



## Original Article

## Association between Vitamin D Deficiency and Preeclampsia among Pregnant Females during First Trimester

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## ABSTRACT

One of issue during pregnancy among women is vitamin D insufficiency and studies have shown a dose-response relationship between development of preeclampsia and maternal vitamin D levels. **Objective:** To determine any association between vitamin D insufficiency in blood during the first trimester of pregnancy and development of preeclampsia. **Methods:** It was a Case Control study conducted in Department of Obstetrics and Gynecology, Lady Willingdon Hospital Lahore, from September 2019 to August, 2020. 150 women fulfilling selection criteria were enrolled from OPD of Lady Willingdon Hospital, Lahore. Informed consent was taken. Demographic variables e.g. age, gestational age, parity and BMI were recorded. Then females were divided in two groups i.e. cases with preeclampsia and controls without preeclampsia. Then medical record was obtained and vitamin D level during first trimester was noted. If vitamin D <20ng/dl, then vitamin D deficiency was labeled (as per operational definition). Data were entered and analyzed in SPSS version 20.0. Frequency and percentages were calculated for qualitative variables. **Results:** Mean age was 28.01±3.43 years. Mean gestational age was estimated as 32.84±4.75 weeks in cases and 32.24±3.55 in controls, Vitamin D deficiency in blood during the first trimester of pregnancy and development of preeclampsia shows that 90.67% in cases and 82.67% in controls had vitamin D deficiency with odds ratio of 2.03. **Conclusions:** We concluded that there is an association between vitamin D deficiency in blood during the first trimester of pregnancy and development of preeclampsia.

## INTRODUCTION

Hypertensive disorders during pregnancy are very prevalent in developing countries with one-quarter of maternal deaths with hypertensive disorders during pregnancy occur in Asia and Africa. Preeclampsia and eclampsia are the major hypertensive disorders that constitute major morbidity and mortality in newborn and mothers [1]. The intrauterine fetal development and infant health later is greatly influenced by Vitamin D status during pregnancy. Among pregnant women vitamin D levels tend to decrease from their normal range and its optimal

requirements for the body is also greatly affected for several reasons. This leads to either development of vitamin D insufficiency or deficiency among pregnant women especially in first trimester of pregnancy. This directly affects both the mother and fetus and later in the offspring. However, there is insufficient high-quality data, especially no randomized controlled trials have been done on vitamin D optimal reference range for both mother and neonate to get the most of the health benefits [2]. Christesen *et al.*, in a different study concluded that there is

an inverse relationship between maternal vitamin D concentrations and specific pregnancy outcomes such as, preeclampsia, gestational diabetes, and other infertility parameters [3]. Vitamin D status is measured by a specific marker concentration that is 25(OH)D, and data suggest there are valid scientific evidence that levels above 50 nmol/l (>20ng/ml) serum values of 25(OH)D are satisfactory level for a good health status especially in females during pregnancy [4]. In an Indian study, it was reported that about 82.8% females with preeclampsia and 31.25% females without preeclampsia were found deficient in vitamin D (<20ng/dl,  $p < 0.05$ ) [5]. In another Indian study, it was found that almost 100% females with preeclampsia and 92% females without preeclampsia were found to have a deficient in 25(OH)D i.e. <20ng/dl, which was statistically significant. ( $p > 0.05$ ) [6]. However, one American study found that about 11% females with preeclampsia and 10% females without preeclampsia were found deficient in vitamin D (<20ng/dl,  $p > 0.05$ ) [7]. The aim of this study is to evaluate any association between vitamin D deficiency in blood during the first trimester of pregnancy and preeclampsia. Literature reported that in pregnant females who belong to developed country, there is no relationship of vitamin D deficiency with preeclampsia but there is a significant association was found between vitamin D deficiencies in first trimester with preeclampsia in developing countries, also varied data has been retrieved from literature. Vitamin D deficiency and insufficiency are prevalent, particularly in pregnant women, worldwide and also in Pakistan, which is considered an important public health concern. So it can be said that if serum vitamin D level is maintained in pregnant ladies then the ratio of morbidity and mortality can be decreased. So, we want to conduct this study to get local evidence and confirm whether association exists. Therefore, this study will help to get updated and confirmed results and we may be able to implement the screening of pregnant females for vitamin D level in early pregnancy in order to prevent preeclampsia and its consequences. The objective of study was to evaluate any association between vitamin D deficiency in blood during the first trimester of pregnancy and development of preeclampsia.

## METHODS

We conducted a case control study at department of Gynecology and Obstetrics out-door patient of Lady Willingdon Hospital, Lahore, Pakistan from September 2019 to August 2020. Sample size of 150 women (75 in Group A (Cases) and 75 in Group B (controls) was calculated with 80% power of study, 5% significance level and taking expected percentage of vitamin D deficiency i.e. 100% in women with preeclampsia and 92% in women without

preeclampsia and selected through non-probability, consecutive sampling. Women aged 18-40 years, parity <5, who were enrolled during third trimester (>20 weeks on LMP) for antenatal care. Cases was women with preeclampsia and normotensive women were taken as controls. Un-booked women or women with incomplete antenatal record, women with chronic hypertension, multiple fetuses, previous abortion and women taking vitamin D supplements from first trimester were excluded. Medical record was obtained and vitamin D level during first trimester was noted. If vitamin D <20ng/dl, then vitamin D deficiency was labeled. Data were entered and analyzed in SPSS v 22.0. Numerical variables like age, BMI, gestational age was presented as mean  $\pm$  SD. Qualitative variables like vitamin D deficiency and parity were presented as frequency and percentage. Association between vitamin D deficiency and preeclampsia was evaluated through Odds ratio with OR > 1 was considered as statistically significant. Data were stratified for confounding variables like age, gestational age, parity and BMI and post-stratification, OR was calculated with p value  $\leq 0.05$  was considered as significant.

## RESULTS

A total of 150 women (75 in Group A (Cases) and 75 in Group B (controls) were enrolled to determine the association between vitamin D deficiency in blood during the first trimester of pregnancy and development of preeclampsia. 74.67% (n=56) in cases and 73.33% in controls were between 18-30 years of age. Mean age was 28.01 $\pm$ 3.43 years in cases and 28.13 $\pm$ 3.53 in controls. Mean gestational age was estimated as 32.84 $\pm$ 4.75 weeks in cases and 32.24 $\pm$ 3.55 weeks in controls. Parity distribution reveals that 57.33% in cases and 62.67% in controls were having 1-2 parity whereas 42.67% (n=32) in cases and 37.33% (n=28) in controls were between 3-4 parity, mean  $\pm$  SD was 2.40 $\pm$ 0.82 in cases and 2.31 $\pm$ 0.72 in controls. Body mass index was 29.17 $\pm$ 3.52 in cases and 29.19 $\pm$ 3.49 in controls (Table 1 and 2).

**Table 1:** Frequency distribution of age, gestational age and parity of respondents (n=150)

Variables		Cases (n=75)	Controls (n=75)
		Frequency (%)	Frequency (%)
Age (years)	18-30	56 (74.67)	55 (73.33)
	31-40	19 (25.33)	20 (26.67)
G. Age (weeks)	20-37	60 (80)	63 (84)
	>37	15 (20)	12 (16)
Parity	1-2	43 (57.33)	47 (62.67)
	3-4	32 (42.67)	28 (37.33)

**Table 2:** Statistics for age, gestational age and BMI of respondents(n=150)

Variables	Cases (n=75)	Controls (n=75)
Age (years)	28.01 ± 3.43	28.13 ± 3.55
G. Age (weeks)	32.84 ± 4.75	32.24 ± 3.55
BMI	29.17 ± 3.52	29.17 ± 3.52

There were 90.67% (n=68) in cases and 82.67% (n=62) in controls had vitamin D deficiency whereas 9.33% (n=7) in cases and 17.33% (n=13) in controls had no vitamin D deficiency, O.R was calculated as 2.03. ( $p > 0.05$ ). The data were stratified for age, gestational age, parity and BMI. Post-stratification, OR was calculated to measure association between vitamin D deficiency and preeclampsia for each strata. OR > 1 with  $p \leq 0.05$  was taken as significant (Table 3).

**Table 3:** Cross tabulation for vitamin D deficiency and age, gestational age, parity and BMI of respondents(n=150)

Variables n=150		Cases (n=75)	Controls (n=75)	O.R	p-value	
Vitamin D Deficiency	Yes	68	62	2.03	0.155	
	No	7	13			
Age (years)	18-30	Yes	47	1.73	0.36	
		No	5			8
	31-40	Yes	17	15	2.83	0.25
		No	2	5		
G. Age (weeks)	20-37	Yes	55	50	2.86	0.06
		No	5	13		
	>37	Yes	13	12	0.21	0.33
		No	2	0		
Parity	1-2	Yes	36	39	1.05	0.92
		No	7	8		
	3-4	Yes	32	23	15.21	0.06
		No	0	5		
BMI	Up to 30	Yes	42	39	1.94	0.27
		No	5	9		
	>30	Yes	26	23	2.26	0.37
		No	2	4		

## DISCUSSION

Vitamin D insufficiency during pregnancy is significant public health issue among females worldwide but it's more marked in developing countries due to poor diet and nutritional status. There are several risk factors especially in Muslim countries for vitamin D insufficiency that includes low dietary vitamin D intake, extensive skin covering and ethnicity. In developed countries excessive use of sun protection, overweight, obesity and smoking seem to be precipitation factors. There is also a seasonal variation observed at temperate latitudes. Our study was conducted to determine any association between preeclampsia development in the first trimester of pregnancy and vitamin D insufficiency. Several studies done in developed countries have found no relationship of

vitamin D deficiency with preeclampsia. On the contrary studies done in developing countries, the vitamin D deficiency in first trimester was found to be significantly associated with preeclampsia; also varied data has been retrieved from literature [7]. This study also attempted to evaluate any association between development of preeclampsia during the first trimester of pregnancy and vitamin D insufficiency. Our data suggest that association between vitamin D insufficiency in blood and development of preeclampsia shows a significant relationship. 90.67% (n=68) of cases and 82.67% (n=62) in controls had vitamin D deficiency (OR 2.03). These findings are supported by an Indian study, where 100% females with preeclampsia and 92% females without preeclampsia were found deficient in vitamin D (<20ng/dl,  $p > 0.05$ ) [6]. There is a conflicting data regarding hypertensive diseases among pregnancy like pre-eclampsia and eclampsia development and Vitamin D insufficiency. Some studies suggest that women with low levels of vitamin D (<50 nmol/l) developed pre-eclampsia and a five-fold increased risk of developing severe pre-eclampsia [8-10]. The risk of developing pre-eclampsia among women with low levels of Vitamin D (<50 nmol/l) in the first half of pregnancy was significant [11] and there is a two-fold increased risk of having vitamin D deficiency (< 37.5 nmol/l) among the neonates of these mothers [12]. Robinson *et al.*, study showed that vitamin D levels <50 nmol/l among pregnant women before 34 weeks of gestation developed severe pre-eclampsia as compared to controls [13]. Additionally, women with early-onset severe pre-eclampsia and with small-for-gestational-age (SGA) neonates have significantly lower vitamin D levels (< 37.5 nmol/l) as compared to women with early-onset severe pre-eclampsia but non-SGA neonates [14]. Ringrose *et al.*, research in their uni-variate analysis showed that pregnant females with low circulating Vitamin D levels (< 37.5 nmol/l) are more likely to have hypertensive disease in pregnancy, but these findings were not substantiated in multivariate analysis [15]. Nevertheless, results of several researchers have shown a weak to non-significant relationship between hypertensive disorders during pregnancy and vitamin D insufficiency [14-16]. A study conducted in 179 patients by Ali *et al.*, concluded that fewer (1.2 %) pre-eclampsia reported in control group having maternal vitamin D level >50 nmol/ml as compared to more pre-eclampsia (8.6%) reported in study group having maternal vitamin D level <50 nmol/ml. Similarly, IUGR was lesser 9.6% and 22.2% respectively [17]. Another study conducted with 172 patients by Shahid S and associates reported significantly lower vitamin D levels ( $p < 0.001$ ) in pre-eclampsia group as compared to normotensive group. This study found a strong relationship between low vitamin D levels and pre eclamptic manifestation [18]. A case control study

conducted by Achkar *et al.*, showed that pre-eclampsia had a significant lower 25(OH) D concentration at 14 weeks gestation as compared women in control group [19]. While another study conducted by Mirzakhani *et al.*, denied with the above said results and reported no reduction in pre-eclampsia incidence in intention to treat paradigm group treated by vitamin D supplementation [20]. Shand *et al.*, was also unable to find any association between gestational hypertension, development of preeclampsia or preterm birth and vitamin D insufficiency [16]. A similar study by Powe *et al.*, also unable to find any association between low vitamin D during first trimester and the consequent development of preeclampsia after controlling BMI [21]. However, two meta- analyses, including 31 studies, demonstrated that there is association between pre-eclampsia and SGA infants and vitamin D insufficiency [21, 22]. A systematic review of several case-control and cross-sectional studies by Purswani *et al.*, have shown as association between vitamin D status and pre-eclampsia [23]. A study by Wei *et al.*, showed that women with circulating 25-hydroxyvitamin D [25(OH)D] level less than 50 nmol/l in pregnancy experienced an increased risk of preeclampsia odds ratio (OR)2.09[24]. In summary, we are of the view that vitamin D insufficiency is very common among pregnant women in this region as our sample size came from a diverse background from different areas in Pakistan. This should be considered a major public health issue among pregnant women especially in first trimester. We recommend that a daily supplementation among women especially during pregnancy oral cholecalciferol or ergocalciferol must be given and that is found to be safe during pregnancy. The NICE guidelines and UK Chief Medical Officers recommendations 2012 suggests that health education must be instituted during pregnancy and among women who are breastfeeding regarding the important role vitamin D plays in fetal and maternal health and a daily recommended allowance of 10 micrograms of vitamin D supplements should be recommended [25, 26]. Women especially pregnant and those who are breast feeding are at high risk of Vitamin D insufficiency and particular care must be taken for them. The NICE guidelines recommend vitamin D supplementation that are based on the established benefits of vitamin D supplementation during stress like pregnancy and lactation among females but many other general actions of vitamin D can also provide additional benefits during and after pregnancy.

## CONCLUSIONS

We concluded that there is a significant association between development of preeclampsia during the first trimester of pregnancy and vitamin D deficiency.

## Authors Contribution

Conceptualization: SZS, BF

Methodology: FW, SB

Formal analysis: NA

Writing-review and editing: SZS, BF

All authors have read and agreed to the published version of the manuscript.

## Conflicts of Interest

The authors declare no conflict of interest.

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