

Association of Low Vitamin D Level Status and Risk of Pre-Eclampsia and Preterm Birth in Women Using Low-Dose Aspirin

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ABSTRACT

Objective: To determine the association between low Vitamin-D status and risk of pre-eclampsia and preterm birth in women using low-dose Aspirin in the tertiary care setting.

Study Design: Prospective comparative study.

Place and Duration of Study: Gynecology and Obstetrics Department, Pak Emirates Military Hospital, Rawalpindi Pakistan from Sep 2018 to Sep 2019.

Methodology: A total of 383 pregnant women were divided into three Groups. Pregnant women were included based on the criteria; if one of the five high-risk factors or more than one moderate risk factors were met. High-risk factors were; 1) Type-1 or 2 diabetes mellitus, 2) chronic hypertension, 3) hypertensive disease in previous pregnancy, 4) autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome, 5) chronic kidney disease.

Results: There were 127 pregnant women in Group-1 with Vitamin-D deficiency. In Group-2, there were pregnant women with Vitamin-D insufficiency; in Group-3, there were 18 pregnant women with Vitamin-D sufficiency. The mean Vitamin-D level in Group-1 was 22.40 ± 1.50 nmol/L, the mean Vitamin-D level in Group-2 was 32.82 ± 9.80 nmol/L and in Group-3 mean Vitamin-D level was 76.63 ± 8.00 nmol/L. Early onset pre-eclampsia, chronic hypertension with superimposed pre-eclampsia, gestational diabetes, spontaneous-vaginal delivery and delivery at term were found to statistically significant among the Groups ($p < 0.05$).

Conclusion: We aimed to determine whether vitamin D status was linked with high-risk pregnancies, which could overshadow the impact of vitamin D under existing conditions. Our findings help relate the status and pre-eclampsia of maternal vitamin D to preterm birth.

Keywords: Aspirin, Labour, Pre-eclampsia, Vitamin-D.

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INTRODUCTION

In 5-10% of pregnancies, hypertension occurs, while in 2-8% of pregnancies, pre-eclampsia generally occurs worldwide.¹ Pre-eclampsia poses immediate and long-term threats to a mother's health and is one of the leading causes of neonatal morbidity.² In 2014, it was estimated that preterm birth was the major single obstetric reason for neonatal deaths in the United States, approximately 10% of total live births.³

The United States' premature birth rate continues to be higher than in countries with high income, and few measures have been shown to reduce premature birth.⁴ In recent decades, a shortfall in vitamin-D has arisen as a question of public health and is related to several adverse effects of pregnancies. The role of mother vitamin-D in both premature birth and pre-eclampsia in general, albeit with some conflicting findings, has been associated.^{5,6}

Studies on maternal vitamin-D and its related adverse pregnancy outcome are performed worldwide.^{7,8} Vitamin-D is considered to have advantages in women at high risk of pregnancy, where conditions previously existing may outweigh the benefits of vitamin-D.^{9,10}

Local data regarding the status of maternal vitamin-D levels and its effects on adverse pregnancy outcomes are quite scarce and relatively homogenous, which restricts the ability of pre-eclampsia and preterm birth sub-categories to conclude. Thus, we performed a study to determine the association between low vitamin-D level status concerning the risk of pre-eclampsia and preterm birth in women using low-dose Aspirin in the tertiary care setting.

METHODOLOGY

This was a prospective comparative study, carried out at the Gynecology and Obstetrics Department of Military Hospital, Rawalpindi Pakistan, from September 2018 to September 2019. A total of 383 pregnant women were recruited after consecutive sampling and

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divided into three Groups. Ethical permission was sought from the IERB committee (IERB no. A/28/Jul-2018), and data was gathered after informed consent. The sample size was calculated using the WHO calculator using reference prevalence of Vitamin-D insufficiency at 53.5%,¹¹ and alpha at 5%.

Inclusion Criteria: Pregnant women were included if one of the five high-risk factors or more than one moderate risk factors were met. High-risk factors were; 1) DM (Type-I/ Type-II), 2) chronic hypertension, 3) hypertensive disease in a previous pregnancy, 4) autoimmune disease as systemic lupus erythematosus or antiphospholipid syndrome, or 5) chronic kidney disease. Moderate risk factors were; 1) first pregnancy, 2) age 40 years or older, 3) pregnancy interval of more than ten years, 4) BMI of 35kg/m², 5) family history of pre-eclampsia, 6) multiple-fetal pregnancy.

Exclusion Criteria: Women who did not give consent were excluded.

Pregnant women were enrolled at 16–26th weeks of gestation and assigned consecutively tablet Aspirin (60 mg daily), or a placebo tablet and patients were followed till the end of pregnancy. During the first antenatal and follow-up visits, urinary protein by dipstick was taken, and BP was monitored. In addition, pregnant women were guided for non-fasting blood and Vitamin-D samples at the baseline and two times later in the pregnancy. Data was collected on the structured questionnaire, and women were followed until delivery.

Outcomes investigated were hypertensive conditions of pregnancy and preterm birth. Pre-eclampsia was taken by the MFMU Network diagnostic criteria.^{8,10} Gestational hypertension was taken as the start of hypertension in the pregnancy for ladies who

were normotensive before the pregnancy (MFMU Network).¹¹ Pre-eclampsia and gestational-hypertension were taken as per the Royal College of Obstetricians and Gynecologists (RCOG) categories.^{4,10}

The cut-points of vitamin D were aligned with the Institute of Medicine and the Endocrine Society definitions of deficiency i.e., risk of deficiency at <25 nmol/L, risk of inadequacy at 25 to <75 nmol/L and sufficiency at 75 to 250 nmol/L.^{11,12}

Statistical Package for Social Sciences (SPSS) version 22.0 was used for the data analysis. First, quantitative data were summarized as mean±SD, and categorical data were summarized as the number with a percentage. Then, one-way ANOVA and chi-square test were applied to find the difference between the Groups, with a significant *p*-value of ≤ 0.05.

RESULTS

A total of 383 pregnant women were enrolled on the study and divided into three Groups according to their vitamin-D levels. There were 127 pregnant women in Group-1 with vitamin-D deficiency. In Group-2, there were pregnant women with vitamin-D insufficiency and in Group-3, there were 18 pregnant women with vitamin-D sufficiency. The mean age of the study population (n=383) was 31.54±5.20 years (Range: 20-42 years).

Ladies with a vitamin-D deficiency (Group-1) were more with BMI over 35(19, 29.2%) compared to the other Groups. While, pregnant women with vitamin-D insufficiency were more with diabetes mellitus, (57, 51.4%), as compared to other Groups (Table-I).

The mean age in Group-1 was 31.83±5.80 years, the mean age in Group-2 was 31.47±4.90 years, and the mean age in Group-3 was 30.50±4.20 years. The mean

Table-I: Comparison of Comorbids and Risk Factors among the Groups (n=383)

Parameters	Group-1(n=127) (Pregnant with Vitamin-D Deficiency)	Group-2(n=238) (Pregnant with Vitamin-D Insufficiency)	Group-3(n=18) (Pregnant with Vitamin-D Sufficiency)	<i>p</i> -value
Chronic Hypertension	37(34.3%)	37(34.3%)	6(5.6%)	0.265
Diabetes Mellitus	18(16.2%)	57(51.4%)	4(3.6%)	0.265
Auto-immune disease (Systemic lupus erythematosus/ Anti-phospholipid Antibody Syndrome)	3(0.7%)	8(2.0%)	-	-
Chronic Renal Disease	-	6(1.5%)	-	-
Hypertension in Previous Pregnancy	29(30.5%)	38(40.0%)	4(4.2%)	0.340
Age more than 40 years	18(34.6%)	6(11.5%)	-	-
Pregnancy Interval more than 10 years	2(5.3%)	8(21.1%)	-	-
Body Mass Index more than 35	19(29.2%)	15(23.1%)	1(1.5%)	0.689
Family History of Pre-eclampsia	4(8.7%)	16(34.8%)	-	-
Multiple Pregnancy	18(38.3%)	18(38.3%)	1(2.1%)	0.203

vitamin-D level in Group-1 was 22.40±1.50nmol/L, the mean vitamin-D level in Group-2 was 32.82±9.80 nmol/L and in Group-3, mean vitamin-D level was 76.63±8.00nmol/L. ANOVA test was applied to find the difference between the Groups, but the result was statistically insignificant (Table-II).

Early onset pre-eclampsia, chronic hypertension with superimposed pre-eclampsia, gestational diabetes, spontaneous-vaginal delivery and delivery at term were found to be statistically significant among the Groups ($p<0.05$) (Table-III).

trimester maternal vitamin-D levels were inversely associated. Moreover, vitamin D level was associated with the risk of preterm birth at <35 weeks of gestation.¹¹⁻¹³

Cochrane meta-analysis done in 2016 showed that the vitamin-D related preterm birth was decreased, but the risk was increased when women had vitamin-D and calcium complemented together.¹

It was quite interesting that we found a correlation between pre-eclampsia early and maternal 25 (OH)D. There is good evidence to support an impact

Table-II: Clinico-demographic Characteristics of the Groups (n=383)

Parameters	Group-1(n=127) (Pregnant with Vitamin-D Deficiency)	Group-2(n=238) (Pregnant with Vitamin-D Insufficiency)	Group-3(n=18) (Pregnant with Vitamin-D Sufficiency)	p-value
Age	31.80±5.8 years	31.47±4.9 years	30.50±4.2 years	0.529
Gravida	4.67±1.9	4.53±1.5	4.41±1.1	0.719
Parity	1.68±1.3	1.79±1.3	1.98±1.2	0.687
Recurrent Miscarriages	2.45±1.9	1.91±1.3	1.62±1.3	0.155
Live Issues	1.21±1.0	1.48±1.3	1.58±1.0	0.157
Vitamin D level	22.40±1.5nmol/L	32.82±9.8nmol/L	76.63±8.0nmol/L	0.148

Table-III: Pregnancy Outcomes in the Groups (n=383)

Parameters	Group-1(n=127) (Pregnant with Vitamin-D Deficiency)	Group-2(n=238) (Pregnant with Vitamin-D Insufficiency)	Group-3(n=18) (Pregnant with Vitamin-D Sufficiency)	p-value
Hypertension in Second trimester	21(16.5%)	13(5.4%)	-	-
Hypertension in the third trimester	35(27.5%)	52(21.8%)	1(0.26%)	0.136
Early onset Pre-eclampsia	29(10.3%)	10(3.5%)	2(0.7%)	<0.001
Chronic Hypertension				
Superimposed Pre-eclampsia	17(6.7%)	8(3.2%)	2(0.8%)	<0.001
Gestational Hypertension	42(14.3%)	49(16.7%)	1(0.3%)	<0.001
Pre-term Labour				
28-32 weeks	-	4(8.2%)	-	
32-35 weeks	4(8.2%)	4(8.2%)	-	
35-37 weeks	25(51.0%)	11(22.4%)	1(2.0%)	0.086
Spontaneous Labour	26(54.2%)	18(37.5%)	2(4.2%)	0.232
Labour Induction	16(36.4%)	28(63.6%)	-	-
Lower Segment Caesarean Section	29(36.3%)	45(56.3%)	6(7.5%)	0.785
Spontaneous Vaginal Delivery	22(33.8%)	38(58.5%)	1(1.5%)	<0.001
Oligo/ Intra-uterine growth retardation	36(27.3%)	26(19.7%)	1(0.8%)	0.055

DISCUSSION

In our study mean vitamin-D level in Group-1 was 22.40±1.5 nmol/L, the mean vitamin-D level in Group-2 was 32.82±9.8nmol/L, and in Group-3, the mean vitamin-D level was 76.63±8.0nmol/L. Early onset pre-eclampsia, chronic hypertension with superimposed pre-eclampsia, gestational diabetes, spontaneous-vaginal delivery and delivery at term were statistically significant among the Groups.

A study on American pregnant women showed that the risk of early-onset pre-eclampsia and second-

on pre-eclampsia in pregnant populations with maternal vitamin- D.^{14,15}

In Canada, Two hundred twenty pregnant women at high risk for pre-eclampsia had 25 (OH)D estimated between 10-20 weeks of gestation and were followed up during pregnancy with.¹⁶ There were no associations between the vitamin D level of the mother and the risk of pre-eclampsia or any other adverse pregnancy-related effects, but only 28 pre-eclampsia cases were reported.

The risk of pre-eclampsia did not vary between the two-weekly doses of 50 000 IU women and women who received a placebo in a randomized-controlled trial of 60 high risks women in Iran, but only four women had pre-eclampsia.¹⁷

Most research in general obstetric populations, separated by intensity or time of pre-eclampsia into classes, find a link between motherly vitamin D and extreme or early-stage pre-eclampsia. Our results were similar, and that was interesting. The association with maternal vitamin D in overall obstetrics is minimal but increasingly evident for premature birth. High-risk pregnancies are not properly reported. No correlation was found between vitamin-D and preterm birth which was estimated at <37 weeks, but no subgroups for the preterm were considered by Shand *et al.*¹²

Another example was that no correlation was found between the mid-gestation vitamin-D maternal levels and preterm birth at <37 or <32 weeks in a clustered case-control sample of women at high risk due to previous preterm birth.¹⁸ While our finding was that vitamin-D status and preterm birth are the product of pre-eclampsia-indicated delivery less than 35 weeks away, in potential vitamin-D studies, subgroups of preterm birth should still be considered.

Previous research has shown that early pre-eclampsia originated from poor implantation, reconstruction of the spiral artery and placental growth. Angiogenic and anti-angiogenic placenta reasons are freed into the mother's circulation, which appears to the suitor of early onset pre-eclampsia maternal vascular damage. The effects of calcitriol are the gene transcript of various proteins, including VEGF, one of the main angiogenic factors.^{12,18}

LIMITATIONS OF STUDY

Observational studies always have the possibility of unmet uncertainty. No details about the consumption of food, vitamins and minerals, sun exposure or skin pigmentation have been found in this research. These factors should be tested in future research with the potential to affect both vitamin-D status and the risk of pre-eclampsia or preterm.

CONCLUSION

We aimed to determine whether vitamin-D status was linked with high-risk pregnancies, which could overshadow the impact of vitamin-D under existing conditions. Our findings help relate the status and pre-eclampsia of maternal vitamin-D to preterm birth.

Conflict of Intrest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

UH: Conception, study design, data acquisition, drafting the manuscript, approval of the final version to be published.

AC & SS: Study design, data analysis, critical review, draf-ting the manuscript, critical review, approval of the final version to be published.

FK & UU: Data analysis, data interpretation, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investi-gated and resolved.

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