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# OBSERVATIONAL STUDY OF PREGNANCY VITAMIN D STATUS AND RISK OF PREECLAMPSIA

Obstetrics & Gynaecology

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## ABSTRACT

**Introduction:**Low vitamin D status, among other risk factors, is linked to the development of preeclampsia. Systematic reviews and meta-analyses have concluded that low serum vitamin D levels (25-hydroxyvitamin D [25OHD]) in pregnancy are associated with a higher risk of preeclampsia and suggest a preventive role of vitamin D supplementation.

**Aim:**To examine the association between maternal serum 25-hydroxyvitamin D (25[OH]D) concentration in early pregnancy and the subsequent diagnosis of preeclampsia.

**Material and methods:** This prospective case control study was carried out at Department of Obstetrics and Gynecology, College of medicine and JNM Hospital, Kalyani, Nadia. Duration of the study was one and half year study period from March 2018-August 2019. Total 100 cases attending regular antenatal OPD was included provided they fulfil the inclusion criteria.

**Result:**It was found that in preeclampsia, 4(66.7%) patients had Vitamin-D Deficiency and 2(33.3%) patients had Insufficiency Vitamin-D. Association of Vitamin-D vs. preeclampsia was not statistically significant (p=0.3135). It was found that in preeclampsia, 6(100.0%) patients had no Previous Eclampsia. Association of Previous Eclampsia vs. preeclampsia was not statistically significant (p=0.6991965055).

**Conclusion:**We concluded that maternal vitamin D deficiency may be an independent risk factor for preeclampsia. Vitamin D supplementation in early pregnancy should be explored for preventing preeclampsia.

## KEYWORDS

25-hydroxyvitamin D, preeclampsia, Vitamin D

## INTRODUCTION

Preeclampsia is a multisystem complex disease of pregnancy with grave maternal-fetal and neonatal consequences that complicates up to 8% of pregnancies. Low vitamin D status, among other risk factors, is linked to the development of preeclampsia. Systematic reviews and meta-analyses have concluded that low serum vitamin D levels (25-hydroxyvitamin D [25OHD]) in pregnancy are associated with a higher risk of preeclampsia and suggest a preventive role of vitamin D supplementation. However, a recent meta-analysis of the 3 vitamin D supplementation randomized clinical trials (RCTs) on pregnancy outcomes found no association between increased serum vitamin D levels and preeclampsia risk. Although these studies vary in the dose of vitamin D supplementation (400–4,000 IU/day) and in the baseline and attained vitamin D levels, it is most important to note that all of the RCTs started the intervention after 20 weeks of gestation. It is noted that this meta-analysis did not include the results of the National Institute of Child Health and Development (NICHD) trial that started vitamin D supplementation before 20 weeks of gestation. A meta-analysis of the abnormal maternal biomarkers found during the first trimester of pregnancy in women who developed preeclampsia and the findings of previous studies on the association of preeclampsia and low vitamin D status in early pregnancy suggests the necessity of early serum vitamin D level surveillance and modification in pregnancy.

Vitamin D3, also known as calciferol, is a prohormone that plays an important role in calcium homeostasis and bone health in addition to its neuromuscular functions. Several studies reported the relationship between maternal Vitamin D deficiency and adverse maternal and fetal outcomes. In the last two decades, the non-classical function of Vitamin D has been suggested; it regulates a large number of human genes (~200 genes), resulting in a wide range of autocrine effects in different tissues. For example, Vitamin D is involved in regulation of cell proliferation, cell differentiation, and apoptosis. It exerts immune responses through regulation of the innate and adaptive immunity.[1] This explains the correlation of vitamin D deficiency to the potential risk of a series of conditions like hypertensive disorders, diabetes mellitus, cancer, multiple sclerosis, allergy, asthma, autoimmune and infectious diseases as well as depression. Hypertensive disorders of pregnancy are the most common medical complication of pregnancy and its association with vitamin D deficiency is worth discussing. Hypertensive disorders affect 7 -15% of all gestations and account for potential maternal and perinatal risks and outcome. It includes gestational hypertension, preeclampsia, eclampsia, chronic hypertension, preeclampsia superimposed on chronic hypertension.[2]

In India incidence of preeclampsia is 5-15%, eclampsia is 1 in 500 to 1 in 30. About 16% of maternal deaths were attributed to hypertensive disorders in developed countries and over half of these were preventable.[3]

Molecular data confirmed with pathological studies directed towards a two-stage disorder. The key features in the pathogenesis of preeclampsia are abnormal trophoblastic invasion of spiral arteries, inappropriate endothelial cell activation and exaggerated inflammatory response. The known racial disparity in preeclampsia, with black women being more likely to develop severe preeclampsia than white women, suggests that Vitamin D may be relevant.[4]

It has been suggested that preeclampsia and eclampsia results from breakdown of tolerance to the developing fetus after maternal immune maladaptation. Vitamin D is a seco-steroid prohormone which has direct effect on molecular pathways such as trophoblastic invasion and immunomodulation.[7]

During pregnancy, Vitamin D may play a role in implantation and placental function due to angiogenic and anti-inflammatory effects. It is important in directing immune responses at the fetal-placental interface as well as immunological adaptation to reduce the risk of inflammation and infection.[8]

Preeclampsia and eclampsia of varying degrees of severity form a considerable portion of admission in hospitals. Despite the considerable morbidity and mortality, the cause of preeclampsia and eclampsia has remained enigmatic.[9]

## OBJECTIVE OF RESEARCH

To examine the association between maternal serum 25-hydroxyvitamin D (25[OH]D) concentration in early pregnancy and the subsequent diagnosis of preeclampsia.

## MATERIALS AND METHODS

**STUDY DESIGN:** Prospective case control study.

**STUDY SETTING:** The propose study was carried out at Department

of Obstetrics and Gynecology, College of medicine and JNM Hospital, Kalyani, Nadia.

**PLACE OF STUDY:** The study was carried out in Department of Obstetrics and Gynecology, College of medicine and JNM Hospital, Kalyani, Nadia.

**PERIOD OF STUDY:**One and half year study period from March 2018-August 2019.

**STUDY POPULATION:** All pregnant women attending antenatal clinic and emergency of department of obstetrics and gynecology, College of medicine and JNM Hospital, Kalyani, Nadia.

**SAMPLE SIZE:**100 cases attending regular antenatal OPD was included provided they fulfill the inclusion criteria.

**Inclusion criteria for selection of case are:**

1. Informed consent.
2. Pregnant women not received Vitamin D supplementation previously.

**EXCLUSION CRITERIA:**

1. Patients not giving consent.
2. Patient with significant medical illness like

- Thyroid, parathyroid or adrenal disease,
- Nephrocalcinosis
- Hepatic or renal failure,
- Metabolic bone diseases
- Those taking medications that might affect vitamin D metabolism
- Multiple Pregnancies

**STATISTICALANALYSIS:**

For statistical analysis data were entered into a Microsoft excel spreadsheet and then analyzed by SPSS 24.0. and GraphPad Prism version 5. A chi-squared test ($\chi 2$ test) was any statistical hypothesis test wherein the sampling distribution of the test statistic is a chi-squared distribution when the null hypothesis is true. Without other qualification, 'chi-squared test' often is used as short for Pearson's chi-squared test. Unpaired proportions were compared by Chi-square test or Fischer's exact test, as appropriate. p-value $\leq 0.05$ was considered for statistically significant.

**RESULT AND DISCUSSION**

**Akbari S et al [8] (2018)** found that women with vitamin D deficiency at cutoff 20 ng/ml are more at risk of preeclampsia. This association can be specific up to 90% at 10.60 ng/ml cutoff. Treatment of vitamin D deficiency is necessary before pregnancy.

**Ullah MI et al [9] (2013)** found that the mean serum 25(OH)D level was 24.86 ng/ml in controls, 23.96 ng/ml in pre-eclamptic women, and 21.56 ng/ml in eclampsia patients. Comparing to those who had a serum 25(OH)D level of ≥30 ng/ml, the odds ratio (95% CI) of developing preeclampsia and eclampsia in mothers with vitamin D insufficiency were 3.9 (95% CI=1.18-12.87) and 5.14 (95% CI=1.98-13.37), respectively (adjusting for age, BMI and duration of pregnancy). The developing preeclampsia and eclampsia may increase by up to 5-fold in women with vitamin D insufficiency.

We found that 4(4.0%) patients had ≤20 years of age, 87(87.0%) patients had 21-30 years of age and 3(9.0%) patients had >30 years of age. 9(9.0%) patients had P0+0, 18(18.0%) patients had P0+1, 17(17.0%) patients had P1+0, 20(20.0%) patients had P1+1, 16(16.0%) patients had P2+0 and 20(20.0%) patients had P2+1. 9(90.0%) patients had upper class, 40(40.0%) patients had lower middle class, 41(41.0%) patients had middle class and 10(10.0%) patients had lower class.

It was found that 78(78.0%) patients had Vitamin-D deficiency, 14(14.0%) patients had Insufficiency Vitamin-D and 8(8.0%) patients had normal Vitamin-D.

In preeclampsia, the mean age (mean± s.d.) of patients was 25.0957 ± 3.1862 years. Distribution of mean age vs. preeclampsia was statistically significant (p=0.0113).

It was found that in preeclampsia, the mean BMI (mean± s.d.) of patients was 24.1167 ± 1.6018 kg/m2. Distribution of mean BMI vs. preeclampsia was not statistically significant (p=0.4228). In preeclampsia, the mean GA (mean± s.d.) of patients was 12.2667 ± 1.0482 weeks. Distribution of mean GA vs. preeclampsia was not statistically significant (p=0.7581).

Present study found that 71(71.0%) patients had anemia, 14(14.0%) patients had diabetes, 4(4.0%) patients had cardiac disease, 6(6.0%) patients had respiratory disease.

We found that 8(8.0%) patients had HTN, 40(40.0%) patients had previous uterine operation.It was found that 4(4.0%) patients had Previous IUFD, 4(4.0%) patients had Previous PPH. We found that 5(5.0%) patients had Previous Eclampsia, 6(6.0%) patients had Preeclampsia.The mean age (mean± s.d.) of patients was 24.6300 ± 2.4106 years.The mean BMI (mean± s.d.) of patients was 24.7830 ± 2.0875 kg/m2.The mean GA (mean± s.d.) of patients was 12.3720 ± .8578 weeks. The mean GA (mean± s.d.) of patients was 16.8270 ± 3.4033 weeks.

**Sharma N et al [10](2019)** found that there is association of preeclampsia, cesarean section, and low birth weight babies with lower level of VD. Prevalence of VDD in pregnancy is as tonishingly high.

**Mirzakhani H et al [11] (2016)** found that low vitamin D status in pregnancy was proposed as a risk factor of preeclampsia after adjustment for confounders, a significant effect of sufficient vitamin D status was observed in both early and late pregnancy compared with insufficient levels

We found that in preeclampsia, 4(66.7%) patients had 21-30 years of age. Association of age vs. preeclampsia was statistically significant (p=0. 0.0007).

It was found that in preeclampsia, 3(50.0%) patients had P0+1, 2(33.3%) patients had P1+1 and 1(16.7%) patient had P2+0. Association of parity vs. preeclampsia was not statistically significant (p=0.2107). We found thatin preeclampsia, 3(50.0%) patients had lower middle class, 1(16.7%) patient had middle class and 2(33.3%) patients had lower class. Association of SES vs. preeclampsia was not statistically significant (p=0.1625).

**Hyppönen E et al [12] (2013)** found that association between vitamin D deficiency and hypertension, including the pregnancy-specific preeclampsia.

**Magnus MC et al [13] (2018)** found that no strong evidence was found to support a causal effect of vitamin D status on gestational hypertension or pre-eclampsia.

**Shand AW et al [14] (2010)** found that all 104 participants had subnormal Vitamin D levels (<30 ng/ml), 2(1.92%) had Vitamin D insufficiency (21-29 ng/ml) and 102(98%) had Vitamin D deficiency (<20 ng/ml). Of the total, 71(75.96%) had severe deficiency (<10 ng/ml). Mean Vitamin D level was 6.78 in cases and 9.43 in controls (p 0.002). Vitamin D level <10 ng/ml was seen in 86.5% hypertensive's and 65.4% controls, values between 10-29 ng/ml were noted in 13.5% hypertensive's and 34.6% controls (p 0.012;OR 3.403). Vitamin D deficiency was associated with Pre-eclampsia/Eclampsia (p=0.045; OR 3.706) and Gestational Hypertension (p=0.025; OR 4.235). Severe Vitamin D deficiency is common in pregnant Pakistanis and is associated with hypertensive disorders of pregnancy.

It was found that in preeclampsia, 4(66.7%) patients had Vitamin-D Deficiency and 2(33.3%) patientshad Insufficiency Vitamin-D. Association of Vitamin-D vs. preeclampsia was not statistically significant (p=0.3135).

In preeclampsia, 1(16.7%) patient had no Anemia and 5(83.3%) patients had Anemia. Association of Anemia vs. preeclampsia was not statistically significant (p=0.8237599079). In preeclampsia, 6 (100. 0 %) patients had Diabetes. Association of Diabetes vs. preeclampsia was not statistically significant (p=0.2450).

We found that in preeclampsia, 4(66.7%) patients had no Cardiac Disease and 2(33.3%) patients had Cardiac Disease. Association of Cardiac Disease vs. preeclampsia was not statistically significant (p=0.0867).

We found that in preeclampsia, 4(66.7%) patients had no respiratory

disease and 2(33.3%) patients had respiratory disease. Association of Respiratory Disease vs. preeclampsia was not statistically significant (p=0.0832522594). It was found that in preeclampsia, 3(50.0%) patients had no HTN and 3(50.0%) patients had HTN. Association of HTN vs. preeclampsia was statistically significant (p=0.0017182133). It was found that in preeclampsia, 2(33.3%) patients had no Previous Uterine Operation and 4(66.7%) patients had Previous Uterine Operation. Association of Previous Uterine Operation vs. preeclampsia was not statistically significant (p=0.3444200138).

It was found that in preeclampsia, 6(100.0%) patients had no Previous IUFD.Association of Previous IUFD vs. preeclampsia was not statistically significant (p=0.5763761839).

In preeclampsia, 6(100.0%) patients had no Previous PPH. Association of Previous PPH vs. preeclampsia was not statistically significant (p=0.5763761839).

**Stougaard M et al [15] (2018)** found that no association between exposure to vitamin D fortification during pregnancy and the risk of any of the pregnancy related hypertensive disorders, including preeclampsia: Odds ratios (OR, 95%) for all hypertensive pregnancy related disorders among exposed vs. unexposed women was (OR 1.04, 95%CI: 0.98,1.10). In conclusion, the extra vitamin D from the mandatory vitamin D fortification did not influence the risk of preeclampsia.

It was found that in preeclampsia, 6(100.0%) patients had no Previous Eclampsia. Association of Previous Eclampsia vs. preeclampsia was not statistically significant (p=0.6991965055).

In preeclampsia, the mean Vitamin-D (mean± s.d.) of patients was 17.6255 ± 5.2937. Distribution of mean Vitamin-D vs. preeclampsia was statistically significant (p=0.5997).

**Wei SQ et al [16] (2012)** found that they conclude lower maternal 25(OH)D levels at late mid-trimester were associated with an increased risk of pre-eclampsia.

**Table: Distribution of Vitamin-D group, Anemia, HTN, Previous Uterine OperationandPrevious IUFD : Preeclampsia**

| | | PREECLAMSIA | | | p-value |
|---|---|---|---|---|---|
| | | NO PREECLAMPSIA | PREECLAMPSIA | TOTAL | |
| **Vitamin-D group** | **Deficiency** | 74 | 4 | 78 | 0.0435 |
| | Row % | 94.9 | 5.1 | 100.0 | |
| | Col % | 78.7 | 66.7 | 78.0 | |
| | **Insufficiency** | 12 | 2 | 14 | |
| | Row % | 85.7 | 14.3 | 100.0 | |
| | Col % | 12.8 | 33.3 | 14.0 | |
| | **Normal** | 8 | 0 | 8 | |
| | Row % | 100.0 | 0.0 | 100.0 | |
| | Col % | 8.5 | 0.0 | 8.0 | |
| | **TOTAL** | 94 | 6 | 100 | |
| | Row % | 94.0 | 6.0 | 100.0 | |
| | Col % | 100.0 | 100.0 | 100.0 | |
| **Anemia** | **No** | 28 | 1 | 29 | 0.0237 |
| | Row % | 96.6 | 3.4 | 100.0 | |
| | Col % | 29.8 | 16.7 | 29.0 | |
| | **Yes** | 66 | 5 | 71 | |
| | Row % | 93.0 | 7.0 | 100.0 | |
| | Col % | 70.2 | 83.3 | 71.0 | |
| | **TOTAL** | 94 | 6 | 100 | |
| | Row % | 94.0 | 6.0 | 100.0 | |
| | Col % | 100.0 | 100.0 | 100.0 | |
| **HTN** | **No** | 89 | 3 | 92 | 0.0717 |
| | Row % | 96.7 | 3.3 | 100.0 | |
| | Col % | 94.7 | 50.0 | 92.0 | |
| | **Yes** | 5 | 3 | 8 | |
| | Row % | 62.5 | 37.5 | 100.0 | |
| | Col % | 5.3 | 50.0 | 8.0 | |
| | **TOTAL** | 94 | 6 | 100 | |
| | Row % | 94.0 | 6.0 | 100.0 | |
| | Col % | 100.0 | 100.0 | 100.0 | |
| **Previous Uterine Operation** | **No** | 58 | 2 | 60 | 0.34442 |
| | Row % | 96.7 | 3.3 | 100.0 | |
| | Col % | 61.7 | 33.3 | 60.0 | |
| | **Yes** | 36 | 4 | 40 | |
| | Row % | 90.0 | 10.0 | 100.0 | |
| | Col % | 38.3 | 66.7 | 40.0 | |
| | **TOTAL** | 94 | 6 | 100 | |
| | Row % | 94.0 | 6.0 | 100.0 | |
| | Col % | 100.0 | 100.0 | 100.0 | |
| **Previous IUFD** | **No** | 90 | 6 | 96 | 0.5763 |
| | Row % | 93.8 | 6.3 | 100.0 | |
| | Col % | 95.7 | 100.0 | 96.0 | |
| | **Yes** | 4 | 0 | 4 | |
| | Row % | 100.0 | 0.0 | 100.0 | |
| | Col % | 4.3 | 0.0 | 4.0 | |
| | **TOTAL** | 94 | 6 | 100 | |
| | Row % | 94.0 | 6.0 | 100.0 | |
| | Col % | 100.0 | 100.0 | 100.0 | |

## CONCLUSION

We found that 78(78.0%) patients had Vitamin-D deficiency and 14(14.0%) patients had Insufficiency of Vitamin-D in pregnant women.

Vitamin D deficiency was associated with Pre-eclampsia. Distribution of mean level Vitamin-D was lower in preeclampsia compared to normal uneventful pregnancy

It was found that more number of Preeclampsia was developed in age group 21-30 years. Preeclampsia was developed in early age group, which was statistically significant.

Anemia was found to be more common in pregnant women with Pre-eclampsia.

We concluded that maternal vitamin D deficiency may be an independent risk factor for preeclampsia. Vitamin D supplementation in early pregnancy should be explored for preventing preeclampsia.

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