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Original Article

Association of Vitamin D Deficiency with Pre-eclampsia

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Abstract

Background: Vitamin D is emerging as a promising agent for pre-eclampsia (PE) prevention. Vitamin D deficiency is highly prevalent in women of reproductive age and in pregnant mothers. Vitamin D receptors on the heart and blood vessels of mother suggest that Vitamin D has a cardioprotective effect, and calcitriol can influence endothelial and vascular smooth muscle cell function as well as controlling inflammation and affecting the regulation of blood pressure through influences on the renin-angiotensin-aldosterone system.

Objective: The objective of the study was to study the prevalence, association, and impact of Vitamin D deficiency with PE and their outcome.

Methods: Before the onset of labor, blood samples were drawn from each participant and sent to laboratory for the estimation of Vitamin D levels. The results were reported deficient if it was <10 ng/ml, insufficient if 10–30 ng/ml, and normal when it was >30 ng/ml.

Results: Maternal complications observed were wound infection and eclampsia. Fetal and neonatal complications included intrauterine device (IUD), respiratory distress, early neonatal death, sepsis, prolonged neonatal intensive care unit (NICU) admission, and meconium aspiration syndrome. About 7.3% of patients with deficient Vitamin D had maternal complications. About 92.7% of live birth were seen in Vitamin D deficient women compared to 100% women with sufficient Vitamin D levels. IUD was seen in 7.3% of women with deficient Vitamin D compared to none in Vitamin D sufficient. Apgar score <7 was observed in 18.4% of women with Vitamin D deficiency compared to 5% women with sufficient Vitamin D. Prolonged NICU admission was observed in 5.3% of neonates of Vitamin D deficient mothers. Intrauterine growth restriction was seen in 13.2% of women with deficient Vitamin D compared to none in Vitamin D sufficient. Neonatal complications were seen in 26.3% of neonates delivered by mothers with deficient Vitamin D levels.

Conclusion: Vitamin D be added to all the antenatal patients as routine supplement to prevent the risk of PE and promote neonatal well-being.

Key words: Intrauterine device, Neonatal intensive care unit, Pre-eclampsia, Vitamin D

INTRODUCTION

Hypertensive disorders of pregnancy are a major cause of maternal and fetal morbidity, disability, and mortality.[1] Globally, 10% of pregnant women suffer from hypertensive disorders[2] including 3–5% of pregnancies that suffer from pre-eclampsia (PE). In recent years, the discovery of Vitamin D-specific receptors and metabolites in the placenta and decidua[3] has highlighted the role of Vitamin D in pregnancy-related disorders. Vitamin D is emerging as a promising agent for PE prevention.[4] Vitamin D deficiency is highly prevalent in women of reproductive age and in pregnant mothers.[5] If proven effective, the population level benefits of Vitamin D supplementation would be substantial and likely to impact the long-term health of offspring.[6]

PE is thought to originate in early pregnancy when the maternal immune system limits placental invasion in mothers vulnerable to cardiovascular disease. Calcitriol can be considered a pregnancy-supporting factor[7] that could work through several mechanisms to reduce PE risk,

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including a direct influence of calcitriol on implantation, placental invasion, and angiogenesis.[8,9] It is also believed to be important in directing immune responses by dendritic cells and macrophages at the fetal-placental interface as well as immunological adaptation by the mother to reduce the risk of infection and inflammation.[4,9] Compared to normal pregnancies, Vitamin D metabolism is markedly altered in PE. This may be due to reduced placental 1α-hydroxylase activity[10] resulting in lower circulating calcitriol concentrations compared to normotensive or chronically hypertensive pregnant women.[11,12] Vitamin D status is reportedly lower in pre-eclamptic mothers at the time of diagnosis,[11,13] but also before disease onset in some studies.[14,15]

Vitamin D receptors on immune cells express key enzymes involved in the hormonal activation (CYP27B1) and catabolism (CYP24A1) of Vitamin D metabolites, suggesting that the availability and effectiveness of calcitriol can be directly regulated by the cells of the immune system.[16] The net result of calcitriol on adaptive immune responses leads to a skewing towards a more tolerogenic status, which is a maternal immune adaptation required for the maintenance of a healthy pregnancy.[17]

In vitro studies have demonstrated that calcitriol administration leads to an upregulation of regulatory T-cell responses while pro-inflammatory responses are typically downregulated,[16] constituting an adaptation to maternal tolerance that would reduce the risk of PE. Vitamin D receptors on the heart and blood vessels of mother suggest that Vitamin D has a cardioprotective effect, and calcitriol can influence endothelial and vascular smooth muscle cell function as well as controlling inflammation and affecting the regulation of blood pressure through influences on the renin-angiotensin-aldosterone system.[18]

Objectives

- To study the association of Vitamin D deficiency with PE
- To study the prevalence of Vitamin D deficiency in the women who suffer from PE
- Impact of different levels of serum Vitamin D on final outcome.

MATERIALS AND METHODS

The present case–control study was conducted in the Postgraduate Department of Obstetrics and Gynaecology, SKIMS Medical College and Hospital, Bemina, Srinagar, over a period of 2 years. The patients fulfilling the selection criteria were recruited for the study.

Inclusion Criteria

Pregnant women with blood pressure more or equal to 140/90 mmHg on two occasions at least 6 h apart within 7 days with proteinuria were included in the study. It was ensured that the participants are not taking any Vitamin D supplementation during the pregnancy.

Exclusion Criteria

(i) Women with other associated comorbidities including gestational diabetes and hypothyroidism and (ii) women with a history of any drug intake except the routine supplements and antihypertensives.

This study was carried out on pregnant women already diagnosed with PE, selected from routine admissions in SKIMS MCH and equal number of healthy pregnant women who were randomly selected as control group.

Written informed consent was taken from all women recruited into the study.

Before the onset of labor, blood samples were drawn from each participant and sent to laboratory for the estimation of Vitamin D levels. The results were reported deficient if it was <10 ng/ml, insufficient if 10–30 ng/ml, and normal when it was >30 ng/ml.

The recorded data were compiled and entered into a spreadsheet (Microsoft Excel) and then exported to data editor of SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as Mean ± SD and categorical variables were summarized as frequencies and percentages. Graphically, the data were presented by bar and pie diagrams. Student's independent t-test or Mann–Whitney U-test, whichever feasible, was employed for comparing continuous variables. Chi-square test or Fisher's exact test, whichever appropriate, was applied for comparing categorical variables. $P < 0.05$ was considered statistically significant. All *P*-values were two tailed.

RESULTS

The mean age of cases was 29.3 ± 42.0 years with a range of 20–37 years, and in controls, the mean age was 29.5 ± 3.49 years with a range of 21–38. Education and socioeconomic level were low in majority of patients in our study showing that lower socioeconomic status and less education are significant risk factors for PE. Out of 61 patients, 35 patients were diagnosed of PIH in their 30–34 weeks of gestation, 20 (32.8%) patients were diagnosed at 25–30 weeks of gestation, and only 6 (9.8%) patients were diagnosed to have PIH at >35 weeks. The mean gestational age of diagnosis of PIH was 30.9 ± 2.79 weeks. Symptomatic

features of PE and eclampsia included headache, edema, blurring of vision, and nausea. 2+ urinary protein was seen in majority of patients followed by 1+ and 3+.

Insufficient (10–30 ng/ml) Vitamin D levels were observed in 65.6% in cases group followed by normal Vitamin D levels (>30 ng/ml) in 32.8% of women while only 1.6% of women were Vitamin D deficient. Deficient (<30 ng/ml) Vitamin D levels were seen in 41 (67.2%) women with PE compared to 28 (45.9%) women without PE. Sufficient (>30 ng/ml) Vitamin D levels were observed with 20 (32.8%) pre-eclamptic women compared to 33 (54.1%) women without PE. Out of a total of 61 patients studied, the mode of delivery was cesarean section in 42 (68.9%) women while as vaginal delivery was observed in 19 (31.1%) patients. Maternal complications observed were wound infection and eclampsia. Fetal and neonatal complications like intrauterine device (IUD) were seen in 3 (4.9%) patients, respiratory distress in 5 (8.2%) patients, early neonatal death, sepsis, and prolonged neonatal intensive care unit (NICU) admission were observed in 2 (3.3%) patients each while as only one fetal/neonate was seen to have meconium aspiration syndrome. Impact of Vitamin D deficiency was in in 12 (29.3%) women who delivered vaginally compared to 7 (35.0%) patients with sufficient Vitamin D. Cesarean delivery was observed in 29 (70.7%) patients with Vitamin D deficient compared to 13 (65.0%) patients with Vitamin D sufficiency. Impact of Vitamin D deficiency on maternal outcome was observed in 41 patients with deficient Vitamin D levels compared to 20 patients with sufficient Vitamin D levels. Only 3 (7.3%) patients with deficient Vitamin D had maternal complications while none of the patient with sufficient Vitamin D levels had maternal complications.

Impact of Vitamin D deficiency on neonatal outcome was observed in this study. Thirty-eight (92.7%) live birth were seen in Vitamin D deficient women compared to 20 (100%) women with sufficient Vitamin D levels. IUD was seen in 3 (7.3%) women with deficient Vitamin D compared to none in Vitamin D sufficient. Apgar score <7 was observed in 7 (18.4%) women with Vitamin D deficiency compared to 1 (5%) women with sufficient Vitamin D. Prolonged NICU admission was observed in 2 (5.3%) neonates of Vitamin D deficient mothers. Intrauterine growth restriction (IUGR) was seen in 5 (13.2%) women with deficient Vitamin D compared to none in Vitamin D sufficient. Neonatal complications were seen in 10 (26.3%) neonates delivered by mothers with deficient Vitamin D levels.

DISCUSSION

The present case–control study was conducted in the Postgraduate Department of Obstetrics and Gynaecology, SKIMS Medical College and Hospital, Bemina, Srinagar, over a period of 2 years. In our study, there were 28 (45.9%) gravida 1 in cases and 21 (34.4%) in controls, 15 (24.6%) women were gravida 2 in cases and 13 (21.3%) in controls, and 14 (23.0%) gravida 3 were in cases and 17 (27.9%) in controls. There were only 4 (6.6%) women with >gravida 4 in cases and 10 (16.4%) in controls. The difference observed was statistically insignificant with $P = 0.261$. Dabbaghmanesh *et al*.[19] found that comparison of 25 (OH) Vitamin D levels between normal primigravida women and severe PE women groups showed no significant differences ($P > 0.05$). Our results are also in conformity with the findings of Bodnar *et al*.[14] wherein 72.7% of women were gravida 1, 16.4% women were gravida 2, and 10.9% were gravida 3. In another study by Jindal *et al*.,[20] gravida 1 was most common in all the study groups (PE without severe features 69.66%, PE with severe features 55.56%, and controls 54.4%) followed by gravida 2 and gravida 3.

Out of 61 patients, 35 patients were diagnosed of PIH in their 30–34 weeks of gestation, 20 (32.8%) patients were diagnosed at 25–30 weeks of gestation, and only 6 (9.8%) patients were diagnosed to have PIH at >35 weeks. The mean gestational age of diagnosis of PIH was 30.9 ± 2.79 weeks. Gong *et al*.[21] confirmed that pregnancy-induced hypertension-associated complications are more frequent in early-onset (<gestational week 32) compared to late-onset PE. In their study, 413 women with severe PE were divided into three groups according to the gestational age at the onset of PE as follows: Group A (<32 weeks, 73 cases), Group B (between 32 and 34 weeks, 71 cases), and Group C (>34 weeks, 269 cases). In the present study, there were 4 (6.6%) women who were having edema as signs and symptoms followed by headache with edema in 3 (4.9%) patients and headache in 2 (3.3%) patients. Headache with blurring of vision and headache with nausea were seen in 1 (1.6%) patient each. Symptomatic features of PE and severe PE include oliguria (<500 mL of urine in 24 h), cerebral or visual disturbances, and pulmonary edema or cyanosis.[22,23]

Majority of patients were found to have 2+ urinary protein followed by 20 (32.8%) patients who had 1+ protein in urine. 3+ urinary protein was observed in 4 (6.6%) patients and 4+ urinary protein in 2 (3.3%) patients. PE is hypertension and proteinuria (protein in urine >0.3 g/24 h (1+ dipstick) on two occasions >6 h apart) or edema (Roberts *et al*., 2003[24] and Zhang *et al*., 1997[25]). Insufficient (10–30 ng/ml) Vitamin D levels were observed in majority of patients, that is, 40 (65.6%) in cases group. Normal (>30 ng/ml) Vitamin D levels were seen in 20 (32.8%) patients while as deficient Vitamin D levels were found in 1 (1.6%) patient. Ullah *et al*.[26] did a study on the prevalence of Vitamin D deficiency. Among all the subjects, 78.19%

had serum 25 (OH) D levels <30 ng/ml. The mean (±standard deviation, SD) 25 (OH) D level was 24.53 (±0.71) ng/ml in our study population. It was lowest among women with eclampsia (21.56 ± 1.16 ng/ml), slightly higher in PE (23.96 ± 1.31 ng/ml) and highest among controls (24.86 ± 1.02 ng/ml). Normal (>30 ng/ml) Vitamin D levels were seen in 33 (54.1%) patients in control group while as insufficient (10–30 ng/ml) Vitamin D levels were observed in 28 (45.9%) in control group. Deficient (<30 ng/ml) Vitamin D levels were seen in 41 (67.2%) women with PE compared to 28 (45.9%) women without PE. Sufficient (>30 ng/ml) Vitamin D levels were observed with 20 (32.8%) pre-eclamptic women compared to 33 (54.1%) women without PE. The difference observed was statistically significant with $P = 0.018$.

The safety of Vitamin D supplementation during pregnancy has recently been evaluated by several randomized controlled trials. Intake of up to 4000 units of Vitamin D3 daily or 35,000 units weekly for 10 weeks has been reported to be safe during the 3rd trimester of pregnancy, without producing hypercalcemia or other adverse effects (Hollis *et al*., 2011[27] and Roth *et al*., 2011[28]). Jindal *et al*.[20] showed that 68% of controls and 77.53% of PE subjects without severe features were Vitamin D deficient. Vitamin D level of pre-eclamptic women with mild features when compared with controls was not found to be significant ($P = 0.30$). There were 68% of controls and 86.11% of PE subjects with severe features were Vitamin D deficiency. This result showed that more patients of pre-eclampsia with severe features were deficient in Vitamin D levels as compared to controls. This was statistically significant ($P = 0.046$).

The significant difference in the mean Vitamin D levels observed in a study by Jindal *et al*.[20] was observed as compared to the control group indicated a strong association between deficiency of Vitamin D and PE. These findings are also consistent with the studies done by Sharma *et al*.,[29] Nidhi *et al*.,[30] Sahu *et al*.,[31] Sangeeta *et al*.,[32] Kumari *et al*.,[33] and Goel *et al*.[34]

In our study, out of a total of 61 patients studied, the mode of delivery was cesarean section in 42 (68.9%) women while as vaginal delivery was observed in 19 (31.1%) patients. Impact of Vitamin D deficiency was in 12 (29.3%) women who delivered vaginally compared to 7 (35.0%) patients with sufficient Vitamin D. Cesarean delivery was observed in 29 (70.7%) patients with Vitamin D deficient compared to 13 (65.0%) patients with Vitamin D sufficiency. The mode of delivery was most likely affected by PE rather than Vitamin D deficiency. Ali *et al*.[35] established the association of Vitamin D deficiency to PE among women of reproductive age. In the control group with healthy pregnancies, 70.5% delivered vaginally and 29.5% delivered by cesarean delivery. In contrast, in the case group who developed PE, only 27% had vaginal deliveries and 73% had a cesarean delivery. It was also noticed that healthy pregnant group was more likely to be taking vitamin supplements than PE group ($P = 0.001$). The percentage of premature delivery (<36 weeks) was higher with eclampsia (56.09%) and PE (24.39%) than controls (19.51%) in a study done by Ullah *et al*.[26]

In our study, maternal complications were observed in three patients in which wound infection was seen in 2 (3.3%) patients while as eclampsia was seen in 1 (1.6%) women. Fetal and neonatal complications like IUD were seen in 3 (4.9%) patients, respiratory distress in 5 (8.2%) patients, early neonatal death, sepsis, and prolonged NICU admission were observed in 2 (3.3%) patients each while as only one fetal/neonate was seen to have meconium aspiration syndrome. Impact of Vitamin D deficiency on maternal outcome was observed in 41 patients with deficient Vitamin D levels compared to 20 patients with sufficient Vitamin D levels. Only 3 (7.3%) patients with deficient Vitamin D had maternal complications while none of the patient with sufficient Vitamin D levels had maternal complications. Impact of Vitamin D deficiency on neonatal outcome was observed in this study. Thirty-eight (92.7%) live birth were seen in Vitamin D deficient women compared to 20 (100%) women with sufficient Vitamin D levels. IUD was seen in 3 (7.3%) women with deficient Vitamin D compared to none in Vitamin D sufficient. Apgar score <7 was observed in 7 (18.4%) women with Vitamin D deficiency compared to 1 (5%) women with sufficient Vitamin D. Prolonged NICU admission was observed in 2 (5.3%) neonates of Vitamin D deficient mothers. IUGR was seen in 5 (13.2%) women with deficient Vitamin D compared to none in Vitamin D sufficient. Neonatal complications were seen in 10 (26.3%) neonates delivered by mothers with deficient Vitamin D levels. Ullah *et al*.[26] called a study and concluded that since PE and eclampsia can lead to serious complications for both mother and the offspring, Vitamin D may be supplemented during pregnancy in high-risk populations to decrease these adverse consequences. Maternal and neonatal complications are more common in cases of recurrent PE when compared to the initial episode (Dildy *et al*., 2007).[36] Sahu *et al*.[31] conducted a study in which most babies had preterm birth and almost 62 out of 100 required SNCU admission due to prematurity or other neonatal complications such as growth restriction, respiratory distress, meconium aspiration syndrome, or hypoxic ischemic encephalopathy. Babies of PE mothers were calcium deficient which may be because of the prematurity and low birth weight. About 36% of the PE and eclampsia group mothers had preterm babies and 18% in the control group were preterm. About 38%

were admitted to SNCU as compared to the control group with 15% admission.

CONCLUSION

Since PE and eclampsia can lead to serious complications for both mother and the offspring, Vitamin D be added to all the antenatal patients as routine supplement to prevent the risk of PE and promote neonatal well-being.

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