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Association of Vitamin D 25(OH)D Deficiency as a Risk Factor for Pre-Eclampsia

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Abstract

Background: Pre-eclampsia is the major cause of maternal and fetal morbidity and mortality. Research shows the role of Vitamin deficiency in the pathogenesis of pre-eclampsia. The objective of this study was to determine the association between pre-eclampsia and Vitamin D [25(OH) D] deficiency in our pregnant population.

Methods: This was a case-control study, conducted at Outpatient and inpatient Departments of Obstetrics & Gynecology, Combined Military Hospital, Multan from September 2019 to March 2020. A total of 60 patients (30 cases (with pre-eclampsia) and 30 controls (without pre-eclampsia) were included in the study using the convenience (non-probability) sampling technique. After taking informed consent, baseline data including age, gestational age and duration of sun exposure was noted. Blood samples for Vitamin D [25(OH) D] levels were collected aseptically from fresh peripheral venous pricks from cases and controls. Vitamin D [25(OH) D] levels were measured and categorized as adequate and deficient as per operational definitions. All obtained information was recorded in a structured Performa keeping the confidentiality of the patients.

Results: Out of 60 patients (n=60) 30 were cases (with pre-eclampsia) and 30 were controls (without pre-eclampsia). The mean age (years) of patients in our study was 23.32+4.34, whereas the frequencies of Vitamin D [25 (OH)] D deficiency among cases and control groups were 18 (60.0%) and 3 (10.0%) respectively. The difference was statistically significant (p-value 0.000).

Conclusion: Vitamin D [25 (OH)] D deficiency was found to be more in patients with pre-eclampsia as compared to those without pre-eclampsia.

Keywords: Pre-eclampsia, Vitamin-D [25 (OH)]

Introduction

Vitamin D deficiency is a global health problem with approximately one billion people are suffering from vitamin deficiency or insufficiency (1). Vitamin D deficiency is 40% in the European population (2). Hypovitaminosis D is an epidemic in South Asian ethnicity (3). It is very common in the Pakistani population especially in women of reproductive age and is estimated to be 90% (4, 5). This higher prevalence of hypovitaminosis D is due to reduced exposure to sunlight, low intake of Vitamin D, deeply pigmented skin and females covering their bodies with clothing (6). It is associated with many health problems including hypertension, diabetes, coronary artery disease, asthma and certain cancers (7). Both mother and fetus are dependent on

maternal vitamin D stores during pregnancy so adequate Vitamin D levels are required for a healthy pregnancy (8). Research shows an association between Vitamin D deficiency and pregnancy-associated complications like hypertensive disorders of pregnancy, low birth weight and preterm labour (9, 10). Hypertensive disorders of pregnancy affect 5 to 10 % of pregnancies around the world and 14% of Pakistani pregnant women as reported in the Pakistan Maternal Mortality Survey 2019 (11).

Hypertensive disorders of pregnancy are characterized by chronic and gestational hypertension, pre-eclampsia and eclampsia (12). Pre-eclampsia refers to hypertension along with new-onset proteinuria after 20 weeks of gestation (13). The global incidence of pre-eclampsia is 5 to 14% and 1 to 4% in the Pakistani population (11, 12). It has been found that over 30,000 women die each year due to pre-eclampsia and its complications. Among those 98% of deaths occur in developing countries like Pakistan (14). It is responsible for 10-25% perinatal loss (15). Pre-eclampsia can lead to eclampsia, which further increases the risk of maternal and fetal mortality (16). Vitamin D may have a role in the pathophysiology of pre-eclampsia by causing abnormal implantation, angiogenesis, immune dysfunction, excessive inflammation, and hypertension. It aids in gene expression and regulation in placental development (17). The role of vitamin D in pre-eclampsia is related to the effect of vitamin D on the renin-angiotensin system (RAS). Vitamin D is a negative endocrine regulator of RAS, which suppresses renin gene expression. Therefore, serum vitamin D levels are inversely associated with blood pressure and renin activity (18).

Although pre-eclampsia is associated with Vitamin D deficiency, research in the Pakistani population is limited. In this study, we assessed the association of vitamin D deficiency as a risk factor for pre-eclampsia in our pregnant population. The results will be shared with the health care providers so that pregnant women are encouraged for early screening and treatment of Vitamin D deficiency during antenatal visits to prevent pre-eclampsia and its complications.

Methodology

This case-control study was carried out in the Inpatient and Outpatient Departments of Obstetrics and Gynaecology, Combined Military Hospital, Multan over six months, from September 2019 to March 2020. A total of 60 patients; 30 cases (with preeclampsia) and 30 controls (without preeclampsia) were included using the convenience sampling technique. Our Inclusion criteria was Primigravida, 18-35 years old women, at a gestational age of >20 weeks (confirmed by LMP method and dating scan). Exclusion criteria were multiple gestations (on Ultrasound), known diabetics (assessed by the medical record), known hypertensive (assessed by the medical record), chronic kidney disease (creatinine > 1.2 mg/dl for more than 6 months assessed by medical records), women on vitamin D supplements or taking fortified food assessed by history, women using sunscreens assessed by history. These two groups were matched for age, gestational age, BMI and parity. Pre-eclampsia was defined based on the new onset of hypertension and proteinuria (≥1+ reading on dipstick) occurring after the 20th week of gestation in a previously normotensive and non-proteinuric woman. The control group consisted of age and gestation-matched healthy normotensive pregnant women.

The study was conducted after permission from the institutional ethical committee. Informed consent was obtained from patients regarding using of data for research and publication. Baseline data including age, gestational age and duration of sun exposure body mass index was noted. Blood samples for vitamin D [25(OH) D] levels were collected aseptically from fresh peripheral venous pricks and vitamin D [25(OH) D] levels were measured using an enzyme-linked immunosorbent assay (ELISA) technique. For vitamin D [25(OH) D] deficiency, a cut off level of <20 nmol/l was taken, as defined by the US Endocrinology Society (ES) (19). All obtained information was recorded on a structured questionnaire keeping the confidentiality of the patient.

Data analysis: All the data were entered into a statistical package for social sciences (SPSS) Version 21.0 and analyzed. Quantitative variables like BMI, age, gestational age, duration of sun exposure hours were presented as mean and standard deviation. Vitamin D [25(OH) D] status between cases and controls were compared using Chi-Square test and presented as Odds ratio with 95% confidence interval. A P-value of ≤0.05 was be taken as significant.

Results

Table 1 shows the demographic profile of the study participants. The mean age of patients in our study was 23.32 ± 4.34. The mean gestational age (weeks) of

patients in our study was 31.28 ± 1.20. The mean body mass index of patients in our study was 26.65 ± 2.51. The mean duration of sun exposure of patients in our study was 3.85 ± 1.44 hrs.

Table 1. Demographic profile (n=60)

	N	Mean	Std. Deviation
Age (years)	60	25.32	4.34
Cases	30	25.83	4.91
Controls	30	24.80	36.69
Gestational Age(weeks)	60	31.28	1.20
		30.83	1.08
Cases	30	31.73	1.17
Control	30		
Body Mass Index	60	26.65	2.510
Cases	30	26.10	2.57
Controls	30	27.20	2.35
Duration (hours) of sun exposure	60		1.44
	30	3.85	1.37
	30		1.51
Cases		3.66	
Control		4.03	

Table 2 shows vitamin D [25 (OH)] D deficiency among cases and control groups was 18 (60.0%) and 3 (10.0%) respectively. The odds of vitamin D deficiency in pre-eclamptic women was 13.5 (95% CI) times that of controls. The difference was statistically significant (p-value 0.000).

Table 2. Comparison of Vitamin D [25(OH) D] levels in cases and controls (n=60)

		Two groups		Total	p-value	Odds Ratio (0R)
		Cases (With preeclampsia)	Controls (Without preeclampsia)			
Vitamin D [25 (OH)] D status	Deficient	18	3	21	0.000	13.50
		60.0%	10.0%	35.0 %		
	Not deficient	12	27	39		
		40.0%	90.0%	65.0 %		
Total		30	30	60		

Effect modifier like age stratification was studied for the association of pre-eclampsia and vitamin D [25(OH)] D deficiency as given in Table 3. Among patients with age 18 – 30 years, frequency and percentage of vitamin D [25 (OH)] D among cases and control groups were 13 (54.2%) and 3 (10.0%) respectively which was statistically significant (p-value 0.000). The odds of vitamin D deficiency in pre-eclamptic women of this age group was 11 (95% CI) times that of controls. While among patients with age 31 – 35 years, frequency and percentage of vitamin D [25 (OH)] D among cases and control group was 05 (83.3%) and 0 (0.0%) respectively which was statistically significant (p-value 0.000), as shown in Table 3.

Table 3. Association between Pre-eclampsia and Vitamin D [25(OH) D] levels in different age groups

Age groups	Vitamin D [25 (OH)] D status	Two groups		Total	p-value	odd ratio
		Case	Control			
18 - 30 years	Deficient	13	3	16		
		54.2%	10.0%	29.6%	0.000	10.63
	not deficient	11	27	38		
		45.8%	90.0%	70.4%		
31 - 35 years	Deficient	5	0	5		
		83.3%	0.0%	83.3%	0.000	0.0
	not deficient	1	0	1		
		16.7%	0.0%	16.7%		

Effect modifier like gestational age (weeks) stratification was studied for the association of pre-eclampsia and vitamin D [25(OH)] D deficiency as given in Table 4. Among patients with gestational age (weeks) <30 weeks, frequency and percentage of vitamin D [25 (OH)] D among cases and control group was 15 (65.2%) and 1 (9.1%) respectively which was statistically significant (p-value 0.000). The odds of vitamin D deficiency in pre-eclamptic women was 18.75 (95% CI) times that of non-pre-eclamptic at this gestation. Whereas, among patients with gestational age > 31 weeks, frequency and percentage of vitamin D [25 (OH)] D among cases and control group were 3 (42.9) and 2 (10.5) respectively which was statistically not significant (p-value 0.064) with odds ratio 6.37 (95% CI), as shown in Table 4.

Table 4. Association between Preeclampsia and Vitamin D [25(OH) D] Levels at different gestations

Gestational Age (months)	Vitamin D [25 (OH)] D status	Two groups		Total	p-value	odds ratio
		Case	Control			
< 31	Deficient	15	1	16		
		65.2%	9.1%	47.1%	0.002	18.75
	not deficient	8	10	18		
		34.8%	90.9%	52.9%		
> 31	Deficient	3	2	5		
		42.9%	10.5%	19.2%	0.064	6.37
	not deficient	4	17	21		
		57.1%	89.5%	80.8%		

Effect modifier like duration (hours) of sun exposure was studied for the association of preeclampsia and vitamin D [25(OH)] D. Among patients who have less than 3 hours of sun exposure, frequency and percentage of vitamin D [25 (OH)] D among cases and control group were 10 (76.9) and 0 (0.0) respectively which was statistically significant (p-value 0.000). The odds of vitamin D deficiency in pre-eclamptic was 4.33 (95% CI) times that of control in this group. Whereas among patients who has more than 3 hours of duration of sun exposure, frequency and percentage of vitamin D [25 (OH)] D among cases and control group were 8 (47.1) and 3 (15.0) respectively which was statistically significant (p-value 0.033) with odds ratio 5.03 (95%CI), as shown in Table 5.

Table 5. Association between Preeclampsia and Vitamin D [25(OH) D] Levels to Duration (hours) of Sun Exposure

Duration (hours) of sun exposure	Vitamin D [25 (OH)] D status	Two groups		Total	p-value	odds ratio
		Case	Control			
< 3 hours	Deficient	10	0	10		
		76.9%	0.0%	43.5%	0..000	4.33
	not deficient	3	10	13		
		23.1%	100.0%	56.5%		
> 3 hours	Deficient	8	3	11		
		47.1%	15.0%	29.7%	0.033	5.03
	not deficient	9	17	26		
		52.9%	85.0%	70.3%		

Discussion

Pre-eclampsia is associated with adverse maternal and perinatal outcomes. Therefore, it is important to identify its modifiable risk factors to prevent its development. Some cohort and case-control studies have found an association between vitamin D deficiency and pre-eclampsia. The findings of our study suggest that pre-eclamptic women have lower levels of Vitamin D as compared to normotensive healthy controls. Similar results were found in a study where 75% of the cases (a hypertensive group with either preeclampsia or eclampsia) had vitamin D deficiency as compared to 25% in the control group (20). Similarly, another study depicted that patients with preeclampsia had significantly decreased levels of serum Vitamin D with p 0.01, as compared to the normotensive group (p 0.16) (21). However, a recent study showed similar levels of Vitamin D3 in pre-eclamptic and normotensive pregnant women. However, a higher concentration of Vitamin D3 metabolites and reduced uptake by the placenta was found in patients with pre-eclampsia signifying the role of vitamin D metabolism in the pathophysiology of pre-eclampsia (22). The odds of developing pre-eclampsia in women with vitamin D deficiency was 13.50 as likely as non-pre-eclamptic who have had vitamin D deficiency. The results of a prospective cohort study in nulliparous women showed that the level of vitamin D deficiency was significantly lower in patients who developed pre-eclampsia with odds ratio of 3.24 for pre-eclampsia (23). A study among Danish women showed a positive association between parity and vitamin D deficiency (24). The findings of our study show a stronger association as both nulliparous and multiparous women were included in the study.

A study conducted in 2015, showed that mean gestation (weeks) in pre-eclamptic women who had Vitamin D deficiency was 30.95 weeks whereas our study findings showed mean gestational age of 31 weeks (25). Pre- eclamptic are 18.75 times as likely as non-pre-eclamptic women to have had vitamin D deficiency before 31 weeks of gestation. This result shows that the effect is observed more before 31 weeks of gestation. These findings suggest early screening and treatment of vitamin D deficiency.

Our study findings showed mean body mass index (BMI) was 26.65+2.5 whereas a study conducted in Iran in 2015 showed that the average body mass index among pre-eclampsia patients with vitamin D deficiency was 33.49+6.06 (25). The findings suggest that Vitamin D deficiency is associated with pre-eclampsia more in overweight and obese patients. Contrary to our findings where exposure to the sun for less than 3 hours was found to be associated with pre-eclampsia. A study showed that vitamin D supplementation does not reduce the risk of pre-

eclampsia (25). This may due to different effects of Vitamin naturally synthesized from the sun as compared to Vitamin D supplements (26, 27). Thus pregnant women should be educated regarding exposure to the sun along with Vitamin D supplements and a diet rich in Vitamin D during their antenatal visits.

Limitations of the Study

This study has certain limitations. These include small sample size and limited to a single centre. Further studies with a larger sample size and at multicenter are recommended to explore the association between Vitamin D deficiency and pre-eclampsia.

Conclusion

Vitamin D deficiency was found to be associated with preeclampsia in our pregnant women. Mass awareness is needed through public health campaigns, social media postings and articles in newspapers to educate women of childbearing age to improve their Vitamin D levels through sun exposure, Vitamin D supplements and dietary intake of Vitamin D.

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