RESEARCH ARTICLE

Association of vitamin D deficiency to the risk of preeclampsia in Saudi Arabia

Aisha Mansoor Ali,[1] Munazzah Rafique,[2] Zarqa Saleem[3]

Abstract

Objective: Vitamin D levels have shown significant geographical distribution, therefore, this study was conducted to evaluate its relationship to a specific geographic area with a high prevalence of vitamin D deficiency to the important maternal manifestation of preeclampsia. This study established the association of vitamin D deficiency to preeclampsia among women of reproductive age.

Method: It is a retrospective case-control study done to measure serum vitamin D levels in pregnant women receiving care at the King Fahad Medical City Riyadh with preeclampsia (n=100) and normal pregnancy (controls, n=200) from 2012 to 2014. Odds of developing preeclampsia with vitamin D deficiency were calculated using logistic regression analysis.

Results: The mean serum vitamin D level was 25.35?ng/ml in controls and 15.95?ng/ml in pre-eclampsia women. Comparing to those who had a serum vitamin D level of <50ng/ml,, the odds ratio of developing preeclampsia in women with vitamin D deficiency was 4.2 (95% CI=1.23-14.35) while adjusting for age, BMI and duration of pregnancy.

Conclusion: The risk of developing preeclampsia might increase by up to 4-fold in women with vitamin D deficiency. Since preeclampsia could lead to maternal and neonatal complications, vitamin D could be added during pregnancy to decrease these adverse consequences.

Keywords: Vitamin D deficiency, preeclampsia, BMI, hypertension. (JPMA 71: 257; 2021)

DOI: https://doi.org/10.47391/JPMA.600

Introduction

Preeclampsia is a common medical complication of pregnancy and is characterized by hypertension, oedema and proteinuria.[1] It is a life-threatening multisystem syndrome that develops after 20 weeks of gestation in women having short and long term consequences. It requires enormous demands from the health care system with regard to maternal and neonatal wellbeing.[2] Pre-eclampsia is defined as hypertension with a blood pressure ≥140mmHg systolic or ≥ 90mmHg diastolic found on two separate occasions at least 4 hours apart after 20th week of gestation with proteinuria (urine protein excretion of ≥ 0.3 gram in a 24h urine collection).[2,3] Maternal vitamin D deficiency is a widespread public health problem throughout the world in all socioeconomic strata. Vitamin D deficiency has been recently reported to be associated with hypertension, coronary artery disease, diabetes, asthma, rheumatoid arthritis, other autoimmune diseases, and certain cancers.[4-6] Pre-eclampsia is a pregnancy-specific syndrome that affects approximately 3-10% of pregnancies and is associated with adverse maternal and foetal outcomes.[7]

Pregnant women are at increased risk of nutritional deficiencies due to increased demand of growing foetus.[8] Vitamin D acts as a trace element that is involved in cellular metabolism and various biochemical pathways. Any change in homeostasis of vitamin D can contribute to the pathophysiology of multiple disorders and diseases.[9] Vitamin D deficiency is highly prevalent in Saudi Arabia predominantly among females.[10]

Despite the abundance of sunshine, most people have the lowest levels of vitamin D and the highest rates of hypovitaminosis D, especially pregnant women. The limited sun exposure due to cultural practices, dark skin colour, and hot climate, limited outdoor activities, rising obesity, and lack of government regulation for vitamin D fortification of food, justify the reason for vitamin D deficiency in several, if not all countries.[11] Vitamin D deficiency is caused by a lack of adequate sunlight exposure needed to synthesize it in the skin. However, in pregnancy inadequate oral intakes that meet the increased demands of pregnancy is contributing to its deficiency. Routinely, prenatal vitamins containing 400 IU vitamin D3 are used by the pregnant population.[12,13] Even though several recent clinical studies have reported an association of vitamin D deficiency with preeclampsia,[14,15]

[1,2]Department of Obstetrics and Gynaecokogy, Women Specialized Hospital, King Fahad Medical City, Riyadh, [3]Department of Obstetrics and Gynaecokogy, Sulaiman Habib Hospital, Riyadh, Saudi Arabia.

Correspondence: Munazzah Rafique. Email: munazzahr@yahoo.com

and previous studies had shown a 27% reduction in the risk of preeclampsia with vitamin D supplementation (400-600 IU or 10-15mcg per day),[16] no study had looked at its association with eclampsia. Treatment of the deficient group with Vitamin D supplementation reduces the risk of pre-eclampsia in addition to IUGR in a dose dependant manner.[17]

Though, there are conflicting results about the role of vitamin D to preeclampsia, these patients are high risk and need tertiary care multidisciplinary approach, with all available facilities of anaesthesia, obstetrics, neonatal intensive care, intensivist.[2] A cut off point of a plasma vitamin D level of <50ng/ml was used to define maternal vitamin D deficiency.

Not only there is paucity of data but also deficient literature about relationship of vitamin D status and preeclampsia in many regions raises the need of more studies for clarity. The hypothesis of this study was that the altered levels of vitamin D in patients could help in the prediction of preeclampsia during pregnancy. This study, demonstrated the association of vitamin D deficiency with pre-eclampsia.

Materials and Methods

Ethical approval was taken from the institutional board with IRB Registration H-01-R-012. Three hundred antenatal patients were purposely selected retrospectively through medical records from January 2012 to December 2014 for this case-control study in whom vitamin D levels were checked routinely as part of antenatal screening in first trimester at booking visit.

The patients visited the antenatal clinic of Obstetrics and Gynaecology Department, Women's Specialized Hospital, King Fahad Medical City, Riyadh, Saudi Arabia. There were100 women of preeclampsia that were selected as cases and 200 women with normal blood pressure were chosen as controls. Both control and cases were matched depending on inclusion and exclusion criteria. All patients have the results of vitamin D levels available before delivery. Clinical information of these patients was retrieved from medical records to find out their age, parity, gestational age, BMI, intake of vitamin D during pregnancy, delivery date and vitamin D level cut-off levels as sufficient is >50 (ng/ml) and deficient is < 50 (ng/ml).

Control group included pregnant women with normal BP, no proteinuria, normal renal function and devoid of any other systemic or endocrine disorder. All subjects included were in their third trimester. While, case group included pregnant women with preeclampsia, selection of which was according to the definition of American College of Obstetrics and Gynecologists (ACOG practice bulletin, 2002).[2] The patients with other risk factors for preeclampsia including history of preeclampsia, hypertension, diabetes mellitus, thromboembolic disease, multiple pregnancies, autoimmune or chronic disease, malignancies, chronic liver or kidney disease were excluded.

Vitamin D levels of women were taken as part of routine prenatal visits and measured using the Roche Diagnostic Vitamin D total assay. Venous blood was drawn into EDTA tubes, and plasma samples were separated immediately by centrifugation for 10 min at 4°C. Then, these samples were frozen and stored at -80°C and transported to the laboratory for analysis. Serum 25(OH)D was estimated by electrochemiluminescence immunoassay (ECLIA) on automated Roche immunoassay analyzer, Cobas e601 using Vitamin D3 (25-OH) Kit (Roche Diagnostics, Germany). This method used a competitive assay with a polyclonal antibody directed against 25-OH vitamin D3. Results were determined via a calibration curve, which was generated by Vitamin D3 (25-OH) CalSet (Roche Diagnostics). Commercial quality control material from Roche Diagnostics was used as internal quality control.

Patients with vitamin D level of less than 50 ng/dl were considered to have vitamin D deficiency, and those with vitamin D of 50 ng/dl or more were considered to be vitamin D sufficient.

Their blood samples were drawn on first antenatal visit before initiating treatment with antenatal vitamins to check serum vitamin D level. Another 200 consecutive patients with healthy pregnancy presenting at the out-patient clinic for prenatal care at/after 20 weeks of gestation were taken as controls, and their serum vitamin D levels were drawn within one week before the next follow up antenatal visit.

The parameters of cases and controls were compared using Student's t-test, Fisher's exact test, Wilcoxon rank test, and chi-square tests. Logistic regression analyses were piloted to estimate the odds ratio (OR) of developing pre-eclampsia due to vitamin D deficiency, adjusting for potential confounders. The odds ratio with 95% CI of developing pre-eclampsia with vitamin D deficiency were calculated, comparing to those who had a plasma 25(OH)D level <50ng/ml. The covariables assessed for confounding included maternal age, parity, body mass index (BMI) and gestational age. The covariables were tested in bivariate regression models, and a p-value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS 22.0 software supplied by IBM in 2009 (SPSS Inc., Chicago, IL, USA) package.

Results

The study population had a very high prevalence of vitamin D deficiency. Demographics for both the groups were similar in age, parity and BMI with no statistical difference between both groups. With regard to vitamin D levels, women who developed preeclampsia had a significantly low level of vitamin D compared to the controls with mean Vitamin D level in control group was 25.35 and in pre eclampsia group was 15.95 (p<0.001). The gestational age at delivery was also found to be less in women who developed pre-eclampsia with a statistically significant difference between the two groups. (p<0.001). Healthy pregnant women in the control group delivered at an average gestational age of 39 weeks and women who developed preeclampsia delivered at an average gestational age of 36 weeks (Table-1). The mean level of vitamin D in control was 25.35 ng/ml (95% CI 7.7-94.5), while in cases 15.95 ng/ml (95% CI 7.5-52) (Table-1). Mode of delivery also being significantly different in both groups, with vaginal deliveries more in number in healthy pregnant group and caesarean mode of delivery being more in women who developed pre-eclampsia. In the control group with healthy pregnancies, 70.5% delivered vaginally and 29.5% delivered by caesarean delivery. In contrast, in the case group who developed preeclampsia only 27% had vaginal deliveries and 73% had a caesarean delivery. It was also noticed that healthy pregnant group were more likely to be taking vitamin supplements than preeclampsia group (p-value 0.001).

Table-2: Independent Risk Factors Associated with pre-eclampsia.

Variable	Odds ratio	Univariate 95% CI	p-value
Vitamin D status			
< 50	1.06	1.04-1.08	<0.001*
≥ 50	4.2	1.23-14.35	

*Statistically significant results p=<0.05.

The mean maternal age was 29.53 and 30.26 years in control and case groups respectively, which did not vary significantly. The mean BMI 30-35 kg/m^2 was not significant (p<0.47) among women; 63% women in pre eclampsia group being obese and 70% in the control group were obese. The percentage of premature delivery (< 36 weeks) was also higher <0.001with pre-eclampsia (51%) than controls (32%). Nulliparity (n=94) was more common among women in controls (37.04%) than among women with pre-eclampsia (46%). Prenatal vitamin use (not containing any vitamin D) was common in the study population. There were 61.6% of all subjects reported to use prenatal vitamin during pregnancy, and vitamin D levels were particularly very low among women having pre-eclampsia (p<0.001).

Last but not the least, about timing of delivery was noted that healthy women delivered most in summer season, compared to women who developed preeclampsia having deliveries distributed all through the seasons but compared to healthy women having 23% more deliveries during winter season.

Table-1: Characteristics of participants(n=300).

Variable		Normal blood pressure (control) n=200	Pre-eclampsia (case) n=100	p-value
Maternal age (years)		29.53 ±4.63	30.26 ±4.85	0.2
Parity	Primiparous	94(47.0%)	46(46.0%)	0.87
	Multiparous	106(53.0%)	54(54.0%)	
Duration of pregnancy (weeks)	Preterm	32(16.0%)	51(51.0%)	<0.001
	Term	168(84.0%)	49(49.0%)	
BMI (kg/m2)	Normal	23(11.5%)	14(14.0%)	0.47
	Overweight	37(18.5%)	23(23.0%)	
	Obese	140(70.0%)	63(63.0%)	
Antenatal multivitamin	No	66(33.0%)	49(49.0%)	<0.001
	Yes	134(67.0%)	51(51.0%)	
Mode of delivery	Vaginal	141(70.5%)	27(27.0%)	<0.001
	Caesarean	59(29.5%)	73(73.0%)	
Serum vitamin D levels	Mean (min, max)	25.35 (7.7, 94.5)	15.95(7.50, 52)	<0.001
Vitamin D deficiency	< 50 ng/ml	177 (88.5%)	97 (97%)	0.01
	>= 50 ng/ml	23 (11.5%)	3 (3%)	
Season	Summer	127(64.8%)	38(39.6%)	
	Spring	32(16.3%)	17(17.7%)	<0.001
	Winter	2(1.0%)	23(24.0%)	
	Fall	35(17.9%)	18(18.8%)	

*Statistically significant results p=<0.05, BMI=body mass index.

Analysis of the data also revealed that it was 4.2 fold less likely for women to develop preeclampsia in pregnant women if her vitamin D level was more than 50 nmol/L (CI 1.23-14.35) p-value <0.001 as shown in Table-2. Using simple and multiple logistic regression analysis, we calculated the odds ratio (95% CI) of developing pre-eclampsia with vitamin D deficiency, comparing to those who had plasma 25(OH) vitamin D3 level ≥50ng/ml. The odds ratio of developing preeclampsia was 4.2 (95% CI=1.23-14.35) (Table-2).

Discussion

Consistent with previous studies, this study showed a 3-5 fold increase in the risk of preeclampsia in vitamin D deficient mothers with increasing the risk of preterm and caesarian deliveries. The study participants were mostly young in their early 20s, had high BMI, with a high prevalence of vitamin D deficiency. Every 4 out of 5 mothers in the study had a vitamin D level <50ng/ml. The median vitamin D level was lowest among women with pre-eclampsia, which might represent their overall poor nutritional status. Premature delivery was much more common (51%) among women with preeclampsia compared to controls (16%). Additionally, obesity is a growing problem associated with pregnancy-related complications in most developed countries, in this study population both control and case groups have a maximum number of obese patients (70% and 63% respectively), which is also consistent with other studies performed.[17]

The pathogenesis of pre-eclampsia and eclampsia are still not clearly understood. Several hypotheses have been proposed for the development of these conditions. It is proposed that a poorly perfused placenta produces factors that lead to clinical manifestations of pre-eclampsia.[19] The placental abnormality associated with pre-eclampsia occurs before the completion of remodelling of vessels supplying placental site. It has been postulated that the initial insults that lead to clinical manifestations of pre-eclampsia occur long before 12-20 weeks of gestation.[20] This poor placentation may be precipitated by several maternal and environmental factors including genetic predisposition, obesity, diabetes, diet, nutrient deficiency, etc. Although factors released from the placenta have been considered as toxins, it has been suggested that these factors might have been released appropriately to help the foetoplacental unit overcome reduced nutrient availability. These factors might not be tolerated by some women, leading to maternal clinical manifestation of preeclampsia. Vitamin D has been implicated to have an important role in the expression and regulation of genes in early stage of development of placenta.[20] Therefore, hypovitaminosis D might be one of the predisposing factors leading to the development of poor placentation in early pregnancy and clinical manifestation of pre-eclampsia. Dysregulated vitamin D metabolism in the foetoplacental unit promotes aberrant inflammatory responses to immune challenges with vitamin D being a potent suppressor of placental inflammation.[22] Collectively, these data suggested that vitamin D plays an important role in controlling the foetal-placental immune responses during pregnancy. In pre-eclampsia, hypertension is an integral component of the disease process and might be emphasized by vitamin D deficiency during pregnancy.[23]

Despite being a sunny country, Saudi Arabia has a high prevalence of hypovitaminosis D, similar to other sunny countries in Gulf region, due to decreased skin contact to sun exposure.[24] Regardless of the differences in age-groups, lifestyle, or clothing, prevalence of vitamin D deficiency in women of childbearing age is above 75% in this country. Moreover, prenatal vitamin supplements manufactured in Saudi Arabia typically contain little amount of vitamin D. Improving vitamin D status in pregnant mothers might have a significant impact in reducing the risks of these pregnancy-related complications. 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 D daily or 35000 units weekly for ten weeks have been reported to be safe during the 3rd trimester of pregnancy, without producing other adverse effects.[25] Thus, if vitamin D is given as a supplement to women at risk of developing vitamin D deficiency, it might decrease the prevalence of pre-eclampsia. Studies from developing countries had also produced similar results showing statistically approved relationship of vitamin-D deficiency to occurence of pre-eclampsia.[26]

The prevalence of vitamin-D deficiency ranges between 0-97% in the world and found to be highest in regions like South Asia (Pakistan 90%) and Middle East (Saudi Arabia) and is predominant amongst females.[27,28] These findings correlate to the results produced by this study as well. The main strength of this study is to report an association of pre-eclampsia with vitamin D deficiency. As this study showed, the adjusted odds of having pre-eclampsia is four times higher when vitamin D level is <50ng/ml. Moreover, the study had adjusted the outcome for seasonal variation, and there are some recent data suggesting that seasonal variations might influence vitamin D related outcome.

There were several limitations in this study. Since this was

a case-control study conducted in a tertiary care centre, the findings could represent the product of selection bias. We did not have any baseline maternal serum vitamin D levels in early pregnancy or before conception to examine the temporal association with pre-eclampsia. It is known that under normal circumstances, placental unit produces vitamin D and that maternal serum vitamin D levels progressively increase during pregnancy. Women who had normal vitamin D level in third trimester might have had a low vitamin D level during early gestational period leading to poor placentation already.

Conclusions

The study showed a high prevalence of vitamin D deficiency in Saudi Arabia. It also showed that vitamin D deficiency is associated with a 3-5 fold elevated risk of preeclampsia. Since pre-eclampsia could lead to serious complications for both mother and foetus, vitamin D might be supplemented during pregnancy in high-risk populations to decrease these adverse consequences.

Disclaimer: None to declare.

Conflict of Interest: The authors declare that they have no conflicts of interest in the authorship or publication of this contribution.

Funding Disclosure: No funding had been utilized for this study.

References

1. Chaurasia P, Jadav P, Jasani J. CHANGES IN SERUM CALCIUM AND SERUM MAGNESIUM LEVEL IN PREECLAMPTIC VS NORMAL PREGNANCY. Int J Biomed Adv Res 2012;3.
2. ACOG Practice Bulletin No. 33: Diagnosis and Management of Preeclampsia and Eclampsia. Obstet Gynecol. 2002;99:159-67.
3. ACOG. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol. 2000;183:s1-s22.
4. Ganji V, Zhang X, Shaikh N, Tangpricha V. Serum 25-hydroxyvitamin D concentrations are associated with prevalence of metabolic syndrome and various cardiometabolic risk factors in US children and adolescents based on assay-adjusted serum 25-hydroxyvitamin D data from NHANES 2001–2006. Am J Clin Nutr. 2011;94:225-33.
5. Judd SE, Tangpricha V. Vitamin D deficiency and risk for cardiovascular disease. Am J Med Sci. 2009; 338: 40.
6. Holick MF. Vitamin D deficiency. N Engl J Med 2007; 357: 266-281
7. Giapros VI, Challa AS, Cholevas VL, Evagelidou EN, Bairaktari ET, Andronikou SK. Vitamin D Levels and Insulin Resistance in Children Born with Severe Growth Restriction. Horm Metab Res 2013; 45: 226-230
8. King J. Physiology of pregnancy and nutrient metabolism. Am J Clin Nutr. 2000;71:1218S-1225S.
9. Ulmer D. Trace elements. N Engl J Med. 1977;297:318–321.
10. Rafique M, Nuzhat A, Jaroudi D. Role of Vitamin D deficiency in female infertility and IVF outcomes in Saudi Arabia. J Soc Obstet Gynaecol Pak. 2018;8:243-9.
11. Bandeira F, Gris L. Vitamin D deficiency a global perspective. Arq Bras Endocrinol Metab. 2006;50:640–6.
12. Lips P. Vitamin D status and nutrition in Europe and Asia. J Steroid Biochem Mol Biol. 2007;103:620-5.
13. Al-Saleh Y, Al-Daghri NM, Alkharfy KM, Al-Attas OS, Alokail MS, Al-Othman A, et al. Normal Circulating PTH in Saudi Healthy Individuals with Hypovitaminosis D. Horm Metab Res. 2013;45:43-6.
14. Bodnar LM, Catov JM, Simhan HN, Zmuda JM, Cooper ME, Parrott MS, et al. Maternal Vitamin D Deficiency Increases the Risk of Preeclampsia. J Clin Endocrinol Metab. 2007;92:3517-22.
15. Robinson CJ, Alanis MC, Wagner CL, Hollis BW, Johnson DD. Plasma 25-hydroxyvitamin D levels in early-onset severe preeclampsia. Am J Obstet Gynecol. 2010;203:361-6.
16. Haugen M, Brantsaeter AL, Trogstad L, Alexander J, Roth C, Magnus P, et al. Vitamin D supplementation and reduced risk of preeclampsia in nulliparous women. Epidemiology. 2009;20:720-6.
17. Ali AM, Alobaid A, Malhis TN, Khattab AF. Effect of vitamin D3 supplementation in pregnancy on risk of pre-eclampsia - Randomized controlled trial. Clin Nutr. 2019;38:557-63.
18. Lapillonne A. Vitamin D deficiency during pregnancy may impair maternal and fetal outcomes. Medical hypotheses. 2010;74:71-5.
19. Roberts JM, Hubel CA. The two stage model of preeclampsia: variations on the theme. Placenta. 2009;30:32-7.
20. Huppertz B. Placental origins of preeclampsia challenging the current hypothesis. Hypertension. 2008;51:970-5.
21. Fischer D, Schroer A, Ludders D, Cordes T, Bücker B, Reichrath J, et al. Metabolism of vitamin D3 in the placental tissue of normal and preeclampsia complicated pregnancies and premature births. Clin Exp Obstet Gynecol. 2007; 34:80-4.
22. Liu NQ, Kaplan AT, Lagishetty V, Ouyang YB, Ouyang Y, Simmons CF, et al. Vitamin D and the Regulation of Placental Inflammation. J Immunol. 2011;186:5968-74.
23. Li YC, Qiao G, Uskokovic M, Xiang W, Zheng W, Kong J. Vitamin D: a negative endocrine regulator of the renin-angiotensin system and blood pressure. J Steroid Biochem Mol Biol. 2004;89:387-92.
24. Elsammak MY, Al-Wosaibi AA, Al-Howeish A, Alsaeed J. Vitamin d deficiency in Saudi Arabs. Horm Metab Res. 2010;42:364-8.
25. Hollis BW, Johnson D, Hulsey TC, Ebeling M, Wagner CL. Vitamin D supplementation during pregnancy: Double-blind, randomized clinical trial of safety and effectiveness. J Bone Miner Res. 2011;26:2341-57.
26. Mehmood S and Karim SA. Vitamin D Deficiency during Pregnancy and its Relationship with Pre-Eclampsia, Eclampsia and Gestational Hypertension. Austin J Nutr Metab. 2016; 3: 1040.
27. Edwards MH, Cole ZA, Harvey NC, Cooper C. The global epidemiology of vitamin D status. J Aging Res Clin Prac. 2014;3:148–58.
28. Hossain N, Khanani R, Hussain Kanani F, Shah T, Arif S, Pal L. High prevalence of vitamin D deficiency in Pakistani mothers and their newborns. Int J Gynaecol Obstet 2011; 112:229-33.