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# Vitamin D Status and Hypertensive Disorders in Pregnancy

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## Abstract

**Purpose—**Several studies have reported increased risk of preeclampsia when 25-hyrdoxyvitamin D (25[OH]D) levels are low. The extent to which 25(OH)D may lower risk for hypertensive disorder during pregnancy remains unclear.



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**Methods—**Among women enrolled in the Project Viva prenatal cohort in Massachusetts, we examined associations of 25(OH)D levels obtained at 16.4 –36.9 weeks of gestation (mean 27.9 weeks) with hypertensive disorders of pregnancy, including preeclampsia (56/1591, 3.5%) and gestational hypertension (109/1591, 6.9%).

**Results—**We did not detect an association between plasma 25(OH)D concentration (mean 58, SD 22 nmol/L) and preeclampsia. For each 25 nmol/L increase in 25(OH)D, the adjusted odds ratio for preeclampsia was 1.14 (95% confidence interval: 0.77, 1.67). By contrast and contrary to hypothesis, higher 25(OH)D concentrations were associated with higher odds of gestational hypertension: adjusted odds ratio for gestational hypertension was 1.32 (95% confidence interval: 1.01, 1.72) per each 25nmol/L increment in 25(OH)D. Vitamin D intake patterns suggest this association was not because of reverse causation. While the elevated hypertension risk may be due to chance, randomized trials of vitamin D supplementation during pregnancy should monitor for gestational hypertension.

**Conclusions—**These data do not support the hypothesis that higher 25(OH)D levels lower the overall risk of hypertensive disorders of pregnancy.

### MeSH headings

Pregnancy; Pre-Eclampsia; Hypertension; Pregnancy-Induced; Vitamin D; 25-hydroxyvitamin D

## INTRODUCTION

Beyond its well-established role in bone health, vitamin D has been studied as a potentially modifiable factor contributing to extraskeletal health during pregnancy(1). During pregnancy, vitamin D may play a role in implantation and placental function potentially due to angiogenic, immunomodulatory and anti-inflammatory effects(2). While still incompletely understood, the pathophysiology of preeclampsia likely involves abnormal placentation and angiogenesis (3). Several studies have demonstrated an association between higher 25-hydroxyvitamin D (25[OH]D) levels in pregnancy and reduced risk of preeclampsia(4–9), especially severe preeclampsia(4, 5, 8). The National Institutes of Health has funded several ongoing trials to assess the extent to which vitamin D supplementation during pregnancy may prevent perinatal complications(10). However, vitamin D supplementation may not be without risk. In a study of dietary intake of several micronutrients, we observed a potential increased risk of gestational hypertension with higher dietary intakes of vitamin D during pregnancy (adjusted OR 1.11, 95%: 1.01, 1.21 per 100 IU of dietary vitamin D(11). In that earlier analysis, however, we did not have access to plasma 25(OH)D concentrations, a better estimate of vitamin D status because 25(OH)D includes vitamin D from both diet and sun exposure. Our objective in this paper is to determine the extent to which plasma 25(OH)D concentrations during pregnancy are associated with hypertensive disorders of pregnancy, namely preeclampsia and gestational hypertension.

## MATERIALS and METHODS

We studied women participating in Project Viva, a prospective, prenatal cohort study in Massachusetts. We recruited women who were attending their initial prenatal visit (mean 10.5 weeks gestation) at one of 8 urban and suburban obstetrical offices of Harvard Vanguard Medical Associations, a multi-specialty group practice located in eastern Massachusetts. Women provided written informed consent. Details of cohort recruitment and retention are published elsewhere(12). Of the 2128 participants who delivered live infants, we classified 28 women as chronically hypertensive (defined as taking antihypertensive medications or with two elevated clinically measured blood pressure values [systolic (SBP) >140 mm Hg or diastolic (DBP) >90 mm Hg] before 20 weeks gestation), and excluded them from all analyses. Of the 2100 remaining, we obtained plasma samples from 1591 at the time of the routine blood collection to screen for gestational diabetes (mean 27.9 weeks gestation; range 16.4–36.9 weeks). All had assessments of hypertensive outcomes. The institutional review boards of participating institutions approved the study.

Blood samples were initially refrigerated and then we separated the plasma and stored aliquots at −80°C. We analyzed each sample in duplicate for 25(OH)D concentration, once using an automated chemiluminescence immunoassay (13) and once using a manual radioimmunoassay (r=0.81)(14). As we have done in prior studies, we averaged the two values to obtain more stable estimates of 25(OH)D level(15, 16). Analyses using either the chemiluminescence data only or radioimmunoassay data only yielded similar results but with wider confidence intervals (Supplementary Tables 1). For quality control, the laboratory used U.S. National Institute of Standards and Technology level 1. We categorized vitamin D status according to clinical guidelines (17–19), as we have done previously: < 25, 25 – < 50, 50 – < 75, and ≥ 75 nmol/L.

For the endpoints preeclampsia and gestational hypertension, as described previously (11), we reviewed outpatient charts for blood pressure and urine protein results. Briefly, we defined gestational hypertension as elevated blood pressure (SBP≥140 or DBP≥90) on 2 or more occasions on or after 20 weeks of gestation, and preeclampsia as elevated blood pressure plus concurrent proteinuria (1+ twice > 4 hours but < 7 days apart or ≥ 2+ once) on or after 20 weeks gestation(20).

We performed unadjusted and then multivariable-adjusted multinomial logistic regression models to examine associations of 25(OH)D categories and continuous 25(OH)D values with odds of preeclampsia or gestational hypertension. We used categories of 25(OH)D to assess potential non-linear associations of 25(OH)D and hypertensive disorders. We included as covariates factors that could confound the association between 25(OH)D status and hypertension: maternal age, race/ethnicity, smoking, education, marital status, parity, season of last menstrual period and gestational age at time of blood draw. Because 25(OH)D levels are inversely associated with adiposity(21), we added prepregnancy body mass index and gestational weight gain (up to the time of the blood draw) to adjusted models in a separate step. To further evaluate potentially modifiable factors that might be related to 25(OH)D levels, we then added second trimester physical activity and dietary intakes of calcium and fish to the adjusted models. We defined physical activity as self-reported hours

spent walking or performing light-to-moderate or vigorous activity in the three months before the second trimester blood draw(22). We estimated dietary intakes of calcium, vitamin D and fish from a validated, semi-quantitative food frequency questionnaire(23, 24). We were missing data on 6 women for body mass index, 145 for dietary intake, 11 for marital status, 285 women for physical activity, 10 for race/ethnicity, 8 for smoking, 289 for 25(OH)D levels, and 31 for weight gain. To address missing data, we used chained equations to multiply impute values(25–27). We generated 50 imputed datasets and combined them in the reported results(28). We used all 2128 Project Viva subjects in the imputation process(26), but the analysis sample included only the 1591 eligible participants(25). All analyses were performed using SAS software(version 9.3; SAS Institute Inc, Cary, NC).

## RESULTS

Fifty-six of the 1591 participants (3.5%) had preeclampsia and 109 of 1591 (6.9% had gestational hypertension. Participant characteristics and 25(OH)D categories are included in Table 1. Mean 25(OH)D level was 58 nmol/L(standard deviation 23). There was little evidence of differing odds of preeclampsia or gestational diabetes by 25(OH)D category (Table 2) . Expressing 25(OH)D as a continuous variable, we also did not detect an association with preeclampsia in unadjusted (odds ratio [OR] per 25 nmol/L 0.89, 95% confidence interval [CI]: 0.62, 1.26) or fully-adjusted models (1.14, 95% CI: 0.77, 1.67) (Table 2). In contrast, for each 25 nmol/L increment in 25(OH)D, we observed a higher odds of gestational hypertension in unadjusted models (OR 1.25, 95% CI: 0.98, 1.58) and fully-adjusted models (OR 1.32, 95 % CI: 1.01, 1.72). Restricting to mothers whose blood was drawn prior to 30 weeks' gestation (n=1504) made little difference. There was no association with preeclampsia (adjusted OR 1.11, 95% CI 0.75, 1.66), but higher 25(OH)D levels were associated with higher odds of gestational hypertension (adjusted OR 1.37, 95% CI: 1.04, 1.80).

This finding might result from reverse causality if women who were diagnosed with gestational hypertension after 20 weeks' gestation subsequently increased their vitamin D intake. However, on analysis of food frequency questionnaire data, women with gestational hypertension had similar mean vitamin D intake from food and supplements combined in first (538 IU per day [SD 257]) and second (574 IU per day [SD 156]) trimesters. In contrast, normotensive women had a larger increase in vitamin D intake from 487 IU (SD 206) to 595 IU (187). Additionally, just 43% of women with gestational hypertension increased their energy-adjusted vitamin D intake from foods and supplements by more than 100 IU between the first and second trimesters compared to 49% of normotensive women.

## DISCUSSION

In this cohort study, we did not find an association between 25(OH)D level at mean of 27.9 weeks gestation and risk of preeclampsia. By contrast, we did find an association between higher pregnancy 25(OH)D levels and increased risk of gestational hypertension; for each 25 nmol increment of 25(OH)D, the odds of GH were 33% higher, a clinically important effect size.

The lack of an association between 25(OH)D level and preeclampsia may be because we obtained samples later in pregnancy than other studies(4, 5) or because we did not focus on severe preeclampsia which has been more consistently linked to vitamin D status(4, 6, 9). In one meta-analysis that included studies irrespective of adjustment for confounding variables, Wei and colleagues reported that women with 25(OH)D levels <50 nmol/L (vs. higher) had higher odds of preeclampsia(crude OR 2.09, 95% CI: 1.50–2.90)(29). In another meta-analysis that adjusted for unspecified "critical confounders," Aghajafari et al. reported a weaker, and nonsignificant association (adjusted OR 1.51, 95% CI: 0.89 to 2.57), albeit for a different cutpoint, 25(OH)D levels < 75 nmol/L vs. higher(30). In a third meta-analysis, Tabesh and colleagues reported a significant association between low 25(OH)D and preeclampsia association with a cutpoint of <50 nmol/L but not <38 nmol/L vs. higher(31). Both Tabesh et al. an Aghajafari et al. raised the possibility of publication bias. Our null results are consistent with other studies that incorporated control for covariates(32, 33). Wetta et al. performed a nested case-control study comparing 89 women with preeclampsia that developed before 37 weeks' gestation and 177 controls. They measured 25(OH)D concetnrations from serum obtained between 15 and 21 weeks' gestation and found that mean 25(OH)D levels did not differ in preeclamptic cases (68 nmol/L) and controls (71 nmol/L) ($P$= 0.92) (32). Adjustment for confounding variables made did not change their estimates. Additionally, Yu et al analyzed serum 25(OH)D levels at 11–13 weeks in 90 cases that developed early (before 34 weeks' gestation) and late preeclampsia (after 34 weeks' gestation) and 1000 controls and found no difference in median 25(OH)D level ($P$=0.14 and 0.23 comparing early and late preeclampsia cases to controls, respectively) (33).

The increased risk of gestational hypertension we observed among women with higher 25(OH)D levels was somewhat surprising. We are aware of only one other cohort study that examined gestational hypertension separately from preeclampsia. Shand et al. reported a lower OR of 0.6 but with a wide 95% CI(0.2, 1.67) for gestational hypertension among women with 25(OH)D level >37.5 nmol/L vs. lower(34). Their OR was in the opposite direction of ours, but their study was much smaller; just 22 of 221 participants developed gestational hypertension vs. our 109 of 1591. Most prior studies of vitamin D status and preeclampsia used a case-control design(4–6) and thus excluded women with gestational hypertension or included them in the non-affected comparison group(7). In contrast we assessed the 3 distinct outcome groups: preeclampsia, gestational hypertension, and normal. We do not have a biological explanation for our finding of an association between higher 25(OH)D and gestational hypertension risk. In addition to chance or unmeasured confounding, we considered whether it could be due to reverse causation. It is possible that when women were diagnosed or in the process of being diagnosed with gestational hypertension they became more adherent to their multivitamin intake which led to higher 25(OH)D levels. However, normotensive women increased their mean intake of vitamin D more than hypertensive women between the first and second trimesters. While it is possible that this would indicate that increasing vitamin D intake throughout pregnancy could be helpful, in the setting of higher 25(OH)D levels being associated with gestational hypertension, such an assertion is premature. Furthermore, while gestational hypertension can develop any time after 20 weeks' gestation,(35) 80% of diagnoses are made after 36

weeks' gestation (36), well after the timing of blood collection in our cohort(mean 27.9 weeks gestation), which also argues against reverse causation. Physiologic reverse causation cannot be excluded. For example if placental expression of 1-alpha-hydroxylase increased in the setting of hypertension, it is possible that 25(OH)D levels would be higher in hypertensive women.

Our study had several strengths including a prospective cohort design, with inclusion of women with gestational hypertension in addition to preeclampsia. Moreover, outcome data were based on vital signs rather than clinical diagnosis, and we had detailed information on multiple potential confounding variables. The main limitation was too few cases (n=2) to analyze severe preeclampsia (defined as very elevated blood pressure (SBP ≥160 or DBP ≥110) on 2 or more occasions on or after 20 weeks of gestation in the presence of proteinuria), which limits comparison with some published case-control studies(4, 6, 9). An additional limitation is that we did not measure first trimester 25(OH)D concentrations, which may be more relevant to the pathogenesis of preeclampsia. Also, although the prevalence of preeclampsia and gestational hypertension were similar to population-based data from Massachusetts obtained from hospital discharge data(37), the small number of women with these outcomes especially at low 25(OH)D levels resulted in wide confidence intervals. We measured 25(OH)D from blood obtained for clinical reasons and thus had a wide-range of gestational ages at which our blood was analyzed. Only 51 women both delivered before 37 weeks' gestation and did not have plasma analyzed for 25(OH)D levels and thus were not included in this analysis. In this subset, 4 (7.8%) had gestational hypertension and 7 (13.7%) had preeclampsia. Lastly, we recognize the continued uncertainty as to the optimal method of measuring 25(OH)D levels(1, 38–40), however, we used established assays (chemiluminescence(13) and radioimmunoassay(14)) to estimate the 25(OH)D levels of each participant.

In conclusion, we did not detect an association between 25(OH)D levels obtained at mean of 27.9 weeks gestation and preeclampsia. Counter to our expectations, we found that each additional 25 nmol/L in 25(OH)D level was associated with 33% higher risk of gestational hypertension. This finding may be due to chance. If the association is confirmed in other studies, the magnitude of the association could be of concern as typical supplements contain 600 IU, enough to raise 25(OH)D levels by about 15 nmol/L(41) which could raise an individual's odds of gestational hypertension based on our data by 20%. While complications of pregnancies complicated by preeclampsia clearly exceed those of gestational hypertension, women with hypertension alone are more likely to be delivered late preterm or early term compared to normotensive controls (42) and remain at risk after pregnancy of developing cardiovascular disease (43). Trials of vitamin D supplementation during pregnancy should be alert to a possible increase in risk of gestational hypertension and should be sure to study this outcome in addition to preeclampsia.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Abbreviations

| | |
|---|---|
| **25(OH)D** | 25-hydroxyvitamin D |
| **BMI** | body mass index |
| **CI** | confidence interval |
| **OR** | odds ratio |

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**Table 1**

Characteristics of Participants, Overall and by Category of 25-hydroxyvitamin D Concentration. Data From 1591[a] Pregnant Women in Project Viva.

| | | Category of plasma25(OH)D (nmol/L) | | | | |
|---|---|---|---|---|---|---|
| | **Overall n=1591** | **< 25 n=81** | **25 -<50 n=472** | **50 -<75 n=743** | **≥75 n=295** | |
| | | **Mean (Standard Deviation)** | | | | ***P* value** |
| Plasma 25(OH)D (nmol/L) | 58 (23) | 20 (18) | 39 (15) | 62 (11) | 90 (37) | <0.0001 |
| Maternal age at enrollment (years) | 32.1 (5.0) | 29.2 (6.7) | 31.5 (5.6) | 32.5 (4.6) | 32.9 (4.8) | <0.0001 |
| Prepregnancy body mass index (kg/m$^2$) | 24.8 (5.4) | 28.8 (8.2) | 25.7 (6.4) | 24.1 (5.0) | 23.6 (4.7) | <0.0001 |
| Physical activity during pregnancy (hours/week) | 7.3 (8.2) | 9.6 (11.4) | 7.4 (8.4) | 7.0 (8.2) | 7.2 (7.2) | 0.11 |
| Gestational weight gain up to blood draw (kg) | 10.4 (4.3) | 8.6 (6.1) | 10.3 (4.9) | 10.7 (4.0) | 10.0 (4.4) | 0.13 |
| Second trimester calcium intake (mg/day) | 1427 (407) | 1250 (435) | 1328 (433) | 1480 (430) | 1499 (411) | <0.0001 |
| Second trimester fish intake (servings/week) | 1.6 (1.5) | 1.9 (2.2) | 1.6 (1.6) | 1.5 (1.5) | 1.6 (1.5) | 0.54 |
| | | n (%) | | | | |
| Race/ethnicity | | | | | | <0.0001 |
| Black | 225 (14.1) | 42 (51.4) | 93 (19.8) | 68 (9.2) | 22 (7.3) | |
| Hispanic | 96 (6.0) | 10 (12.5) | 37 (7.9) | 37 (5.0) | 11 (3.8) | |
| White | 1143 (71.8) | 21 (26.0) | 293 (62.0) | 579 (77.9) | 250 (84.9) | |
| Other | 127 (8.0) | 8 (10.1) | 49 (10.3) | 59 (7.9) | 12 (4.0) | |
| Smoking status | | | | | | 0.01 |
| Never | 1086 (68.2) | 60 (74.4) | 316 (67.0) | 508 (68.3) | 201 (68.5) | |
| Former | 317 (19.9) | 9 (10.7) | 88 (18.6) | 152 (20.4) | 69 (23.4) | |
| During pregnancy | 188 (11.8) | 12 (14.9) | 68 (14.4) | 84 (11.3) | 24 (8.1) | |
| Education | | | | | | <0.0001 |
| Less than college graduate | 517 (32.5) | 56 (68.8) | 190 (40.2) | 208 (28.0) | 64 (21.6) | |
| College graduate | 1074 (67.5) | 25 (31.2) | 282 (59.8) | 535 (72.0) | 231 (78.4) | |
| Marital status | | | | | | <0.0001 |
| Single | 109 (6.9) | 16 (19.2) | 45 (9.6) | 36 (4.8) | 12 (4.2) | |
| Married or cohabitating | 1482 (93.1) | 66 (80.8) | 427 (90.4) | 707 (95.2) | 282 (95.8) | 0.04 |
| Parity | | | | | | |
| 0 | 768 (48.3) | 28 (33.9) | 219 (46.4) | 376 (50.6) | 145 (49.3) | |
| > 0 | 823 (51.7) | 54 (66.1) | 253 (53.6) | 367 (49.4) | 149 (50.7) | |

| | Category of plasma25(OH)D (nmol/L) | | | | | |
|---|---|---|---|---|---|---|
| | **Overall n=1591** | **< 25 n=81** | **25 -<50 n=472** | **50 -<75 n=743** | **≥75 n=295** | |
| | **Mean (Standard Deviation)** | | | | | ***P* value** |
| Season of last menstrual period | | | | | | <0.0001 |
| Winter | 315 (19.8) | 12 (14.4) | 69 (14.5) | 149 (20.1) | 85 (29.0) | |
| Spring | 388 (24.4) | 20 (24.1) | 121 (25.6) | 186 (25.1) | 61 (20.7) | |
| Summer | 434 (27.3) | 18 (22.4) | 130 (27.6) | 204 (27.4) | 82 (27.7) | |
| Fall | 454 (28.5) | 31 (39.1) | 152 (32.2) | 204 (27.4) | 67 (22.6) | |

Abbreviation: 25(OH)D, 25-hydroxyvitamin D

**Table 2**

Associations of 25-hydroxyvitamin D Concentration with Hypertensive Disorders of Pregnancy. Data from 1591 Participants of Project Viva.

| | | Model 1 | | Model 2 | | Model 3 | | Model 4 | |
|---|---|---|---|---|---|---|---|---|---|
| **Outcome** | **Cases / Eligible** | **OR** | **95 % CI** | **OR** | **95 % CI** | **OR** | **95 % CI** | **OR** | **95 % CI** |
| **Preeclampsia** | 56/1591 | | | | | | | | |
| Continuous 25(OH)D (per 25 nmol/L) | | 0.89 | 0.62, 1.26 | 0.94 | 0.64, 1.39 | 1.15 | 0.79, 1.69 | 1.14 | 0.77, 1.67 |
| Category of 25(OH)D | | | | | | | | | |
| < 25 nmol/L | 4/81 | 1.30 | 0.37, 4.53 | 1.08 | 0.28, 4.23 | 0.57 | 0.13, 2.44 | 0.60 | 0.14, 2.56 |
| 25 - <50 nmol/L | 16/472 | 1.03 | 0.52, 2.05 | 0.97 | 0.47, 1.98 | 0.78 | 0.37, 1.61 | 0.79 | 0.38, 1.65 |
| 50 - <75 nmol/L | 25/743 | 1.00 | (ref) | 1.00 | (ref) | 1.00 | (ref) | 1.00 | (ref) |
| ≥ 75 nmol/L | 11/295 | 1.12 | 0.52, 2.42 | 1.16 | 0.53, 2.55 | 1.33 | 0.59, 2.99 | 1.34 | 0.60, 3.01 |
| **Gestational hypertension** | 109/1591 | | | | | | | | |
| Continuous 25(OH)D (per 25 nmol/L) | | 1.25 | 0.98, 1.58 | 1.18 | 0.91, 1.54 | 1.31 | 1.00, 1.70 | 1.32 | 1.01, 1.72 |
| Category of 25(OH)D | | | | | | | | | |
| <25 nmol/L | 2/81 | 0.33 | 0.05, 2.13 | 0.47 | 0.07, 3.24 | 0.36 | 0.05, 2.54 | 0.34 | 0.05, 2.40 |
| 25 - < 50 nmol/L | 33/472 | 1.08 | 0.66, 1.78 | 1.16 | 0.69, 1.95 | 1.02 | 0.60, 1.72 | 0.98 | 0.57, 1.66 |
| 50 - <75 nmol/L | 48/743 | 1.00 | (ref) | 1.00 | (ref) | 1.00 | (ref) | 1.00 | (ref) |
| ≥ 75 nmol/L | 26/295 | 1.39 | 0.79, 2.43 | 1.37 | 0.78, 2.42 | 1.46 | 0.82, 2.60 | 1.46 | 0.82, 2.60 |

**Model 1**. Unadjusted

**Model 2**. Adjusted for maternal age, race/ethnicity, smoking, education, marital status, parity, season of last menstrual period, and gestational age at blood draw

**Model 3**. Model 2 + pre-pregnancy BMI and gestational weight gain (up to the time of blood collection)

**Model 4**. Model 3 + 2$^{nd}$ trimester physical activity and 2$^{nd}$ trimester dietary intakes of fish and calcium

**Abbreviations**: 25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; CI, confidence interval; OR, odds ratio

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