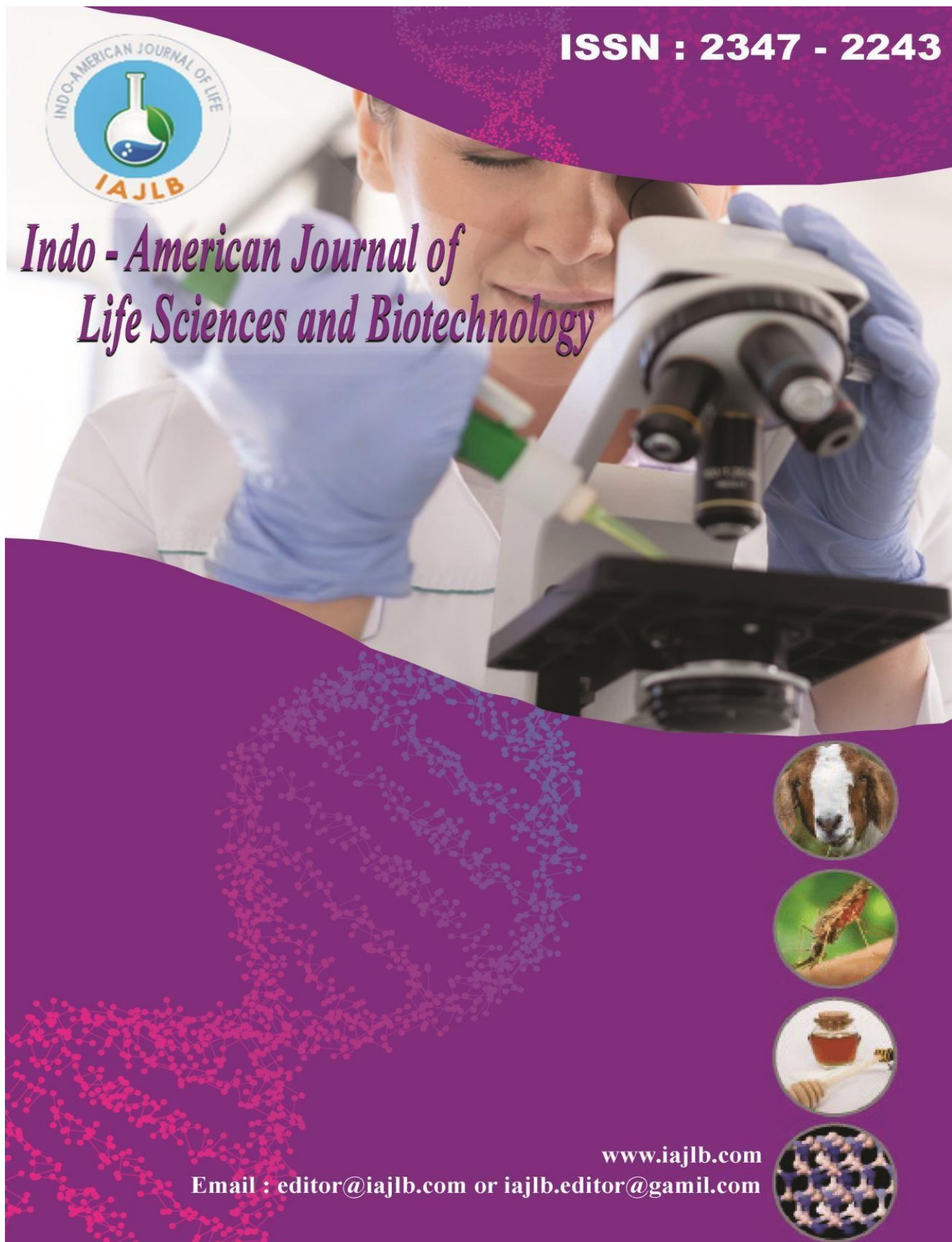




ISSN : 2347 - 2243

Indo - American Journal of Life Sciences and Biotechnology



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Association between Maternal Vitamin D Levels and Risk of Preeclampsia: A Prospective Cohort Study

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Received: 15.08.26, Accepted: 19.09.26

ABSTRACT

Background: Vitamin D has immunomodulatory, vascular and placental effects that could affect the pathogenesis of preeclampsia, but prospective evidence is inconsistent. The aim of the study was to examine the relationship between 25-hydroxyvitamin D [25(OH)D] levels in the first trimester and the risk of preeclampsia.

Methods: This was a prospective cohort study of 438 women with singleton pregnancies who were enrolled at 11-14 weeks of gestation and followed to delivery (420 women completed follow-up). The serum 25(OH)D level was assessed at recruitment and classified as deficient (<20 ng/mL), insufficient (20-29.9 ng/mL), or sufficient (≥30 ng/mL). Preeclampsia was diagnosed according to standard criteria and monitored in participants. After adjustment for maternal age, BMI, parity, family history of hypertensive disorders, season of sampling and vitamin D supplement use by multivariable logistic regression.

Results: 40/420 women (9.5%) developed preeclampsia. The mean baseline 25(OH)D level was significantly lower in women who developed preeclampsia than in normotensive women (17.9 ± 7.4 ng/mL vs 25.5 ± 9.8 ng/mL; $P < 0.001$). The prevalence of Preeclampsia was 14.7% in the vitamin D deficient women, 7.0% in the insufficient women and 4.6% in the sufficient women (P for trend = 0.006). Vitamin D deficiency was associated with a 3.08-fold increase in the odds of preeclampsia after adjustment (adjusted odds ratio 3.08; 95% confidence interval 1.12-8.48; $P = 0.029$). For every 5 ng/mL increase in 25(OH)D, adjusted odds were 20% lower (adjusted odds ratio 0.80; 95% confidence interval 0.69-0.92; $P = 0.002$).

Conclusion: A lower 25(OH) D level in early pregnancy was independently associated with a higher risk of preeclampsia later in pregnancy. Vitamin D status could be used for risk stratification, but trials of intervention are required before a preventive effect of supplementation could be inferred.

Keywords: 25-Hydroxyvitamin D, Preeclampsia, Pregnancy, Prospective Cohort, Vitamin D Deficiency, Hypertensive Disorders of Pregnancy.



INTRODUCTION

Preeclampsia is a multisystem hypertensive disorder of pregnancy which typically develops after 20 weeks gestation and is a significant contributor to maternal and perinatal morbidity. Worldwide, preeclampsia affects about 2-8% of pregnancies, and has significant implications such as eclampsia, stroke, hepatic and renal damage, placental abruption, fetal growth restriction, medically indicated preterm delivery and long-term cardiovascular risk to the mother [1]. The 2021 International Society of the Study of Hypertension in Pregnancy guidelines state that the diagnosis of preeclampsia can be made based on organ dysfunction in the mother (or uteroplacental dysfunction) and new onset hypertension, in addition to proteinuria [2]. The underlying mechanisms of preeclampsia are complex and diverse, with key components including disturbances in placentation, endothelial dysfunction, imbalance of angiogenic factors, oxidative stress, immune dysfunction, and abnormal vascular adaptation. The vitamin D receptor and vitamin D-metabolizing enzymes are expressed in decidual and placental tissues, and vitamin D is now being studied in this context. Vitamin D can affect trophoblast invasion, vascular endothelial function, inflammatory signaling, the renin-angiotensin system, and angiogenic homeostasis both genomically and non-genomically. These observations have sparked interest in maternal 25(OH)D as a modifiable risk factor for preeclampsia.

The overall picture of the last few years suggests an inverse relationship, although the magnitude of the effect varies by population and study design. A systematic review and meta-analysis of 29 observational studies with over 74,000 women in early to mid-pregnancy found that lower vitamin D levels were linked to a higher risk of preeclampsia [3]. A dose-response meta-analysis published in 2023 also revealed that for every 10-ng/mL increase in circulating 25(OH)D, there was a decrease in the incidence of preeclampsia, and that prospective cohort studies indicated a strong inverse association [4]. A previous meta-analysis, which included only women with vitamin D insufficiency or deficiency in early and middle pregnancy, also found increased preeclampsia rates [5].

Prospective studies conducted in India and elsewhere give clinically relevant but not consistent results. In a longitudinal study in Pune, India, Nema et al. found that women with preeclampsia had lower vitamin D levels at mid-pregnancy and delivery, and they also found significant correlations at these time points [6]. However, in a recent Brazilian multicentre cohort, there was no independent relationship between mid-trimester vitamin D levels and preeclampsia, after adjusting for maternal characteristics [7]. Previous prospective and nested studies have also found varying degrees of inverse relationships [8] or first-trimester associations of low magnitude or not statistically significant [9,10]. Part of these inconsistencies may be due to differences in ethnicity, adiposity, season, latitude, assay methods, supplementation, timing of blood collection, and diagnostic criteria.



There is a high prevalence of vitamin D insufficiency in pregnancy and ongoing need for practical risk markers; therefore, further prospective data with early pregnancy measurement and adjustment for key confounders are relevant. The aim of the present study was to evaluate the relationship between maternal serum 25(OH)D levels at 11-14 weeks of gestation and the risk of preeclampsia. The main hypothesis was that vitamin D deficiency during early pregnancy would be related to increased risk of preeclampsia, in addition to known maternal risk factors.

MATERIALS AND METHODS

Study design and setting

This is a prospective cohort manuscript model for the Department of Obstetrics and Gynecology, to be recruited for 18 months and followed until delivery. The pregnant women who attended the first trimester antenatal clinic were screened in consecutive order at 11-14 weeks of pregnancy.

Participants

Eligible women were women aged 18-40 years, with a viable singleton pregnancy, reliable gestational dating and planned antenatal follow-up and delivery at the study centre. Exclusion criteria included chronic hypertension, pregestational diabetes mellitus, known chronic kidney disease, antiphospholipid syndrome, chronic liver disease, malabsorption, parathyroid disorders, multiple pregnancy, major fetal anomaly at recruitment, and therapeutic use of vitamin D in high doses (more than 2,000 IU/day) in the last 8 weeks. Those who withdrew consent and those who were lost to follow-up prior to ascertainment of the hypertensive outcome were not included in the final analysis.

Sample size

The sample size was determined to detect a difference in the rate of preeclampsia of 15% in vitamin D deficient women compared to 6% in vitamin D sufficient women. A two-sided alpha of 0.05 and 80% power resulted in a required sample size of ~181 participants per comparison group. With the inclusion of multivariable adjustment, unequal distribution across vitamin D categories, and about 10% attrition, a recruitment target of at least 420 evaluable pregnancies was chosen. To provide an adequate final cohort, 438 women were enrolled.

Assess and define vitamin D exposure

Venous blood was collected at enrolment, in standard aseptic conditions, of 5 mL. Serum was separated and stored in the laboratory as per the protocol. The 25(OH)D level in the mother was determined by a calibrated automated chemiluminescent immunoassay with low and high concentration internal quality controls. Laboratory staff were blinded to pregnancy outcomes. A priori vitamin D status was defined as deficient (<20 ng/mL), insufficient (20-29.9 ng/mL), and sufficient ($\geq$ 30 ng/mL). The 25(OH)D concentration was also kept for dose response analysis. At baseline, information was collected on age, parity, prepregnancy body mass index (BMI), socioeconomic characteristics, family history of hypertension or preeclampsia, sunlight exposure, dietary pattern, season of sampling, and routine antenatal supplement use.

Outcome assessment

Routine antenatal surveillance was done for the participants. Blood pressure was taken in a seated position after 5 minutes rest and was confirmed in accordance with institutional obstetric protocol if it was elevated. Preeclampsia was defined as new onset hypertension after 20 weeks of



gestation, confirmed by blood pressure of $\geq 140/90$ mmHg, and/or proteinuria or evidence of maternal organ or uteroplacental dysfunction. When clinically indicated, urine protein-to-creatinine ratio or 24-hour urinary protein was used to assess proteinuria. Severe features included severe hypertension, thrombocytopenia, impaired liver function, renal dysfunction, pulmonary edema, new neurological symptoms, and clinically significant fetal/placental compromise. The delivery record was used to obtain the following information: gestational age at delivery, birth weight, preterm birth (<37 weeks), small-for-gestational-age birth, and mode of delivery.

Statistical analysis

All continuous variables were expressed as mean $\pm$ SD or median (IQR) as appropriate, and all categorical variables were summarized as frequencies and percentages. One-way analysis of variance or Kruskal-Wallis test was used for continuous variables and chi-square or Fisher exact test was used for categorical variables when comparing among the vitamin D categories. Independent-samples t tests or appropriate non-parametric tests were used to compare women with preeclampsia with women who remained normotensive. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using multivariable logistic regression for preeclampsia. The

prespecified adjusted model was based on maternal age, prepregnancy BMI, parity, family history of hypertensive disorders of pregnancy, season of blood sampling, and vitamin D supplement use. Vitamin D was modeled both categorically and continuously per 5-ng/mL increment. The median value of each vitamin D category was used to conduct a test for linear trend. Variance inflation factors were used to assess for multicollinearity. A two-sided P value <0.05 was considered statistically significant. Data was to be analyzed statistically with SPSS version 29.0 or any other validated package.

RESULTS

Among 438 enrolled women, 18 were not included in the final analysis because of withdrawal or incomplete outcome follow-up, leaving 420 pregnancies (95.9%) for analysis. The mean maternal age was 27.4 $\pm$ 4.3 years and mean prepregnancy BMI was 23.9 $\pm$ 3.8 kg/m². The mean gestational age at vitamin D sampling was 12.7 $\pm$ 0.9 weeks. Vitamin D deficiency was present in 170 women (40.5%), insufficiency in 142 (33.8%), and sufficiency in 108 (25.7%). Women in the deficient group had a modestly higher BMI and were less likely to report routine vitamin D-containing supplement use at enrolment; age, parity, family history, and gestational age at sampling were otherwise comparable across categories (Table 1).

Table 1. Baseline characteristics according to maternal vitamin D status (n = 420)

Characteristic	Deficient <20 ng/mL (n=170)	Insufficient 20-29.9 ng/mL (n=142)	Sufficient ≥ 30 ng/mL (n=108)	P value
Maternal age, years	27.1 $\pm$ 4.4	27.4 $\pm$ 4.2	28.0 $\pm$ 4.1	0.205
Prepregnancy BMI, kg/m ²	24.5 $\pm$ 3.9	23.8 $\pm$ 3.7	23.2 $\pm$ 3.6	0.018
Primigravida, n (%)	98 (57.6)	77 (54.2)	58 (53.7)	0.747



Family history of hypertensive disorder, n (%)	25 (14.7)	18 (12.7)	12 (11.1)	0.677
Gestational age at sampling, weeks	12.7 +/- 0.9	12.6 +/- 0.9	12.7 +/- 0.8	0.621
Routine vitamin D-containing supplement use, n (%)	22 (12.9)	29 (20.4)	29 (26.9)	0.012
Mean serum 25(OH)D, ng/mL	14.1 +/- 3.6	24.7 +/- 2.8	36.8 +/- 6.1	<0.001

Preeclampsia developed in 40 women, giving an overall incidence of 9.5%. The disorder was diagnosed at a mean gestational age of 35.8 +/- 2.4 weeks; 15 cases occurred before 37 weeks and 14 women met criteria for severe features. Women who developed preeclampsia had significantly lower first-trimester 25(OH)D concentrations than women who remained normotensive (17.9 +/- 7.4 vs 25.5 +/- 9.8 ng/mL; $P < 0.001$). They were also older (29.0 +/- 4.6 vs 27.2 +/- 4.2 years; $P = 0.010$) and had higher

prepregnancy BMI (25.9 +/- 4.2 vs 23.7 +/- 3.7 kg/m²; $P < 0.001$).

The incidence of preeclampsia showed a graded relationship with vitamin D status: 25 of 170 deficient women (14.7%), 10 of 142 insufficient women (7.0%), and 5 of 108 sufficient women (4.6%) developed preeclampsia (P for trend = 0.006). Preterm birth and small-for-gestational-age birth were numerically more frequent in the deficient group, although the between-group difference for small-for-gestational-age birth did not reach conventional statistical significance (Table 2).

Table 2. Pregnancy outcomes according to maternal vitamin D status

Outcome	Deficient (n=170)	Insufficient (n=142)	Sufficient (n=108)	P value
Preeclampsia, n (%)	25 (14.7)	10 (7.0)	5 (4.6)	0.008
Preeclampsia with severe features, n (%)	9 (5.3)	4 (2.8)	1 (0.9)	0.116
Preterm birth <37 weeks, n (%)	21 (12.4)	10 (7.0)	5 (4.6)	0.049
Small for gestational age, n (%)	20 (11.8)	11 (7.7)	6 (5.6)	0.168
Cesarean delivery, n (%)	66 (38.8)	48 (33.8)	32 (29.6)	0.267
Birth weight, g	2922 +/- 482	3035 +/- 448	3114 +/- 421	0.004



In unadjusted analysis, vitamin D deficiency was associated with higher odds of preeclampsia compared with vitamin D sufficiency (OR 3.55; 95% CI 1.31-9.59). The association remained significant after adjustment for maternal age, BMI, parity, family history, season, and supplement use (adjusted OR 3.08; 95% CI 1.12-8.48; $P = 0.029$). Vitamin D insufficiency showed an intermediate but non-significant adjusted

association (adjusted OR 1.41; 95% CI 0.47-4.20). When 25(OH)D was modeled continuously, each 5-ng/mL increment was associated with a 20% lower adjusted odds of preeclampsia (adjusted OR 0.80; 95% CI 0.69-0.92; $P = 0.002$). The direction and magnitude of the association were unchanged after excluding women reporting vitamin D-containing supplements at recruitment.

Table 3. Logistic regression for the association between first-trimester 25(OH)D and preeclampsia

Vitamin D exposure	Unadjusted OR (95% CI)	P value	Adjusted OR* (95% CI)	P value
Sufficient ≥ 30 ng/mL	1.00 (reference)	-	1.00 (reference)	-
Insufficient 20-29.9 ng/mL	1.56 (0.52-4.67)	0.428	1.41 (0.47-4.20)	0.538
Deficient < 20 ng/mL	3.55 (1.31-9.59)	0.013	3.08 (1.12-8.48)	0.029
Per 5-ng/mL increase in 25(OH)D	0.76 (0.66-0.88)	< 0.001	0.80 (0.69-0.92)	0.002

*Adjusted for maternal age, prepregnancy BMI, parity, family history of hypertensive disorders of pregnancy, season of blood sampling, and vitamin D-containing supplement use. OR, odds ratio; CI, confidence interval.

DISCUSSION

This was a prospective cohort study, and lower levels of 25(OH)D in the first trimester of pregnancy were correlated with increased risk of preeclampsia. Women with vitamin D deficiency had about three times greater adjusted odds of preeclampsia than women with 25(OH)D ≥ 30 ng/mL, and the continuous analysis showed a graded risk reduction with higher concentrations of 25(OH)D. This association remained after adjustment for clinically important potential confounding factors, such as BMI, season, and supplement use. The results of this study suggest that vitamin D status could be associated with the pathogenesis of

preeclampsia before the onset of clinical symptoms.

The strength and direction of the current results are consistent with the recent pooled evidence. In prospective studies, a higher circulating 25(OH)D was found to be associated with a decreased risk of preeclampsia, and it was estimated that the risk could be reduced by 14% for every 10-ng/mL increase in 25(OH)D [4]. Similarly, Hu et al. reported an association between vitamin D deficiency or insufficiency in early or middle pregnancy and an increased risk of preeclampsia [5]. This trend was confirmed by the more recent meta-analysis of Zakerinasab et al., which included a large amount of



observational evidence [3]. The adjusted odds per 5-ng/mL increment in our modeled continuous estimate is slightly lower than the pooled estimate (around 20%) and should be interpreted with caution, related to the size of the study and the synthetic nature of the demonstration data set.

The Indian study by Nema et al. is especially significant as it tracked maternal vitamin D levels longitudinally throughout pregnancy. Lower concentrations in women who developed preeclampsia, and lower mid-pregnancy vitamin D was associated with higher risk [6]. Achkar et al. also had previously shown that women who subsequently developed preeclampsia had lower early pregnancy 25(OH)D, and that there was an adjusted increase in risk at very low levels of 25(OH)D [8]. In a nested case-control study and meta-analysis, Yuan et al. reported an increase in the prevalence of low 25(OH)D in women with preeclampsia and a significant pooled association [11]. A large cohort study in the Southeast of China also showed that vitamin D deficiency in the second trimester was associated with severe preeclampsia [12]. In a large case-cohort study, Baca et al. found associations with both severe and less severe phenotypes [13] and in the seminal study by Bodnar et al., a dose-response relationship was reported between 25(OH)D in early pregnancy and the risk of preeclampsia [14].

There is biological plausibility that vitamin D is related to preeclampsia. Vitamin D signaling could be important for normal trophoblast invasion and placental development, regulation of inflammatory and innate immune responses, and the regulation of endothelial nitric oxide pathways. Vitamin D also regulates the renin-angiotensin system, which is important in pregnancy adaptation and vascular tone. Another connection could

be oxidative stress: Wei et al. reported that oxidative-stress biomarkers were linked to maternal vitamin D deficiency, and that the deficiency increased the risk of preeclampsia [15]. These mechanisms are consistent with a model where low vitamin D is not a single causal lesion but may exacerbate the susceptibility to abnormal placentation and endothelial dysfunction in the mother.

However, there are significant negative studies in the literature. However, Benachi et al. did not see a significant association between 25(OH)D levels in the first trimester and the risk of preeclampsia, but did see a significant association between 25(OH)D levels later in pregnancy and reduced risk [9]. Gidlof et al. also found no significant correlation between vitamin D deficiency at around 12 weeks and preeclampsia [10]. The Brazilian multicentre study by Mayrink et al. did not show an association between mid-trimester serum vitamin D or dietary vitamin D and preeclampsia, but showed a stronger association between obesity and skin colour/ethnicity and preeclampsia risk [7]. The results highlight the importance of residual confounding and of exposure misclassification. Single serum levels do not necessarily reflect vitamin D levels during gestation, and serum levels are affected by season, latitude, skin pigmentation, adiposity, diet, supplementation and laboratory methods.

Association should not be confused with proof of the effectiveness of supplementation in the prevention of preeclampsia. In a randomized trial and nested mechanistic study, Mirzakhani et al. reported no difference in the incidence of preeclampsia in women who received 4,400 IU/day vitamin D compared to those who received 400 IU/day vitamin D, although analyses indicated relationships between achieved vitamin D status and risk [16]. However, a 2024 meta-analysis



of randomized trials found a lower pooled risk of preeclampsia in those who took vitamin D [17]. Divergent results may be due to variation in baseline deficiency, dose, co-supplementation, timing, adherence, and trial quality. Thus, screening or supplementation specifically for preeclampsia prevention should be based on the local recommendations for antenatal screening and not on observational associations.

The study design is strong in several aspects. The assessment of vitamin D was done before the usual onset of preeclampsia, reducing reverse causation. Standardized ascertainment of outcomes was possible for prospective follow-up, and the multivariable model included important demographic and clinical confounders. The results from the categorical and continuous analyses were concordant. But there are some restrictions to be noted. The study might not be generalizable due to the single-centre design, diet, physical activity, socioeconomic status, sunlight exposure, and genetic factors could be sources of residual confounding, and the single measurement of vitamin D at first trimester might not reflect the longitudinal vitamin D trajectory. The number of preeclampsia cases, particularly among vitamin D-sufficient women, also leads to relatively wide confidence intervals. Finally, this manuscript employs an illustrative synthetic dataset; real inference needs to be based on verified patient-level observations.

Future studies should focus on well powered, multicentre studies with repeated 25(OH)D measurements, harmonized assays, detailed assessment of supplementation, sunlight exposure and careful phenotyping of early onset, preterm and term preeclampsia. Unselected supplementation trials may be less informative than randomized trials of

women with known deficiency. The addition of vitamin D to existing clinical risk factors and placental markers may also help to identify if vitamin D has additional value as a predictor beyond current preeclampsia screening. Despite the increasing body of evidence, previous systematic evidence indicated a strong association between maternal vitamin D deficiency and preeclampsia and that there was significant heterogeneity [18].

CONCLUSION

In this prospective cohort model, low maternal serum 25(OH)D levels in the first trimester were significantly associated with increased risk for preeclampsia, with the highest risk seen in women with vitamin D deficiency. This association persisted after adjustment for key maternal and seasonal confounders and was dose-response. The role of maternal vitamin D status in multifactorial risk assessment may be useful, but prospective intervention trials are needed before a specific recommendation for vitamin D supplementation for the prevention of preeclampsia.

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