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Association of vitamin D levels with preeclampsia

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Abstract

Objectives: This study was aimed to assess maternal vitamin D status during pregnancy and determine the association between maternal 25(OH) D levels with risk of preeclampsia (PE).

Methods: A cross-sectional study was conducted with 172 pregnant women recruited from JPMC between January and December 2017 who were divided as normotensive (n=80) and pre-eclamptic (n=92) groups. Blood pressure was recorded at 20 and 32 weeks of gestation. Five ml of blood sample was collected at 20 weeks of gestation to assess the vitamin D levels by commercially available ELISA assay.

Results: PE group had a significantly higher systolic ($p<0.001$) and diastolic ($p<0.001$) blood pressure at 20 weeks of gestation. Vitamin D levels were reported to be significantly lower ($p<0.001$) in the PE group (17.97±9.38 ng/ml) as compared to normotensive group (42.18±25.17 ng/ml). A strong negative correlation of Vitamin D levels with systolic blood pressure ($r=-0.428$; $p<0.001$) and diastolic blood pressure ($r= -0.375$; $p<0.001$) was found.

Conclusion: This study found a strong relationship between low vitamin D levels and pre-eclamptic manifestation.

Keywords: Vitamin D; Pre-eclampsia; Pregnancy; Hypertension

Introduction

Preeclampsia is a gestational disorder characterized by high blood pressure and proteinuria. It affects approximately 3–7% of first pregnancies, complicates 2–8% of all pregnancies and responsible for 25% of all maternal deaths.[1] Till date, the root cause of pre-eclampsia needs to be speculated, however, various risk factors have been implicated in pathogenesis of pre-eclampsia, in which obesity, old age, first pregnancy, previous pre-eclampsia, chronic hypertension are few.[2] Significant research is taking place worldwide on the effect of Vitamin D deficiency as a risk factor for development of pre-eclampsia.

Vitamin D, a lipid soluble sunlight dependent vitamin acting as a pro-hormone, has diverse functions, which affect not only bone mineralization but also other systems, like cardiovascular, immune and pancreatic functions.[3] Previous studies have found relationship of Vitamin D deficiency to hypertension in general population.[4] Vitamin D is of most importance during pregnancy as low maternal vitamin D levels lead to co-morbidities in mother and fetus including low birth weight and small for age babies. Vitamin D deficiency proved itself to be a worldwide problem, having prevalence of 18% to 84% with highest prevalence in Asians, particularly in females with highly pigmented skin and those with less sun exposure and deficient dietary intake.[5]

One of the mechanisms for active hormone function is “free hormone hypothesis,” which showed that only those hormones that are released from binding proteins are able to enter cells to perform biological functions. Vitamin D binding protein (VDBP) is the major binding protein for both 25(OH) D and 1, 25(OH) 2D acting as both reservoirs and regressors of metabolism for vitamin D.

In high-estrogen states such as pregnancy, levels of VDBP increases accounting for lower levels of vitamin D, with no alteration of free hormone levels.[6] Furthermore, decreased levels of this vitamin and calcium in pre-eclamptic pregnancy have been investigated by some researchers [7]. In the light of some hypothesis, during pregnancy, Vitamin D harmonizes pro-inflammatory response, decreases oxidative stress, promote angiogenesis and control blood pressure,[8] thus showed role in prevention of pre-eclampsia.

Further studies have showed that vitamin D deficiency may lead to abnormal placental implantation, immune dysfunction and excessive inflammation, all contributing to pre-eclampsia.[7] Moreover, multiple studies have suggested that Vitamin D deficiency and endothelial dysfunction have been associated with each other. Vitamin D influences mRNA level gene transcription of vascular endothelial growth factor and in doing so, regulates the conductance and resistance of the blood vessels.[4] Hence, decreased vitamin D levels result in loss of endothelial integrity, which acts as main offender for preeclamptic pathogenesis.

Because there is scanty evidence, whether hypovitaminosis D during pregnancy increases the risk of preeclampsia, recent studies have emphasized the need for prospective longitudinal data on the effect of maternal vitamin D status during pregnancy on the risk of preeclampsia.

Keeping in view the role of vitamin D for endothelial integrity, this study aimed to assess maternal vitamin D status during pregnancy and to determine the association between maternal 25(OH) D levels at early and late mid-trimester gestational age windows and the risk of pre-eclampsia.

Methods

This cross-sectional study was conducted in Basic Medical Sciences Institute (BMSI), Jinnah Postgraduate Medical Centre (JPMC) in collaboration with Department of Biological and Biomedical Sciences Aga Khan University (AKU),

Karachi. A total of 172 pregnant women from JPMC between January till December 2017 consented to participate were included in this study. A minimum sample size of n=170 was required to achieve a power of 80%, with an alpha of 95%, an odds ratio of 2 and risk to prevalence ratio of 3.8. Approval for the study was obtained from the Institutional Review Board of JPMC (Ref: NO.F.2-81/GENL-2017-IRB/15107/JPMC) and AKU (4523-BBS-ERC-16). All the obstetric and medical history (age, weight, height, and education status) was recorded from medical record files. Healthy pregnant women as controls and preeclamptic who were diagnosed on recommended ACOG criteria 2013 were included in the study. Women with maternal co-morbidities (Cardiovascular, urogenital, immunological, endocrinological), renal disease, any history of complication during previous pregnancy including abortion, IU fetal demise, antenatal bleeding were excluded.

The study subjects were divided as Pre-eclamptic group (high blood pressure (>140/90 mmHg) accompanied by proteinuria >300 mg/24 h urine, after 20th week of pregnancy) [9] and control normotensive group. Blood pressure was recorded using a standard protocol at 20 and 32 weeks of gestation. Five ml of blood sample was collected from PE and control group after 20 weeks of gestation to assess the vitamin D levels by commercially available ELISA assay (kit cat number VD220B by Calbiotech USA). Statistical software SPSS version 23.0 was used for data feeding and analysis. A descriptive statistical analysis of continuous variables was performed. Data on continuous variables i.e. biophysical and biochemical parameters were presented as Mean $\pm$ standard deviation (SD) whereas data on categorical variables were presented as absolute number and percentages. Statistical comparisons were performed by using student's t-test, for continuous/quantitative variables, chi square or Fischer's exact test for categorical variables. Using the correlation matrix of Spearman's coefficient of correlation (r), the levels of serum Vitamin D was assessed with

hypertension in preeclampsia phenotypes. In all statistical analysis, only p-value < 0.05 was considered significant.

Results

Of 172 pregnant women who consented to participate in the study, 92 developed pre-eclampsia after week 20. Table 1 summarizes descriptive characteristics of study subjects. The results of this study showed no statistically significant difference in mean age, weight and BMI between normotensive and pre-eclamptic groups. However, both groups fell in overweight range according to the Centers for Disease Control and Prevention cutoffs. Statistically significant difference was recorded for both Diastolic and Systolic blood pressures between the two groups at 20 weeks. However, after diagnosis of pre-eclampsia, these patients were put on Methyldopa (250mg for 2 times per day). As a result, when blood pressure readings were repeated at week 32, no significant difference was recorded for both DBP and SBP between the groups. Vitamin D levels were reported to be significantly lower in the PE group as compared to normotensive group. The correlation of Vitamin D levels with Systolic blood pressure ($r=-0.428$; $p<0.001$) and Diastolic blood pressure ($r= -0.375$; $p<0.001$) is shown in Figure 3. Relationships between educational level and PE status have been summarized in Figure 2. Amongst PE population, 53.76% constituted the illiterate study subjects, while only 5.38% constituted of graduate study subjects.

Discussion

Pre-eclampsia remains the second leading direct cause of maternal death,[10] contributing to 20-80% of maternal deaths in developing countries [11], and has reported to have a strong influence on restricted fetal growth.[12] Sablok et al., reported that 25.6% of babies born to vitamin D deficient mothers were small for gestational age as compared to only 3.4% of the group with normal vitamin D levels. [5] Among major risk factors for pre-eclampsia, low vitamin D levels are

highly debated upon. In a recent study done on vit D levels in general population of Pakistan, out of 4830 randomly selected citizens, only 15.3% had normal vitamin D levels. [13] Despite the known association of low vitamin D levels with increased risk of recurrent pregnancy losses, pre-eclampsia, gestational diabetes and maternal infections, [14] prevalence of vitamin D deficiency in pregnant women is striking.[15] This study aimed at assessing the relationship between vitamin D and pre-eclampsia.

The findings of this study did not show any significant effect of age on outcome of pre-eclampsia. While findings of this study were consistent with one study,[5] other studies reported advanced maternal age (>40 years) to be a significant risk factor for developing pre-eclampsia [16]. The findings of this study found no significant relationship between increased BMI, Vitamin D levels and pre-eclampsia. However, other studies reported a statistically significant relationship between BMI of >25 and low vitamin D levels,[5] while one reported a negative relationship between vitamin D deficiency pre-pregnancy BMI. [17] It could be postulated that since increased body fat sequesters Vitamin D and prevents it from participating in metabolic functions, it could have aggravated hypovitaminosis D for the preeclamptic group. On the contrary, a study by Abedi P et al., of 59 preeclamptic and 59 normotensive pregnant women concluded that a woman with BMI <20 is more likely to develop PE. [18]

This study found a strong relationship between low vitamin D levels with pre-eclamptic manifestation. Many studies supported findings of this study, [19, 20] and also reported maternal vitamin D deficiency to be an independent risk factor for pre-eclampsia. [21] Sablok et al., in a prospective study of 165 pregnant women reported Vitamin D >25nmol/L to have a protective effect for preterm labor reduction and pre-eclampsia. [5]

Regarding education status of our subjects, 53.76% in PE group were illiterate, hence they could not read or write. A few studies reported low educational level to be associated with a high risk of pre-eclampsia [22] and with vitamin D levels as

well.[17] A study done in Saudi Arabia observed that low education status is significantly associated with pregnancy related hypertensive disorders.[23] The higher illiteracy rate in the PE group supported the fact that these females did not understand the importance of antenatal care along with nutritional requirements, thus any risk factor could be the cause of pre-eclamptic development, without timely screening. In addition, illiteracy results in low patient compliance, hence it could lead to sudden occurrence of pre-eclamptic episode. Low education is also stated as a reason for poor perception regarding medication during pregnancy, which refrain women from taking even the basic supplements necessary for healthy pregnancy. [24]

Our understanding about Vitamin D and its relationship with maternal and neonatal health has improved over the years. The UK Department of Health recommends a daily intake of 400 IU cholecalciferol regardless of ethnicity or other risk factors. [25] Various studies have proven the role that Vitamin D plays in fetal bone development, adequate insulin sensitivity, inflammatory regulation, maintaining pelvic muscle strength for delivery, and desired birth weight of infants. [26] It is, therefore, important for health service providers to ensure to check for vitamin D deficiency especially in pregnant women and mitigate for complications accordingly.

Conclusion

This study found a strong relationship between low vitamin D levels and pre-eclamptic manifestation.

Disclaimer: The title of the IRB is different from the paper submitted. This is due to that fact that the IRB was taken for a larger project i.e. ‘Identification of some screening biomarker for PE and hypertensive disorders in pregnancy’. The submitted paper is a part of this broad study and this is why it cannot have the same title as of the project.

Conflict of interest: The authors declare that they have no conflict of interest.

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References

1. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. Lancet. 2010;376:631-44.

2. Nejadi N, Hantoushzadeh S, Masti SM, Sadat Z, Tavirani R, Golmohammadi T. Vitamin D Binding Protein as screening biomarker candidate for late-onset preeclampsia without intrauterine growth restriction during 16 week of gestation. J Paramed Scien. 2015;6:2008-4978.

3. Mason R, Sequeira V, Gordon-Thomson C. Vitamin D: the light side of sunshine. Europ j clin nutri. 2011;65:986.

4. Al Mheid I, Patel R, Murrow J, Morris A, Rahman A, Fike L, et al. Vitamin D status is associated with arterial stiffness and vascular dysfunction in healthy humans. J Am Coll Cardiol. 2011;58:186-92.

5. Sablok A, Batra A, Batra A, Joshi D, Aggarwal A, Kabi B, et al. Vitamin D deficiency in pregnancy: An independent risk factor for increased maternal and foetal co-morbidities. Intern J Health Sci Res. 2017;7:57-63.

6. Powe CE, Seely EW, Rana S, Bhan I, Ecker J, Karumanchi SA, et al. First trimester vitamin D, vitamin D binding protein, and subsequent preeclampsia. Hyperten. 2010;56:758-63.

7. Shin J, Choi M, Longtine M, Nelson D. Vitamin D effects on pregnancy and the placenta. Placenta. 2010;31:1027e34.

8. Carvalho LSF, Sposito AC. Vitamin D for the prevention of cardiovascular disease: are we ready for that? Atheros. 2015;241:729-40.

9. Kallela J, Jääskeläinen T, Kortelainen E, Heinonen S, Kajantie E, Kere J, et al. The diagnosis of pre-eclampsia using two revised classifications in the Finnish Pre-eclampsia Consortium (FINNPEC) cohort. BMC preg childbirth. 2016;16:221.

10. von Dadelszen P, Magee LA. Pre-eclampsia: an update. Curr hypert rep. 2014;16:454.

11. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. Obstet Gynecol. 2002;99:159-67.

12. Xiao R, Sorensen T, Williams W, Luthy D. Influence of pre-eclampsia on fetal growth. J Matern Fetal Neo Med. 2003;13:157-62.

13. Riaz H, Finlayson A, Bashir S, Hussain S, Mahmood S, Malik F, et al. Prevalence of Vitamin D deficiency in Pakistan; implications for the future. Expert Rev Clin Pharmacol. 2015.

14. Ponsonby AL, Lucas RM, Lewis S, Halliday J. Vitamin D status during pregnancy and aspects of offspring health. Nutrients. 2010;2:389-407.

15. Rodríguez-Dehli A, Riaño IG, Fernandez-Somoano A, Navarrete-Muñoz E, Espada M, Vioque J, et al. Prevalence of vitamin d deficiency and insuffiency and associated factors in pregnant women of northern Spain. Nutricion hospitalaria. 2015;31:1633-40.

16. Khalil A, Syngelaki A, Maiz N, Zinevich Y, Nicolaides KH. Maternal age and adverse pregnancy outcome: a cohort study. Ultrasound Obstet Gynecol. 2013;42:634-43.

17. Pratumvinit B, Wongkrajang P, Wataganara T, Hanyongyuth S, Nimmannit A, Chatsiricharoenkul S, et al. Maternal vitamin D status and its related factors in pregnant women in Bangkok, Thailand. PloS one. 2015;10:e0131126.

18. Abedi P, Mohaghegh Z, Afshary P, Latifi M. The relationship of serum vitamin D with pre-eclampsia in the I ranian women. Matern & child nutr. 2014;10:206-12.

19. Abedi P, Mohaghegh Z, Afshary P, Latifi M. The relationship of serum vitamin D with pre-eclampsia in the Iranian women. Matern Child Nutr. 2014;10:206-12.

20. Ullah M, Koch C, Tamanna S, Rouf S, Shamsuddin L. Vitamin D deficiency and the risk of preeclampsia and eclampsia in Bangladesh. Horm Metabo Res. 2013;45:682-7.

21. Achkar M, Dodds L, Giguère Y, Forest J-C, Armson BA, Woolcott C, et al. Vitamin D status in early pregnancy and risk of preeclampsia. Am J obstet gynecol. 2015;212:511. e1-. e7.

22. Kiondo P, Wamuyu-Maina G, Bimenya GS, Tumwesigye NM, Wandabwa J, Okong P. Risk factors for pre-eclampsia in Mulago Hospital, Kampala, Uganda. Trop Med Intern Health. 2012;17:480-7.

23. Suleiman AK. Risk factors on hypertensive disorders among Jordanian pregnant women. Global j health sci. 2014;6:138.

24. Lupattelli A, Picinardi M, Einarson A, Nordeng H. Health literacy and its association with perception of teratogenic risks and health behavior during pregnancy. Pat educ counsel. 2014;96:171-8.

25. Curtis EM, Moon RJ, Harvey NC, Cooper C. Maternal vitamin D supplementation during pregnancy. Brit medic bulle. 2018;126:57-77.

26. Namgung R, Tsang RC, Lee C, Han DG, Ho ML, Sierra RI. Low total body bone mineral content and high bone resorption in Korean winter-born versus summer-born newborn infants. J Pediatr. 1998;132:421-5.

Table 1: Descriptive characteristics of the study subject

	PE n=92	Control n=80	P value
Age (year)	27.62±4.82	27.94±6.83	0.726
Weight (kg)	69.78 ±18.23	67.61±18.47	0.256
BMI (kg/m^2)	27.918±7.23	26.46±6.79	0.179
Systolic Blood Pressure-1(mm Hg)	156.02±17.702	116.58 ±15.680	<0.001
Diastolic Blood Pressure-1(mm Hg)	103.01±13.65	74.87±13.265	<0.001
Systolic Blood Pressure-2 (mm Hg)	136.15± 8.22	117.74±13.51	0.043
Diastolic Blood Pressure-2 (mm Hg)	84.26 ± 7.23	75.52±9.79	0.041
Vitamin D (ng/mL)	17.97±9.38	42.18±25.17	<0.001

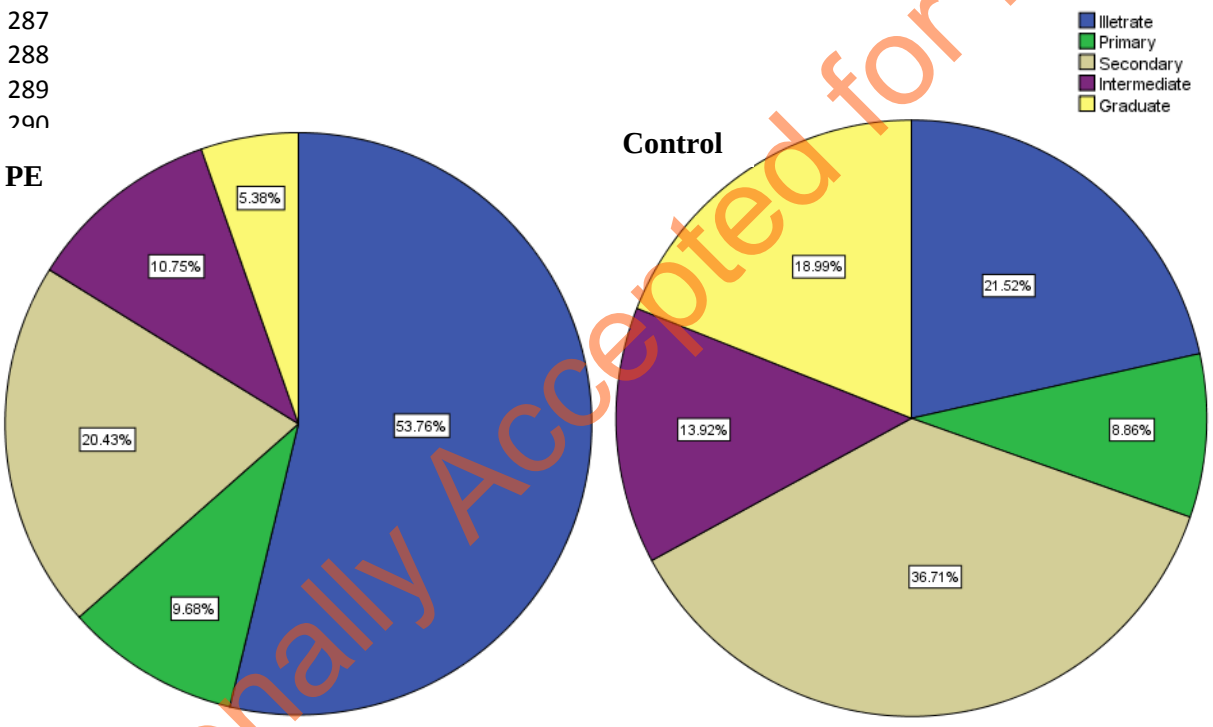
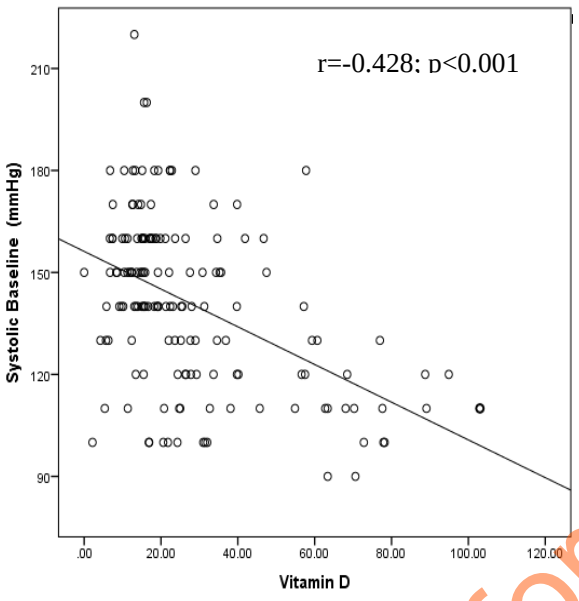


Figure 1: Education of the study subjects

(a)



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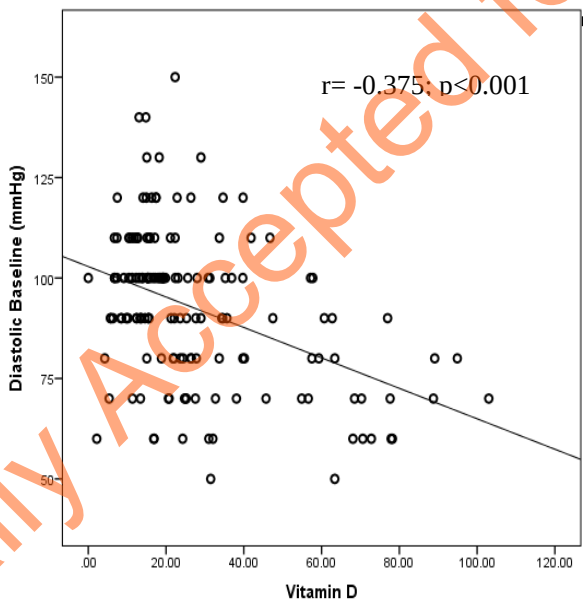

Figure 2: Correlation between vitamin D and Blood pressures in PE patients