DOI: https://doi.org/10.53350/pjmhs2216860

ORIGINAL ARTICLE

Association of Serum 25(OH) D Levels with Gestational Hypertension and Risk of Pre-eclampsia in Our Population

NOOR-UL-AIN AINEE[1], UZMA MALIK[2], AATKA NISAR[3], HAFIZA HALEEMA ABID[4], SAMINA NAZ[5]
[1]*MS Gynaecology and Obstetrics, Lady Willingdon Hospital, Lahore*
[2]*Senior Registrar, Department of Obstetrics & Gynaecology, Ittefaq Hospital, Lahore*
[3]*Postgraduate Trainee, Department of Obstetrics & Gynaecology Unit-I, Lady Willingdon Hospital, Lahore*
[4]*District Gynaecologist, THQ Hospital, Chakdara Dir Lower*
[5]*WMO, THQ Hospital, Chichawanti*
Correspondence to Dr. Noor-ul-Ain Ainee, E-mail: ainee.noorulain@yahoo.com, Cell: 0305-4904990

ABSTRACT

Background: Pre-eclampsia is a syndrome of immune system of pregnant females, which causes severe obstetrical complications. Low serum level of 25-hydroxyvitamin-D is common during pregnancy complicated with preeclampsia but local evidence is missing.

Aim: To determine the association of pre-eclampsia with decreased vitamin- D levels during two phases of gestation (after 20 weeks) over a period of six months.

Study design: Cohort study

Place and duration of study: Department of Obstetrics and Gynaecology, Lady Willingdon Hospital, Lahore from 4th February 2019 to 3rd August 2019.

Methodology: One hundred and seventy females were enrolled in study at 20 weeks gestational age. They were divided into two groups (85 patients in each group). Those with normal Vitamin D_3 levels (>30 ng/ml) were grouped as Low risk group and those with relatively low (insufficient) serum vitamin D_3 levels (between 21-29 ng/ml) were grouped as high-risk group with potential risk factor for pre-eclampsia. Both groups were followed from 24^{+1} weeks to 36 weeks of gestation with every two weeks' interval, for assessment of development of pre-eclampsia or not. Both groups were followed up and outcome was noted.

Results: The mean age of the patients was 26.44±4.08 years and mean gestational age was 35.47±2.34 weeks. One hundred and 42(83.53%) patients appeared with PIH while 28(16.47%) patients appeared with preeclampsia. Among high risk patients, preeclampsia was noted in 26(30.6%) patients while in low risk group patients, preeclampsia was noted in 2(2.4%) patients (p<0.001).

Conclusion: A significant association observed between pre-eclampsia and decreased vitamin D level during phases of pregnancy.

Keywords: Vitamin D level, Preeclampsia, Hypertension

INTRODUCTION

Every year, about >50% females die during pregnancy or due to its related complications. About 99% of such cases belong to poor middle-income republics. In several these countries, the pregnancy or delivery related complications are the foremost cause of mortality in females. About 10% of females get new onset hypertension during pregnancy, and this complicates about 2-8% of all the pregnancies. Generally, 10-15% maternal mortality occurs because of pre-eclampsia or eclampsia. The only management protocol to prevent pre-eclampsia is to administer anti-platelet therapy, usually low-dose aspirin or calcium supplements[1].

Pre-eclampsia is a syndrome which is pregnancy specific. It is familiar from ancient times as the leading cause of death of pregnant females as well as her neonate. It is normally diagnosed as high blood pressure along with presence of proteinuria[2].

Oxidative stress has been found involved in the mechanism causing poor placental perfusion (main factor in pre-eclampsia with its clinical manifestations)[3]. Vitamin D can defend from developing pre-eclampsia through improvement of the immune system as well as vascular function[4]. So, vitamin D deficiency may have a promising role regarding development of pre-eclampsia.

A study which was conducted including individuals having early onset severe pre-eclampsia (<34 weeks with severe pre-eclampsia) noted that the Subjects with early onset severe preeclampsia (n=50) showed relatively less vitamin D level in blood than healthy females (p<0.001). This difference in total vitamin D level was significant when controlled for possible effect modifiers[5].

In a study, systemic data and meta-analysis of 3357 studies were reviewed. Then, 31 studies were incorporated in the analysis. Reduced serum Vitamin D_3 levels were significantly associated with preeclampsia (1.79, 1.25 to 2.58)[6]. Another study found that females who received vitamin D supplementation in early trimesters showed lower odds of pre-eclampsia [pooled OR 0.81, 95% CI; 0.75-0.87, p<0.01]. It was suggested that a significant association exists in high serum vitamin D level and less hazard of preeclampsia (pooled OR=0.52, 95% CI; 0.30-0.89, p<0.05). Few randomized studies also proved the protective effect of vitamin D supplementation with less chances of developing pre-eclampsia (pooled OR=0.66, 95%CI; 0.52-0.83, p<0.001)[4].

Another nested case-control study done on gravid females in starting second trimester and were followed-up till delivery. Patients that were included were primigravida with single developing fetus who developed pre-eclampsia (n=55) or did not show signs of developing pre-eclampsia (n=219). Blood samples were taken to assess concentration of vitamin D_3 levels. The basic outcome was pre-eclampsia. After controlling for confounders, a 50 nmol/L decrease in serum vitamin D_3 level increased twice the hazard of developing pre-eclampsia (OR=2.4; 95% CI, 1.1-5.4), showing that vitamin D deficiency in pregnant females is an independent risk factor for pre-eclampsia.[7] In a parallel study, done in seventeen urban maternity hospitals in Canada, it was reported that after gestation of 24-26 weeks, a Vitamin D_3 level of <50nmol /L in pregnant females had 3.2-fold higher risk of pre-eclampsia (OR=3.24, 95% CI; 1.37-7.69), but during gestational age 12-18 weeks, a rise was statistically insignificant[8].

Deficiency of vitamin D_3 is an emerging health-related problem in Pakistan. A study conducted in Pakistan reflected that 77.50% were deficient for Vitamin D. While 18% have insufficient Vitamin D level. Only, 4.5% females had normal level of vitamin D. The overall prevalence of Vitamin-D deficiency together with insufficiency was reported as 95.5%[9].

It can be said that pre-eclampsia would be more prevalent in our population due to severely lacking Vitamin D_3 levels. The intention of this study is to fetch out the difference in the vitamin D_3 levels during a specific time period of pregnancy and its

Received on 06-03-2022
Accepted on 26-07-2022

association with risk of pre-eclampsia in our population. That a proper initiative of its supplementation should be taken in time, as our geographical factors, lifestyle, skin colour and sunlight exposure is different from Western population. Under these conditions, our population may have comparably different 25(OH) D levels and results may differ than the findings of parallel study.

MATERIALS AND METHODS

This cohort study was conducted at Inpatient and outpatient Departments of Lady Willingdon Hospital, Lahore from 4th February 2019 to 3rd August 2019. Sample size of 170 patients, (85 patients in each group) was estimated by using Confidence level 95%, Absolute Precision 7% with expected percentage of insufficient serum Vitamin D level (high risk group) as 9.2% and normal Vitamin D levels (low risk group) as 2.4%[10].

Patient were enrolled from 20 weeks of their gestational age onwards, all primigravida with gestational hypertension (BP=140/90mmHg) with no previous history of chronic hypertension, reproductive age, not taken Vitamin-D supplementation for six months prior or after conception, normotensive by history prior to conception with their serum uric acid levels within normal range, and pregnant women having singleton pregnancy were included. All patients who had any other co-morbidity e.g. diabetes mellitus, chronic hypertension, history of chronic kidney disease, childhood history of rickets, history of smoking and had BMI >30, signs and symptoms of urinary tract infection, i.e. pus cells > 4 on urine complete examination were excluded.

All data was duly filled and safety and privacy issues were discussed with the participants. The consent about withdrawal of blood sample was also taken. The venous samples were drawn to test the 25 (OH) D levels as Baseline levels by ELISA method among the participants visiting from 20 weeks' gestational age to 24 weeks' gestational age (first enrolment visit) and their results were noted. On the basis of baseline 25(OH) vitamin D levels, the participants were divided into two equal groups; those with normal 25(OH) vitamin D levels (i.e.>30ng/ml) were grouped as Low risk group and those with relatively low (insufficient) serum 25(OH) vitamin D levels (between 21-29ng/ml) were grouped as high-risk group with potential risk factor for pre-eclampsia. Both groups were followed from 24^{+1} weeks to 36 weeks of gestation with every two weeks' interval, for development of pre-eclampsia or not. A venous sample for 25(OH) D was taken at a gestational age when ever patient was developing pre-eclampsia. Each time the date for next follow up was given to the participant. From 24thweek onward till 36thweek; each participant was followed up on her usual OPD visits or after every two weeks, if in-patient, in order to monitor the outcome of the risk factor was recorded.

On each interval, the development of pre-eclampsia was monitored according to criteria mentioned under the heading of Diagnostic Criteria of Pre-eclampsia[12] and results were entered into the data and case report form, accordingly. In case of deficient 25-(OH) D_3 levels below 20ng/ml with any sign or symptom of pre-eclampsia, vitamin D supplement was prescribed to the patient. At the end, all the data obtained were compiled and it was used to define a specific phase of time (in terms of gestational age in weeks) during which low 25(OH) vitamin D levels increase the chances of developing pre-eclampsia. The data was entered and analyzed through SPSS-26. Comparison of two groups, high-risk group with low vitamin D levels and the other low risk group with normal vitamin D levels were applied with independent sample t-test. P≤0.05 was considered as significant.

RESULTS

The mean age of patients was 26.44±4.08 years with minimum and maximum age were 17 & 35 years respectively. The mean gestational age was 35.47±2.34 weeks with minimum & maximum gestational ages were 26.29±37.57 weeks (Table 1).

Among high risk patients, PIH was noted in 59(69.4%) patients while in low risk group, PIH was noted in 83(97.6%) patients. Similarly, among high risk patients the pre-eclampsia was noted in 26(30.6%) patients while in low risk group patients, the pre-eclampsia was noted in 2(2.4%) patients. This variation was statistically significant (P<0.001) (Table 2).

On pre-evaluation among high risk patients, the mean 25-hydroxyVitamin D level of the patients was 27.12±2.14 ng/ml while in low risk patients; the mean 25-hydroxyVitamin D level of the patients was 62.67±23.35ng/ml. This disparity was statistically significant (P<0.001) (Table 3).

On post-evaluation, among high risk patients, the mean 25-hydroxyVitamin D level of the patients was 19.95±4.26ng/ml while in low risk patients; the mean 25-hydroxyVitamin D level of the patients was 41.47±20.46ng/ml. This difference was statistically significant (P<0.001) (Table 4).

Table 1: Descriptive statistics of the patients (n=170)

Variable	Mean±SD
Age (years)	26.44±4.08
Gestational age (weeks)	35.47±2.34

Table 2: Association of diagnosis between study groups

Diagnosis	High Risk	Low Risk	P value
Pre-eclampsia	26 (30.6%)	2 (2.4%)	<0.001
PIH	59 (69.4%)	83 (97.6%)	

Table 3: Comparison of pre-evaluation of vitamin D level

Pre-Vitamin D level	High Risk	Low Risk	P value
	27.12±2.14	62.67±23.35	<0.001

Table 4: Comparison of post-evaluation of vitamin D level

Post-Vitamin D level	High Risk	Low Risk	P value
	19.95±4.26	41.47±20.46	<0.001

DISCUSSION

Pre-eclampsia is pregnancy-related syndrome. It affects several organs of the body. It characterizes as elevation in blood pressure level along with presence of proteinuria, after 20th week of gestation. It complicates around 2-8% pregnancies and raises the feto-maternal mortality and morbidity. Various factors are involved in development and progression of pre-eclampsia (angiogenic factors, maternal legitimate factors, endothelial dysfunction, inflammatory activation and syncytio-trophoblastic micro-particles). During pregnancy, deficiency of vitamin D can be associated with several numbers of severe short and long term health problems in neonate, which can be retarded growth, skeletal diseases, type 1 diabetes, asthma or even schizophrenia[11-13].

In this study, 142 (83.53%) patients appeared with PIH while 28(16.47%) patients appeared with pre-eclampsia. Among high risk patients, the PIH was noted in 59(69.4%) patients while in low risk group patients, the PIH was noted in 83(97.6%) patients. Similarly, among high risk patients the pre-eclampsia was noted in 26(30.6%) patients while in low risk group patients, the pre-eclampsia was noted in 2(2.4%) patients. This difference was statistically significant i.e. p-value=<0.001 and on pre-evaluation the mean 25-hydroxyVitamin D level of the patients was 44.89±24.31 ng/ml while on post-evaluation the mean vitamin D level of the patients was 30.71±18.26 ng/ml (p<0.001).

Akbari et al[14] reported that vitamin D deficient women at cut off level 20ng/ml were at higher risk of pre-eclampsia as compared to women having normal vitamin D level. Lower concentration of 25-hydroxy vitamin D was significantly (P<0.001) associated with development of pre-eclampsia. Based on a forest plot, vitamin D deficiency (<20 ng/ml) was significantly associated with risk of pre-eclampsia (fixed OR=1.33, P<0.0001; random OR=1.54, P=0.0029). Robinson et al[5] conducted a study on females with severe pre-eclampsia (at <34 weeks) who showed less concentration of vitamin D level than healthy ones (p<0.001).

Aghjafari et al[6] conducted a meta-analysis of 3357 studies and 31 were found to be eligible in final analysis. Insufficient serum vitamin D level was significantly related with pre-eclampsia (OR=1.79, 95%CI; 1.25-2.58).

Hypponen et al[4] proposed that there is a significant relativity of higher level of serum vitamin D and decreased risk of pre-eclampsia (pooled OR=0.52, 95% CI; 0.30-0.89, p=0.02). Randomized controlled trials showed that supplementation of vitamin D had a protective role against pre-eclampsia (pooled OR=0.66, 95% CI; 0.52-0.83, p=0.001).

Few epidemiological trials focused on the role of low 25-hydroxy vitamin D levels in pathophysiology of pre-eclampsia.[15] Two in-vitro trials showed the improvement of angiogenesis and inhibition of adhesion molecules release from endothelial cells by vitamin D[16,17].

The role of vitamin D deficiency in immunomodulation and development of placenta has been highlighted in several studies. Therefore, they put the importance on 25-hydroxyVitamin D deficiency, concerning its potential role in development of pre-eclampsia[18,19]. Few other studies also showed similar findings.[20,21]

Tabesh et al[22] conducted a meta-analysis and found a significant association of low 25-hydroxyVitamin D level and pre-eclampsia. Wei et al[15] also conducted a cohort study and reported that maternal vitamin D level during 24-26thweeks of gestation was 14% lesser in females with preeclampsia than controls (48.9nmol/L-57nmol/L).

Bodnar et al[23] conducted another study and concluded that 25-hydroxy Vitamin D deficiency in pregnancy is an independent risk factor of pre-eclampsia. So, females should be screened for 25-hydroxyVitamin D deficiency and supplementation should be started in early pregnancy to prevent preeclampsia in later pregnancy and to improve obstetrical outcome.

Contrarily, a trial conducted by Goel et al[24] found that mean serum levels of vitamin D was significantly less in females with preeclampsia/eclampsia, but the prevalence of vitamin D deficiency was almost equal in gravid females whether preeclampsia/ eclampsia present or not.

In a similar study, done in seventeen urban maternity hospitals in Canada, it was reported that after 24-26 weeks of gestation, the maternal vitamin D level <50 nmol/l had a 3.2-fold higher risk of pre-eclampsia (OR=3.24, 95% CI; 1.37-7.69), but during gestational age 12–18 weeks, it was statistically insignificant.[8]

CONCLUSION

There is an association between the pre-eclampsia and the decreased level of vitamin D during phases of pregnancy over a period of six months.

Conflict of interest: Nil

REFERENCES

1. Duley L, editor. The global impact of pre-eclampsia and eclampsia. Seminars in perinatology. Elsevier, 2009.
2. Roberts J, Cooper DW. Pathogenesis and genetics of pre-eclampsia. Lancet 2001; 357(9249):53-6.
3. Lopez-Jaramillo P, Narvaez M, Wetgel R, Yepez R. Calcium supplementation reduces the risk of pregnancy-induced hypertension in an Andes population. BJOG 1989;96(6):648-55.
4. Hyppönen E, Cavadino A, Williams D, Fraser A, Vereczkey A, Fraser WD, et al. Vitamin D and pre-eclampsia: original data, systematic review and meta-analysis. Ann Nutr Metabol 2013;63(4):331-40.
5. 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(4):366. e1-6.
6. Aghajafari F, Nagulesapillai T, Ronksley PE, Tough SC, O'Beirne M, Rabi DM. Association between maternal serum 25-hydroxyvitamin D level and pregnancy and neonatal outcomes: systematic review and meta-analysis of observational studies. BMJ 2013;346:f1169.
7. Bodnar LM, Catov JM, Simhan HN, Holick MF, Powers RW, Roberts JM. Maternal vitamin D deficiency increases the risk of preeclampsia. J Clin Endocrinol Metabol 2007;92(9):3517-22.
8. Wei S, Audibert F, Hidiroglou N, Sarafin K, Julien P, Wu Y, et al. Longitudinal vitamin D status in pregnancy and the risk of pre-eclampsia. BJOG 2012;119(7):832-9.
9. Masood Z, Mahmood Q, Ashraf KT. Vitamin D deficiency-an emerging public health problem in Pakistan. JUMDC 2010;1(1):4-9.
10. awlor DA, Tilling K, Davey Smith G. Triangulation in aetiological epidemiology. Int J Epidemiol 2016;45(6):1866-86.
11. James JL, Whitley GS, Cartwright JE. Pre-eclampsia: fitting together the placental, immune and cardiovascular pieces. J Pathol 2010;221(4):363-78.
12. Roberts JM, Hubel CA. The two stage model of preeclampsia: variations on the theme. Placenta 2009;30 Suppl A:S32-7.
13. Holick MF. Resurrection of vitamin D deficiency and rickets. J Clin Invest 2006;116(8):2062-72.
14. Akbari S, Khodadadi B, Ahmadi SAY, Abbaszadeh S, Shahsavar F. Association of vitamin D level and vitamin D deficiency with risk of preeclampsia: A systematic review and updated meta-analysis. Taiwan J Obstet Gynecol 2018;57(2):241-7.
15. Wei SQ, Audibert F, Hidiroglou N, Sarafin K, Julien P, Wu Y, et al. Longitudinal vitamin D status in pregnancy and the risk of pre-eclampsia. BJOG 2012;119(7):832-9.
16. Grundmann M, Haidar M, Placzko S, Niendorf R, Darashchonak N, Hubel CA, et al. Vitamin D improves the angiogenic properties of endothelial progenitor cells. Am J Physiol Cell Physiol 2012;303(9):C954-62.
17. Kudo K, Hasegawa S, Suzuki Y, Hirano R, Wakiguchi H, Kittaka S, et al. 1alpha,25-Dihydroxyvitamin D(3) inhibits vascular cellular adhesion molecule-1 expression and interleukin-8 production in human coronary arterial endothelial cells. J Steroid Biochem Mol Biol 2012;132(3-5):290-4.
18. Novakovic B, Sibson M, Ng HK, Manuelpillai U, Rakyan V, Down T, et al. Placenta-specific methylation of the vitamin D 24-hydroxylase gene: implications for feedback autoregulation of active vitamin D levels at the fetomaternal interface. J Biol Chem 2009;284(22):14838-48.
19. Diaz L, Noyola-Martinez N, Barrera D, Hernandez G, Avila E, Halhali A, et al. Calcitriol inhibits TNF-alpha-induced inflammatory cytokines in human trophoblasts. J Reprod Immunol 2009;81(1):17-24.
20. Xu L, Lee M, Jeyabalan A, Roberts JM. The relationship of hypovitaminosis D and IL-6 in preeclampsia. Am J Obstet Gynecol 2014;210(2):149 e1-7.
21. Baker AM, Haeri S, Camargo CA, Jr., Espinola JA, Stuebe AM. A nested case-control study of midgestation vitamin D deficiency and risk of severe preeclampsia. J Clin Endocrinol Metab 2010;95(11):5105-9.
22. Tabesh M, Salehi-Abargouei A, Esmaillzadeh A. Maternal vitamin D status and risk of pre-eclampsia: a systematic review and meta-analysis. J Clin Endocrinol Metab 2013;98(8):3165-73.
23. Bodnar LM, Catov JM, Simhan HN, Holick MF, Powers RW, Roberts JM. Maternal vitamin D deficiency increases the risk of preeclampsia. J Clin Endocrinol Metab 2007;92(9):3517-22.
24. Goel A, Garg G, Kaur J, Mehra R, Tandon R, Huria A. Association of vitamin D deficiency during pregnancy with preeclampsia and eclampsia. IJRCOG 2016;5(9): 3046-50.