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Plasma 25-OH-Vitamin D Levels in Early Onset, Severe Preeclampsia

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Abstract

OBJECTIVE—Vitamin D deficiency has been linked to adverse pregnancy outcomes. The purpose of this investigation was to assess total 25-hydroxyvitamin D (25-OH-D) levels at diagnosis of early-onset severe preeclampsia (EOSPE).

STUDY DESIGN—Following IRB approval, subjects with EOSPE (< 34 weeks gestation with severe preeclampsia) were enrolled in this case-control investigation in a 1:2 ratio with gestation matched, contemporaneous controls. Demographic and outcome information was collected for each subject. Plasma total 25-OH-D levels were determined by radioimmunoassay and reported in ng/mL. Results were analyzed by Mann-Whitney U and multivariable regression.

RESULTS—Subjects with EOSPE (n=50) were noted to have decreased total 25-OH-D levels relative to healthy controls (n=100; p<0.001). This difference in total 25-OH-D remained significant after controlling for potential confounders.

CONCLUSION—Total 25-OH-D is decreased at diagnosis of EOSPE. Further study is needed to understand the impact of vitamin D deficiency on pregnancy outcomes.

Keywords

25-hydroxyvitamin D; adverse pregnancy outcome; preeclampsia; Vitamin D

Introduction

With the resurgence of rickets in the 1990's, the scientific community has focused increased attention on vitamin D.[1] Vitamin D is a steroid hormone that is primarily derived from synthesis in the skin through exposure to ultraviolet B (UV-B) radiation. Vitamin D undergoes hydroxylation in the maternal liver to form 25-OH-vitamin D (25-OH-D) which is an inactive, supply form of this hormone. The active form of vitamin D (1,25-$(OH)_2$-vitamin D) results from the activity of 1-α-hydroxylase in the maternal kidney or placenta.[2]

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Because the half life of 1,25-$(OH)_2$-vitamin D is only several minutes, the more accurate assessment of an individual's vitamin D status is determined through measurement of 25-OH-D which has a half life of about three weeks.[3] An adequate 25-OH-D level, has been determined to be 32 ng/mL or greater. Vitamin D insufficiency and deficiency are diagnosed at levels of less than 32 ng/mL and less than 20 ng/mL 25-OH-D, respectively.[4] Using these criteria, vitamin D deficiency is very common in pregnancy with up to 50% of individuals classified as vitamin D deficient.[5–8] Vitamin D deficiency has also been noted to have increased incidence among persons of African American race. This deficiency is likely secondary to increased melanin content preventing adequate exposure to UV-B radiation for conversion of 7-dehydrocholesterol within the skin to vitamin D.[2, 7–8] With an increased incidence of vitamin D deficiency documented in these populations, there is heightened awareness of the potential impact on pregnancy outcome.

Vitamin D deficiency has been linked to adverse perinatal outcomes in recent epidemiologic data. Rickets, a hypomineralization of the skeletal structure, is a well described phenomenon of vitamin D deficiency.[1] More recently, data supports associations of vitamin D deficiency and preterm birth, decreased birth weight, and hypertensive disease in pregnancy.[9–14] Authors speculate that these conditions may result from the lack of action of vitamin D in immunosuppression or placental development among deficient patients.[9, 15–17] Thus, vitamin D deficiency may be involved in the pathophysiology of preeclampsia.

Preeclampsia remains poorly characterized with regard to pathophysiology involved in the development of hypertensive disease in pregnancy. Preeclampsia has been described as a two stage disease in which stage I is heralded by poor placental invasion, development, and remodeling. Stage II develops later and involves the clinical recognition of preeclampsia in the form of maternal hypertension, proteinuria, and end-organ disease.[18] Data suggesting an association between preeclampsia and vitamin D deficiency is now developing. In a recent investigation of 25-OH-D levels in pregnancy prior to the onset of preeclampsia, vitamin D levels assessed in early pregnancy were found to be lower among women who eventually developed preeclampsia. In fact, these investigators noted a two-fold increased risk for preeclampsia when serum vitamin D levels decreased by 20 ng/mL after adjusting for confounders.[10] Another population based investigation in Norway among 23,423 nulliparious women found that vitamin D intake of 15–20 micrograms per day relative to less than 5 micrograms per day was associated with a 27% reduction in the risk for preeclampsia.[13] Both of these investigations suggest an association between vitamin D deficiency and development of preeclampsia.

Early onset, severe preeclampsia (EOSPE) contributes 15% of the preterm births in the United States per annum and may also have ongoing increased risks for vascular disease in later life.[19–20] These women and their fetuses are also recognized to be at the greatest risk for adverse outcomes in pregnancy with a 20-fold increased risk for maternal mortality and several-fold increased risk for neonatal morbidity or mortality dependent upon gestational age at delivery and presence of growth restriction in the fetus.[21] Thus, this group may serve as a target population for improving outcomes of preeclampsia.

The purpose of this investigation was to examine the maternal plasma level of 25-OH-D in cases of EOSPE relative to controls that experience a normal pregnancy outcome. The hypothesis for this investigation was that women who were diagnosed with EOSPE would have decreased 25-OH-D levels relative to controls that experience a normal pregnancy outcome. This association would further support the significance of vitamin D deficiency in preeclampsia.

Methods

The Institutional Review Board at the Medical University of South Carolina (MUSC) approved this case control investigation. Patients included in this investigation had to consent for collection of demographic and outcome data as well as venipuncture for collection of plasma used in 25-OH-D analysis. Cases were recruited from the inpatient Labor and Delivery unit at the Medical University of South Carolina after confirmation of a diagnosis of EOSPE. EOSPE cases had to meet the American College of Obstetrics and Gynecology criteria for severe preeclampsia and present with this diagnosis prior to 34 weeks completed gestational age.[22] Patients with EOSPE were excluded if they also had a diagnosis of chronic hypertension, pregestational diabetes, renal disease, lupus, or multiple gestation. Contemporaneous control patients with a singleton gestation were recruited in a 2:1 match from the ambulatory care setting. Control patients were matched according to race and gestational age at the time of sample collection for the EOSPE case. Controls were followed through pregnancy to assess pregnancy outcomes in this cohort of patients. The control patients were excluded for the same exclusion diagnoses for EOSPE cases. Demographic data were collected on each case and control at the time of plasma collection which included gestational age, maternal age, maternal prepregnancy body mass index (BMI), maternal systolic and diastolic blood pressure, and urine protein. Plasma was collected from EOSPE cases at the time of diagnosis. The two gestation matched control samples were also obtained at a similar (within one week) gestational age for each EOPSE case. Plasma was collected in the BD P100 v1.1, EDTA vacutainer tube (Becton Dickinson, Franklin Lakes, NJ) which contains a protease inhibitor cocktail. Samples were processed and frozen in aliquots within thirty minutes of collection from each subject. The antepartum plasma sample collected at the time of diagnosis in EOSPE or matched gestational age for controls was assessed for total 25-OH-D in ng/mL using double antibody radioimmunoassay (DiaSorin, Stillwater, MN). In our lab, this assay has a less than 10% inter-assay and intra-assay reliability. Vitamin D status was reported for both EOSPE and control groups according to the following 25-OH-D cutpoints: normal > 32 ng/mL; insufficient ≥20 and ≤32 ng/mL; and deficient < 20 ng/mL.[2] Using a sample size of 50 patients with EOSPE compared to 100 controls would allow detection of a 25% difference in 25-OH-D with 80% power given an alpha of 0.05. Following delivery, outcome data were collected on both EOSPE cases and control patients that included birth weight, gestational age at delivery, and an assessment of intrauterine growth restriction (IUGR) based on less than 10th%ile birth weight as assessed by gestational age at delivery.[23]

Results of continuous and categorical variables were reported as median (25 percentile to 75 percentile) and percentage by case or control group, respectively. Bivariable analysis was conducted using the Mann Whitney U test for examination of continuous variables (maternal age, prepregnancy BMI, gestational age at plasma sample collection, gestational age at delivery, mean arterial pressure at sample collection, birth weight, and plasma 25-OH-D levels) by case or control group. Proportions were compared by case or control group using chi-square test. Unadjusted and adjusted odds ratios and associated 95% confidence intervals were calculated for each covariate based on fitted simple and multiple logistic regressions for the outcome EOSPE. A multiple logistic regression was conducted to estimate the effect of plasma 25-OH-D level on the risk EOSPE with the following additional variables included in the model: prepregnancy body mass index, maternal age, African American race, and gestational age at plasma sample collection. Continuous variables were assessed for linearity in the logit and transformed as necessary. Model adequacy was assessed using the Hosmer Lemeshow goodness-of-fit (GOF) test. The area under the receiver operator characteristic (ROC) curve was used to assess the predictive accuracy of the fitted multivariable model. All statistical tests were two-sided with alpha set at 0.05 to control for Type I error. Data analysis was performed with SAS v.9.2 (SAS, Cary,

NC). A secondary analysis of 25-OH-D level was examined by race and EOSPE status. Comparison of means by these groups was accomplished by Tukey-Kramer test.

Results

Fifty patients with EOSPE and 100 matched controls were consented and included in this investigation. Pregnancy demographic and outcomes are summarized by EOSPE or control pregnancy in Table 1. (Table 1) Patients with EOSPE were noted to be younger with a greater prepregnancy BMI. As expected, all cases of EOSPE were delivered preterm due to their disease with a median gestational age at delivery of 29 weeks relative to 39 weeks in the control group. The hypertension encountered in the EOSPE group was severe as noted by a median mean arterial pressure of 125 mmHg relative to 78 mmHg at delivery for healthy controls. The incidence of IUGR in the EOSPE group was significantly greater relative to healthy controls (42% vs. 10%; $p < 0.001$). Plasma 25-OH-D was significantly decreased among patients with EOSPE compared to healthy controls (18 vs. 32 ng/mL; $p < 0.001$) as shown in Figure 1. (Figure 1)

To assess the effect of maternal plasma 25-OH-D on the odds of having a diagnosis of EOSPE, a multiple logistic regression analysis was performed. Model fit and predictive accuracy were determined to be adequate by Hosmer-Lemeshow GOF ($p=0.35$) and area under the ROC curve (AUC = 0.82), respectively. Results of this analysis are presented in Table 2. (Table 2) After adjusting for all covariates, the association of increased maternal plasma 25-OH-D levels and decreased risk for diagnosis of EOSPE remained statistically significant. Specifically, a 10 ng/mL increase in 25-OH-D yields a 63% decrease in the odds of EOSPE among these patients and would move 83% of this group into either the normal or insufficient category of Vitamin D status. A 1-unit increase in the prepregnancy BMI was also associated with an 8% increase in the odds of EOSPE. African American race was noted to carry a 12-fold increased odds of EOSPE in this investigation. There was no significant effect of the timing of plasma sampling on the odds of EOSPE as expected given that patients were matched for this characteristic in this case control investigation. Upon examination of the bottom quartile of maternal plasma 25-OH-Vitamin D (≤19.6 ng/mL), there was a 3.6-fold increased odds of diagnosis of EOSPE among this group (OR 3.60 [1.71–7.58], $p < 0.001$).

A secondary analysis of 25-OH-D plasma levels was also conducted by race given the increased odds for EOSPE in African Americans seen in the regression analysis. In Figure 2, both African American and Caucasian women who developed EOSPE had decreased levels of 25-OH-D relative to race-matched controls. (Figure 2) However, African Americans who developed EOSPE were noted to have the lowest mean plasma level of 25-OH-D among groups.

Comment

In this investigation, we examined plasma 25-OH-D among those patients who experience EOSPE, one of the most serious forms of hypertensive disease in pregnancy. This study found significantly decreased levels of 25-OH-D at the time of diagnosis of EOSPE. To our knowledge, this is the first report of maternal vitamin D status among patients with EOSPE. This is a significant strength of this investigation as future clinical trials will most benefit this population which contributes 15% of the preterm births observed in the U.S. per annum and significant maternal-fetal morbidity and mortality.[19, 21] The observations of decreased vitamin D status among African Americans who experienced EOSPE and the twelve-fold increased risk for diagnosis of EOSPE in the regression model suggests vitamin D deficiency may be a factor in explaining their disproportionate incidence of adverse

pregnancy outcomes. This observation is particularly important given these women also had the most decreased vitamin D levels among the population studied (Figure 2). In fact, their 25-OH-D levels in the control group were below that of Caucasian women who were diagnosed with EOSPE. This observation may suggest a threshold effect of Vitamin D deficiency effect upon EOSPE. Future investigations in longitudinal populations of African American women may assist in a better understanding of this observation. Alternatively, African American women may have unrecognized genetic or epigenetic factors that predispose them to EOSPE. Thus, this population may also benefit most from future prospective randomized trials of vitamin D supplementation for improved pregnancy outcomes.

The further examination of vitamin D deficiency and preeclampsia is warranted as there are multiple potential mechanisms whereby a deficiency of vitamin D may contribute to the pathophysiology of preeclampsia. Vitamin D has been implicated in providing critical signals in gene regulation and expression in early placental development among placental trophoblast models.[9, 15–16, 24–25] In vitamin D deficiency, there is concern that the lack of these signals may play a critical role in Stage I of placental development that leads to the ultimate recognition of Stage II and a diagnosis of preeclampsia.[15, 18, 25] It is not known exactly how these signals might lead to the ultimate diagnosis of preeclampsia, and thus, epidemiological observations from incidence of preeclampsia associated with vitamin D deficiency currently lack fully defined pathways through which biomolecular mechanisms explain this relationship. However, based on the observations of this and other studies that link vitamin D deficiency and preeclampsia, vitamin D supplementation remains a possible target for intervention and possible improved pregnancy outcomes. [10, 13]

This study has important limitations that should be noted and addressed in future investigations of these populations. First, there was no assessment of baseline dietary vitamin D intake or sun exposure. Also, given that prenatal vitamins contain 400 IU of vitamin D, compliance with prenatal vitamin use should be measured in populations where vitamin D is considered. Alternations in these factors may result in effects not measured in our investigation.

This investigation cannot be used alone to assert a role for vitamin D supplementation in pregnancy in order to improve pregnancy outcomes. Given the collection of samples at the time of diagnosis of EOSPE, this investigation cannot determine the effect of this disease on levels of vitamin D at diagnosis. It is also important to point out that acute effects of preeclampsia on vitamin D physiology are not described in the literature and this could also impact levels assessed at the time of disease. A longitudinal cohort study would best address the impact of hypertensive disease on vitamin D physiology. However, prior investigations have demonstrated low second trimester maternal vitamin D as an independent predictor of future onset of term preeclampsia.[10, 13] Thus, additional well-designed, prospective, randomized trials of supplementation that control for dietary exposure and race will be necessary to determine a potential role for vitamin D in the prevention of preeclampsia.

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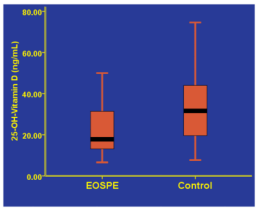

Figure 1. Maternal Plasma 25-OH-D in EOSPE verses Controls

Patients with EOSPE had significantly decreased levels of 25-OH-D relative to healthy control pregnancies matched for gestational age at plasma sampling (median 25-OH-D 18 ng/mL vs. 32 ng/mL; $p<0.001$). P value was determined by Mann Whitney U test.

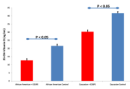

Figure 2. Plasma 25-OH-D by Race and EOSPE Status

African American and Caucasian women with EOSPE were noted to have decreased plasma levels of 25-OH-D relative to matched race, control pregnancies. African American women were noted to have the lowest plasma 25-OH-D levels when compared to Caucasian women. Bars represent mean 25-OH-D levels (mean±SEM). (P values determined using Tukey-Kramer test).

Table 1

Demographics and Outcomes of Pregnancies Complicated by Early-Onset, Severe Preeclampsia vs. Controls

	EOSPE (n=50)	Control (n=100)	P value
Maternal age (years)	24 (21–30)	28 (23–32)	0.001 *
BMI (kg/m^2)	34 (27–38)	28 (24–32)	<0.001*
African American Race (%)	48%	46%	NS †
Nulliparous n (%)	54%	47%	NS †
Gestational age at sample collection (weeks)	29 (28–31)	29 (26–31)	NS *
Gestational age at delivery (weeks)	29 (28–32)	39 (37–40)	<0.001 *
Mean Arterial Pressure at Collection of Sample (mmHg)	125 (116–134)	78 (71–86)	< 0.001*
Birthweight (g)	1170 (880–1420)	3260 (2960–3630)	< 0.001*
IUGR n (%)	42%	10%	<0.001†
Vitamin D Status			0.005†
Normal (25-OH-D > 32ng/mL)	24%	47%	
Insufficient (25-OH-D 20–32 ng/mL)	22%	26%	
Deficient (25-OH-D < 20ng/mL)	54%	27%	
Plasma 25-OH-Vitamin D (ng/mL)	18 (13–31)	32 (20–44)	< 0.001*

% are provided by columns

BMI = body mass index (prior to pregnancy)

IUGR = intrauterine growth restriction (<10th%ile fetal growth for gestational age)

EOSPE = Early onset, severe preeclampsia

25-OH-D = 25-OH-vitamin D

*Mann Whitney U test

†Chi square test

Table 2

Unadjusted and Adjusted Odds Ratios for Early-Onset, Severe Preeclampsia

Variable	Unadjusted Analysis		Adjusted Analysis	
	Odds Ratio (95%CI)	P value*	Odds Ratio (95%CI)†	P value*
Maternal Plasma 25-OH-Vitamin D (per 10 ng/mL)	0.58 (0.43, 0.77)	<0.001	0.37 (0.22, 0.62)	<0.001
BMI (kg/m^2) (per 1 unit)	1.08 (1.03, 1.13)	0.003	1.08 (1.02, 1.15)	0.01
Maternal age (years)	0.89 (0.83, 0.96)	0.002	0.87 (0.80, 0.96)	0.004
African American Race	0.93 (0.46, 1.88)	NS	12.6 (3.1, 50.4)	<0.001
Gestational age at sample collection (weeks)	1.03 (0.82, 1.31)	NS	0.94 (0.70, 1.27)	NS

*Wald Chi square test

†Adjusted odds ratios and confidence intervals were adjusted for maternal plasma 25-OH-Vitamin D level, body mass index, maternal age, African American race, and gestational age at sample collection.

95%CI = 95 % Confidence Interval

BMI = prepregnancy body mass index

Hosmer-Lemeshaw p=0.35; ROC Curve area = 0.82