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FREQUENCY OF PRE-ECLAMPSIA IN WOMEN WITH AND WITHOUT VITAMIN D DEFICIENCY

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Abstract

Background: *Vitamin D deficiency is widely prevalent among pregnant women and has been linked to hypertensive disorders of pregnancy like Pre-eclampsia which are major cause of fetomaternal morbidity and mortality.*

Objectives: *To determine the frequency of vitamin D deficiency among patients with gestational hypertension and to compare the frequency of pre-eclampsia with and without vitamin D deficiency.*

Study design: *Descriptive case series*

Place and duration of study: *Department of Obstetrics and Gynecology, Gujranwala Medical College / District Headquarters Hospital, Gujranwala, over a period of six months 1st July to 31st December 2024.*

Materials and Methods: *This descriptive case series enrolled 95 primigravida patients with singleton pregnancy and gestational hypertension at the end of study. Patients with comorbid conditions or prior vitamin D supplementation within six months were excluded. Serum 25-hydroxyvitamin D levels were measured at presentation. Patients were divided into two groups based on vitamin D levels (with vitamin D levels <30 ng/mL were classified as deficient while with ≥30 ng/mL as sufficient). All patients were followed fortnightly until 36 weeks for the development of pre-eclampsia. Data were analysed using SPSS version 25. The Chi-square test with post-stratification analysis was applied, and a p-value of ≤0.05 was considered statistically significant.*

Results: *The mean age of participants was 28.39 ± 6.16 years and mean gestational age at presentation was 23.91 ± 2.61 weeks. The mean serum vitamin D level was 26.21 ± 6.51 ng/mL. Vitamin D deficiency was found in 74 of 95 (77.9%) patients. Pre-eclampsia developed in 26 of 95 (27.4%) patients overall. Pre-eclampsia was significantly more frequent in the vitamin D deficient group as compared to the vitamin D sufficient group (32.4% versus 9.5%, P=0.038). On stratification by BMI, the association remained statistically significant only in patients with BMI <25 kg/m² (p = 0.046). Rest of the stratification groups did not achieve individual statistical significance.*

Conclusion: *Vitamin D deficiency is highly prevalent among patients with gestational hypertension and is significantly associated with a higher frequency of pre-eclampsia. Routine screening for vitamin D deficiency in this cohort and prompt supplementation should be incorporated as a part of standard antenatal care to reduce fetomaternal morbidity and mortality due to pre-eclampsia.*

INTRODUCTION

Pregnancy related complications contribute over 50% of female deaths annually all over the world. Around 99% of these deaths take place in low- to middle-income countries, where pregnancy related causes are among the leading causes for female mortality.[1, 2] Hypertension develops in roughly 10% of pregnant women and complications arise in approximately 2–8% of all cases. Pre-eclampsia or eclampsia is responsible for 10–15% of maternal deaths. Currently, the main preventive strategy for pre-eclampsia involves anti-platelet therapy (low-dose aspirin) or calcium supplementation. Pre-eclampsia, a pregnancy-specific syndrome, has been recognised for centuries as a primary cause of fetomaternal mortality. The diagnosis is based on elevated blood pressure together with the presence of proteinuria.[2]

In last few years, the impact of vitamin D on maternal health has attracted growing research interest due to its potential to lower the risk of fetal developmental problems. Vitamin D has multiple roles in human body, including immunomodulatory, anti-inflammatory, and developmental roles, along with its function in calcium homeostasis regulation. All of these have a considerable contribution on the health of both mother and fetus.[3] Vitamin D status has been shown to affect various aspects of pregnancy, including gestational diabetes mellitus (GDM), caesarean section rates, postpartum depression, pregnancy induced hypertension (PIH), pre-eclampsia, miscarriage, and preterm delivery.[4] A Sudanese study reported vitamin D deficiency was found in 88% of pre-eclampsia cases and 60% of controls, with cutoff level of 20 ng/ml ($p < 0.05$).[1] Furthermore, another study demonstrated that pregnant females receiving vitamin D supplementation during early trimesters had lower odds of development of pre-eclampsia and higher serum vitamin D levels were associated with a reduced risk of pre-eclampsia.[5] Some other studies also confirmed the association of vitamin D deficiency and preeclampsia and protective effect of vitamin D supplementation in reducing the chances of developing pre-eclampsia as the pregnancy advances.[6-8]

In Pakistan, vitamin D3 deficiency is an increasing public health concern in general population, with a considerable proportion of women in childbearing range having insufficient or deficient vitamin D levels. One local study found pre-eclampsia in 30.6% of vitamin D deficient patients compared to 2.4% in those with sufficient levels ($p < 0.001$).[2] Another study found that there vitamin D deficiency is not associates with risk of preeclampsia in early pregnancy (OR for preeclampsia was 0.59 (95% CI, 0.31-1.14; $p = 0.12$).[9] Sharma, A., et al. found that frequency of vitamin D deficiency in PIH was 88%.[10]

Given the high prevalence of vitamin D deficiency in our population, its potential association with hypertensive disorders of pregnancy especially preeclampsia is grave concern. Therefore, the objective of this study is to compare frequency of pre-eclampsia in women with and without vitamin D deficiency after 20 weeks of gestation. Given the differences in geographical factors, lifestyle, skin color, and sunlight exposure compared to Western populations, it is crucial to implement timely and appropriate vitamin D supplementation measures to prevent its deficiency related complications.

METHODS AND MATERIALS

This descriptive case series was conducted at the Obstetrics and Gynecology Department of Gujranwala Medical College / District Headquarters Hospital, Gujranwala, over a period of six months i.e., 1st of July to 31st December 2024. Ethical approval was obtained from the Institutional Ethical Review Committee prior to commencement of the study. A sample size of 95 cases was calculated by taking the frequency of vitamin D deficiency as 88% in gestational hypertension from a study by Sharma, A., et al.[10] with a confidence level of 95% and a margin of error of 7%.

Patients were recruited from the Outpatient Department of Obstetric clinic through non-probability consecutive sampling. The inclusion criteria comprised primigravida patients with singleton pregnancy, diagnosed with PIH, aged

between 18 to 40 years, with gestational age of 20 to 28 weeks as confirmed by last menstrual period (LMP). Patients with a history of comorbid conditions including chronic hypertension, chronic liver disease (CLD), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), bronchial asthma, or cardiovascular / ischemic heart disease were excluded from the study. Patients who had taken vitamin D supplements within the last six months and those unwilling to provide consent were also excluded from the study.

Informed written consent was obtained from all eligible participants before commencement of study. A thorough clinical evaluation was performed for each patient, including a detailed medical history, clinical examination and blood pressure assessment. PIH was defined as maternal blood pressure greater than 140/90 mmHg recorded on two or more occasions in the absence of proteinuria. Serum 25-hydroxyvitamin D levels were measured at the time of presentation with PIH. Vitamin D status was categorized as sufficient when serum level was ≥30 ng/ml, and deficient vitamin D status was defined as a serum level of <30 ng/ml.

All patients were followed up fortnightly at the OPD until 36 weeks of gestation for evaluation of pre-eclampsia which was defined as PIH in the presence of proteinuria. All participants received standard hospital management protocols, throughout study period including vitamin D supplementation for those found to be deficient. Data were recorded on a specially designed proforma.

All collected data were entered and analyzed using the Statistical Package for Social Sciences (SPSS) version 25 registered for Microsoft Windows. Descriptive statistics were computed for all quantitative variables like age, gestational age, BMI, and vitamin D levels which were expressed as mean ± standard deviation. Qualitative variables including frequency of vitamin D deficiency in PIH and occurrence of pre-eclampsia in both groups were expressed as frequencies and percentages. The Chi-square test was applied to compare the frequency of pre-eclampsia between vitamin D status groups. To control for potential effect modifiers including age, gestational age at presentation, and BMI, stratification was performed to see associations, followed by post-stratification Chi-square test. A p-value of ≤0.05 was considered statistically significant.

RESULTS

We achieved the target sample size of 95 patients at the end of our study period. During the process we lost follow up of 12 patients so total recruitment had 107 patients. Descriptive statistics for quantitative variables are presented in Table 1. The mean age of participants was 28.39 ± 6.16 years. Mean gestational age at presentation was 23.91 ± 2.61 weeks. Mean BMI was 25.47 ± 3.454 kg/m² and mean serum vitamin D level was 26.21 ± 6.51 ng/mL

Table 1: Descriptive statistics of quantitative variables (N = 95)

Variable	N	Mean	Std. Deviation
Age (years)	95	28.39	6.16
Gestational Age (weeks)	95	23.91	2.61
BMI (kg/m²)	95	25.47	3.45
Vitamin D Level (ng/mL)	95	26.21	6.51

Regarding the frequency of vitamin D deficiency, 74 out of 95 (77.9%) patients were found to be vitamin D deficient, while 21 (22.1%) had sufficient vitamin D levels (Table 2).

Table 2: Frequency of Vitamin D deficiency among study participants (N = 95)

Vitamin D Deficiency	Frequency (N)	Percent (%)
Yes (Deficient)	74	77.9
No (Sufficient)	21	22.1
Total	**95**	**100.0**

Pre-eclampsia was recorded in 26 out of 95 (27.4%) patients, while the remaining 69 (72.6%) did not develop pre-eclampsia during the scheduled follow up time (Table 3).

Table 3: Frequency of pre-eclampsia among study participants (N = 95)

Pre-eclampsia	Frequency (N)	Percent (%)
Yes	26	27.4
No	69	72.6
Total	**95**	**100.0**

On comparison of the frequency of pre-eclampsia between vitamin D deficient and vitamin D sufficient groups, pre-eclampsia was observed in 24 out of 74 (32.4%) in vitamin D deficient patients, as compared to only 2 out of 21 (9.5%) vitamin D sufficient patients. This difference was statistically significant (p = 0.038), indicating a significantly higher frequency of pre-eclampsia in patients with vitamin D deficiency (Table 4).

Table 4: Comparison of pre-eclampsia frequency between Vitamin D deficient and sufficient groups (N = 95)

Pre-eclampsia	Vitamin D Deficient (Yes) N (%)	Vitamin D Sufficient (No) N (%)	Total N (%)	p-value
Yes	24 (32.4%)	2 (9.5%)	26 (27.4%)	0.038
No	50 (67.6%)	19 (90.5%)	69 (72.6%)	
Total	**74 (100%)**	**21 (100%)**	**95 (100%)**	

Stratification Results

To control for potential effect modifiers, stratification was carried out for age group, gestational age, and BMI, followed by post-stratification chi-square testing.

Stratification by Age Group (Table 5): In patients aged <30 years (n = 64), pre-eclampsia occurred in 16 of 51 (31.4%) vitamin D deficient patients versus 2 of 13 (15.4%) vitamin D sufficient patients; however, this difference did not reach statistical significance (p = 0.252). In patients aged 30 years and above (n = 31), pre-eclampsia was found in 8 of 23 (34.8%) deficient patients compared to 0 of 8 (0.0%) sufficient patients, with a p-value of 0.053 approaching but not reaching statistical significance.

Table 5: Stratification of pre-eclampsia with regards to age group

Age Group	Pre-eclampsia	Vit D Deficient N (%)	Vit D Sufficient N (%)	Total N (%)	p-value
< 30 years	Yes	16 (31.4%)	2 (15.4%)	18 (28.1%)	0.252
	No	35 (68.6%)	11 (84.6%)	46 (71.9%)	
≥ 30 years	Yes	8 (34.8%)	0 (0.0%)	8 (25.8%)	0.053
	No	15 (65.2%)	8 (100.0%)	23 (74.2%)	

Stratification by Gestational Age Group (Table 6): Among patients presenting at <24 weeks gestation (n = 53), pre-eclampsia was observed in 14 of 41 (34.1%) vitamin D deficient versus 2 of 12 (16.7%) sufficient patients (p = 0.246). In patients presenting at 24 weeks or beyond (n = 42), pre-eclampsia was recorded in 10 of 33 (30.3%) deficient patients and in none of the 9 sufficient patients (p = 0.058). No stratification group achieved statistical significance to ascertain association.

Table 6: Stratification of pre-eclampsia with regards to gestational age group

GA Group	Pre-eclampsia	Vit D Deficient N (%)	Vit D Sufficient N (%)	Total N (%)	p-value
< 24 weeks	Yes	14 (34.1%)	2 (16.7%)	16 (30.2%)	0.246
	No	27 (65.9%)	10 (83.3%)	37 (69.8%)	
≥ 24 weeks	Yes	10 (30.3%)	0 (0.0%)	10 (23.8%)	0.058
	No	23 (69.7%)	9 (100.0%)	32 (76.2%)	

Stratification by BMI Group (Table 7): Among patients with BMI < 25 kg/m² (n = 47), pre-eclampsia was found in 15 of 36 (41.7%) vitamin D deficient patients compared to 1 of 11 (9.1%) sufficient patients, a statistically significant difference (p = 0.046). In patients with BMI ≥ 25 kg/m² (n = 48), pre-eclampsia occurred in 9 of 38 (23.7%) deficient versus 1 of 10 (10.0%) sufficient patients; this difference was not statistically significant (p = 0.343).

Table 7: Stratification of pre-eclampsia with regards to BMI group

BMI Group	Pre-eclampsia	Vit D Deficient N (%)	Vit D Sufficient N (%)	Total N (%)	p-value
< 25 kg/m²	Yes	15 (41.7%)	1 (9.1%)	16 (34.0%)	0.046
	No	21 (58.3%)	10 (90.9%)	31 (66.0%)	
≥ 25 kg/m²	Yes	9 (23.7%)	1 (10.0%)	10 (20.8%)	0.343
	No	29 (76.3%)	9 (90.0%)	38 (79.2%)	

DISCUSSION

This study aimed to assess the frequency of vitamin D deficiency in patients with PIH and to find its association with the development of pre-eclampsia. A total of 95 patients with gestational hypertension were enrolled at the end of specified study period. The mean age was 28.39 ± 6.16 years, mean gestational age at presentation was 23.90 ± 2.61 weeks, and mean BMI was 25.47 ± 3.454 kg/m². The mean serum vitamin D level was 26.21 ± 6.51 ng/mL, and vitamin D deficiency was found in quite high proportion i.e., 77.9% of participants. Pre-eclampsia was recorded in 27.4% of the total cohort. The data showed that pre-eclampsia was more frequent among vitamin D deficient patients (32.4%) than vitamin D sufficient patients (9.5%), and this difference was statistically significant (p = 0.038). These findings point to vitamin D deficiency as a potential contributing factor in the progression of PIH to pre-eclampsia.

The high prevalence of vitamin D deficiency seen in this study is in line with previous reports from similar studies done in low- to middle-income country settings. Sharma et al. found vitamin D deficiency in 88% of patients with hypertensive disorders of pregnancy, versus 50% in normotensive pregnant women (p = 0.001).[10] A study by Noor-Ul-Ain Ainee et al. found that 28(16.47%) patients appeared with preeclampsia. Among vitamin D deficient patients, preeclampsia was noted in 26 (30.6%) patients while in vitamin D sufficient patients, preeclampsia was noted in 2(2.4%) patients (p<0.001).[2] Such high rates may be contributed by limited sun exposure, poor dietary intake, and the increased metabolic demands of pregnancy. These factors are more pronounced in the South Asian population.

The overall pre-eclampsia rate of 27.4% in this study is higher than globally reported rates. Worldwide, pre-eclampsia complicates approximately 2–8% of all pregnancies.[11] The higher rates are expected in resource limited settings where there is lack of intensive antenatal care. Nirupama et al. found the incidence at around 8–10% in the general obstetric population.[12] The higher rate in our cohort is possibly be a reflection of the population who is already at risk due to comorbid of PIH.

The key finding of this study that pre-eclampsia was significantly more common among vitamin D deficient patients is consistent with a growing body of evidence in the literature where data showed the association of low vitamin D to adverse hypertensive outcomes in pregnancy is evident. In a systematic review and metanalysis by AlSubai et al. which included 34 studies, found that vitamin D deficiency was significantly associated with a higher risk of pre-eclampsia (OR: 4.30; 95% CI: 2.57–7.18; p < 0.00001).[13] Similarly, Yuan et al., showed in meta-analysis of 39,031 participants, that low serum 25-hydroxyvitamin D levels were associated with a 62% higher risk of pre-eclampsia (pooled OR = 1.62, 95% CI = 1.36–1.94).[7] These findings suggest that this association is due to the biological basis due to well-established immunomodulatory and anti-inflammatory properties of vitamin D, along with its role in calcium homeostasis and endothelial function. All of these functions are relevant to the pathophysiology of preeclampsia.[4]

Case-control studies across different geographic and ethnic settings have further supported this association of vitamin D deficiency and preeclampsia. Abdelrahiem et al., in a Sudanese case-control study, found that vitamin D deficient women faced a 4.51-fold higher risk of pre-eclampsia development (AOR = 4.51, 95% CI: 1.70–11.94).[1] Pashapour et al. similarly found quite lower 25-OH-D levels in pre-eclamptic women than in healthy controls, with a significant adjusted odds ratio (OR = 4.79, CI = 1.45–9.87, p = 0.01).[6]. El-Maghraby and Allam, in an Egyptian case-control study, found that serum vitamin D was substantially lower in pre-eclamptic patients than controls, thus further enforcing the idea that adequate vitamin D status may be protective.[14] With these figures looking similar among different populations, suggest that the vitamin D–pre-eclampsia relationship is broadly generalisable.

The literature shows that the timing of vitamin D deficiency and pre-eclampsia risk is also important. Yue et al., in a large study of 7,976 pregnant women, found that vitamin D deficiency before 20 weeks' gestation was an independent risk factor for

pre-eclampsia (OR = 1.55, p = 0.031). The risk rises further with severe deficiency (OR of 2.6, p = 0.005).[8] Another study found that women who maintained sufficient vitamin D levels during first and third trimester of pregnancy had notably lower risk of preeclampsia (OR = 0.34, 95% CI 0.13–0.86, p = 0.02).[9] These observations suggest that sustaining sufficient vitamin D levels across the all phases of pregnancy may be more important rather than at a single measurement point. In our study, we have captured women at the most critical period of risk i.e., mean gestational age at presentation of around 24 weeks. Vitamin D is thought to influence the development of pre-eclampsia through several mechanisms as it plays a regulatory role in placental implantation, trophoblast invasion, and angiogenesis. The imbalance in these processes is the basis of pathophysiology of pre-eclampsia. Raia-Barjat et al. found that vitamin D deficiency at 32 weeks was associated with a five-fold higher risk of placenta-mediated complications (RR: 5.14, 95% CI: 1.50–17.55), thus pointing to a meaningful role for vitamin D in preserving placental function.[3] Another study also found that severe vitamin D deficiency in pregnant women with pre-eclampsia and PIH was linked to significantly worse arterial stiffness parameters, thus showing notable involvement of vitamin D in cardiovascular regulation in hypertensive pregnancy disorders.[15] Its immunomodulatory effects are equally relevant, given that pre-eclampsia involves a dysregulation in systemic inflammatory response that vitamin D is known to affect.[4]

The research data highlights the role of genetic basis of vitamin D's role in hypertensive disorders of pregnancy. Si et al., in a prospective cohort of 3,699 pregnant women, found that polymorphisms in the CYP24A1, GC, and LRP2 genes of the vitamin D metabolic pathway were associated with blood pressure levels and hypertensive disorders of pregnancy.[16] Similarly certain gene variants who were vitamin D deficient in second trimester showed elevated risk to PIH.

In our study, the effect of vitamin D was observed in hypertensive disorders of pregnancy, but role of vitamin D goes beyond to wider range of fetomaternal complications. There is direct correlation between vitamin D deficiency during pregnancy and neonatal health.[17] Chen et al. reported higher rates of preterm birth in women with severe vitamin D deficiency in a retrospective study of 1,079 singleton pregnancies.[18] Similarly another study found vitamin D deficiency as independent risk factor for postpartum haemorrhage (AOR: 0.93, CI: 0.89–0.98, p = 0.006).[19] Suarez-Varela et al., in a systematic review of 28 studies, concluded that vitamin D supplementation in pregnancy can help reduce the risks of gestational diabetes, PIH, pre-eclampsia, and preterm labour.[20] These findings are strong bases for the universal vitamin D screening and supplementation in pregnancy.

In the literature the protective role of vitamin D for the development of preeclampsia has been debated. Fogacci et al. pooled data from 27 RCTs (4,777 participants) and found supplementation was associated with reduced risk of pre-eclampsia (OR 0.37, 95% CI: 0.26–0.52). The risk reduction was more prominent when the supplementation was done before 20 weeks of gestation.[21] Similarly in a more recent meta-analysis of 33 RCTs (10,613 participants), Moghib et al. found that vitamin D supplementation reduced pre-eclampsia risk by 44.8% and preterm labour risk by 30%.[11] The protective role has been shown in other studies also with similar findings.[13] Cagiran and Kali, however, found no statistically significant difference in PIH between supplemented and non-supplemented groups.[22] This discrepancy may reflect differences in study populations, and the timing and dosage of supplementation.

The local literature showed that PIH was observed in just 6.3% of vitamin D3-supplemented women compared to 17.5% in the non-supplemented group, lending further support to the protective value of early supplementation in our population.[23]

Stratification analysis was carried out to check whether the association between vitamin D deficiency and pre-eclampsia held across age, gestational age and BMI. By age group, the association did not reach statistical significance in either the <30 years (p = 0.252) or ≥30 years (p = 0.053) subgroups, though the direction of the

trend was consistent in both. Stratification by gestational age likewise did not show significant results for individual subgroups ($p = 0.246$ for <24 weeks; $p = 0.058$ for ≥24 weeks), though trends were maintained. These findings for non-significant subgroups are most likely reflecting reduced statistical power after stratification rather than true absence of association. The analysis after BMI stratification showed that there was significant association between vitamin D deficiency and pre-eclampsia in patients with BMI < 25 kg/m² ($p = 0.046$), while no significant association was found in the BMI ≥ 25 kg/m² group ($p = 0.343$). This divergence is worth considering women with higher BMI have underlying additional metabolic and adiposity driven inflammations. The adipose tissue captures vitamin D which leads to more complex picture in this cohort. The underlying metabolic and dose dependant relationships may vary in various populations.[5]

This study has several limitations that should be noted. The findings of single-centre, cross-sectional design pose restrictions that how far the findings can be generalised. While the sample of 95 patients was adequate to show an overall significant association, but limited statistical power in the stratified subgroup analyses should be considered as well. Vitamin D levels were measured only once, with no account taken of changes across gestation. The repeated measures would be more helpful, but they should be carefully tackled due to laboratory costs. Many potential cofounders like sun exposure, diet, socioeconomic status, and comorbidities were not systematically controlled. Given the study design, it is not possible to establish a causal relationship between vitamin D deficiency and pre-eclampsia and there should be prospective cohort studies or interventional trials that would confirm causality. Despite these limitations, this study contributes to the expanding body of evidence from South Asian populations that there is high prevalence of vitamin D deficiency in women with PIH and its association with pre-eclampsia. Given the high deficiency rates observed, routine vitamin D screening in women with PIH should be considered in a part of standard antenatal care. Early detection and correction of deficiency (ideally before 20 weeks' gestation) may lower the risk of progression to pre-eclampsia, a condition that carries substantial fetomaternal morbidity and mortality.

CONCLUSION

Vitamin D deficiency is highly prevalent among patients with PIH, affecting around 78% of the study population. Vitamin D deficient patients had a significantly higher rate of pre-eclampsia than those with sufficient levels (32.4% vs. 9.5%; $p = 0.038$), and this association maintained its statistical significance in patients with BMI below 25 kg/m². These results support incorporating routine vitamin D screening into the antenatal management of women with PIH. Early identification and correction of deficiency may help to reduce progression to pre-eclampsia and its associated fetomaternal complications. Larger prospective studies preferably multicentric, are needed to confirm these findings and to determine the full impact of vitamin D supplementation on pre-eclampsia outcomes in our population.

Authors with contributions:

Sr. No	Author	Role
1	Dr.Anum Sarwar	Conception and design, Critical revision for important intellectual content, final approval, and guarantor
2	Dr.Tahira Akhtar	Collection and assembly of data
3	Dr.Amina Ansar	Analysis and interpretation of data

4	Dr.Aliya Zainab	Statistical expertise

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