severe PE as compared to mild PE and control (p-value=0.0001).

Table 3. Mean serum vitamin D level in various groups of patients

Groups of Patients (N)	Vitamin D (mean \pm SD) ng/ml	p-value*
Normotensive Controls (125)	19.08 \pm 9.47	<0.0001
PE Without Severe Features (89)	14.33 \pm 7.78	
PE With Severe Features (36)	8.59 \pm 5.62	

*paired t test, p-value < 0.05 significant

As can be seen in table 3, mean serum Vitamin D level was found to be lower in the preeclamptic subjects with and without severe features as compared to normotensive

patients. The mean value in patients with severe features of preeclampsia was 8.59 \pm 5.62 ng/ml, in patients without severe features of preeclampsia was 14.33 \pm 7.78 ng/ml and in controls was 19.08 \pm 9.47 ng/ml. This difference was statistically significant (p-value<0.001).

Table 4. Distribution of patients in study group and controls according to serum vitamin D levels

Vitamin D (ng/ml)	Study Group N=125 (%)	Controls N=125 (%)	p-value*
< 20	100 (80)	85 (68)	0.03
21-29	18 (14.4)	25 (20)	0.41
30-100	7 (5.6)	15 (12)	0.02

* χ^2 test, p-value < 0.05 significant

Table 4, shows that more numbers of subjects of study group (80%) were vitamin D deficient as compared to 68% of controls. This difference was statistically significant (p-value=0.03). It can also be seen that 5.6% of study group & 12% of controls had sufficient levels of vitamin D. It was statistically significant when compared to controls (p-value=0.02). This result showed that more numbers of subjects of control group had sufficient levels of vitamin D.

Table 5. Distribution of patients of preeclampsia without severe features and controls according to serum vitamin D levels

S. Vitamin D Level (ng/ml)	PE Without Severe Feature N= 89(%)	Controls N=125 (%)	p-value*
<20	69 (77.53)	85 (68)	0.30
21-29	13 (14.61)	25 (20)	
30-100	7 (7.87)	15 (12)	

* χ^2 test, p-value < 0.05 significant

Table 5, shows that 68% of controls & 77.53% of preeclampsia subjects without severe features were vitamin D deficient. Vitamin D level of preeclamptic women with mild features when compared with controls were not found to be significant (p-value=0.30).

Table 6. Distribution of patients of preeclampsia with severe features and controls according to serum vitamin D levels

S. Vitamin D level (ng/ml)	PE with severe feature N=36 (%)	Controls N=125 (%)	p-value*
<20	31 (86.11)	85 (68)	0.046
21-29	5 (13.89)	25 (20)	
30-100	0 (0)	15 (12)	

* χ^2 test, p-value < 0.05 significant

As shown in table 6, 68% of controls & 86.11% of preeclampsia subjects with severe features were vitamin D deficient. This result showed that more patients of preeclampsia with severe features were deficient in vitamin D levels as compared to controls. This was statistically significant (p-value=0.046).

Discussion

Preeclampsia is taking an enormous toll in developing country like India as well as the western society. Although manageable and preventable, these hypertensive disorders remain the leading cause of maternal death. Research over last two decade proved the role of inflammatory mediators in the pathophysiology of preeclampsia. Vitamin D is one of those parameters. In view of this, the present study has been taken up to assess the association between deficiency of vitamin D and the severity of preeclampsia and to assess if it can be of some prognostic significance in preeclampsia.

In terms of age, BMI, Mean gestational age there was no difference in the study and control group indicating that they were comparable. Similarly, Sahu M et al. (2017)¹³ and Goel P et al. (2016)¹⁴ observed no significant difference in their age group. Like our study, Goel P et al. (2016)¹⁴

and Bakacak M et al. (2015)¹⁵ also observed no significant difference of BMI in study and control group.

The distribution of patients of preeclampsia with and without severe features in our study was similar to Baror S et al. (2017),¹⁶ Rao et al. (2018),¹⁷ Mehta S et al. (2016)¹⁸ and Arumaikannu J et al. (2018)¹⁹ 55.55% subjects with preeclampsia with severe features and 21.6% controls were unbooked. It was statistically significant (p value<0.0001) indicating more patients with severe preeclampsia were unbooked than booked (55.55% and 44.44%). This reflects that timely booking is an important determinant of the severity of preeclampsia thereby enabling the reduction in its morbidity. Also, keeping in mind the very definition of preeclampsia it was not surprising to note that the mean systolic BP and Diastolic BP was significantly higher in the group of preeclampsia with severe features as compared to controls. Our study is similar in terms of mean SBP & DBP to studies of Samir Abdalla A et al. (2018),²⁰ Bakacak M et al. (2015),¹⁵ Sadin B et al (2015)²¹ and Xiao JP et al (2017).²²

The significant difference in the mean vitamin D levels observed in our study group as compared to the control group indicated a strong association between deficiency of Vitamin D and preeclampsia. Our study finding was consistent with the studies conducted by Sharma N et al. (2019),²³ Choudhary N et al. (2018),²⁴ Sahu M et al. (2017),¹³ Baror S et al. (2017),¹⁶ Kumari A et al. (2017),²⁵ Goel P et al. (2016),¹⁴ Sadin B et al. (2015),²¹ Singla et al. (2015)²⁶ and Bakacak et al. (2015).¹⁵ Our study also demonstrated that though vitamin D deficiency was common in all antenatal patients but it was significantly more prevalent in preeclamptic women. This was comparable to the results were obtained by Rao et al. (2018) who showed the women with preeclampsia with vitamin deficiency were 67.5 %, ¹⁷ similar to Baror S et al. (2017) reporting 72%¹⁶ and Mehta S. Singh A et al. (2016) reporting a prevalence of 90%.¹⁸ Sadin B et al. (2015)²¹ observed that serum Vitamin D level less than 10 ng/ml was associated with a 15 times increase in the odds ratio of preeclampsia. Unlike our study, Hasheimpour S et al. (2017),²⁷ Goel P et al. (2016)¹⁴ and Shand AW et al. (2010)²⁸ observed no significant difference of Vitamin D in preeclamptic women as compared to controls, Looking at table 5 and 6, it can be observed that severity of preeclampsia correlated with deficiency of vitamin D level. None of the cases with severe preeclampsia had normal levels of Vitamin D which was statistically significant (p-value=0.046). This was comparable to studies by Rao et al. (2018),¹⁷ Baror S et al. (2017)¹⁶ and Mehta S et al. (2016).¹⁸ Ullah et al. (2013)²⁹ in his study concluded that the odds of developing preeclampsia and eclampsia increased upto 5 times in women with Vitamin D insufficiency. Similarly, Singh A et al. (2016)³⁰ and Mehmood et al. (2016)³¹ (p-value=0.045) also found that most of the

patients of severe preeclampsia had very low (<10 ng/ml) Vitamin D level.

Conclusion

Our study showed a significant association of Vitamin D deficiency with preeclampsia and its severity. As preeclampsia remains to be an important cause of maternal and fetal mortality and morbidity, it is imperative that preventive strategies may be employed to reduce the burden of this condition. Correction of vitamin D deficiency amongst antenatal women may provide such an opportunity.

Conflict of Interest: None

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