Plasma 25-hydroxyvitamin D levels in early-onset severe preeclampsia

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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: After institutional review board approval, we enrolled subjects with EOSPE (<34 weeks' gestation with severe preeclampsia) in this case-control investigation in a 1:2 ratio with gestation-matched, contemporaneous control subjects. Demographic and outcome information was collected for each subject. Plasma total 25-OH-D levels were determined by radioimmunoassay and reported in nanograms per milliliter. 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 control subjects (n = 100; $P <$ .001). This difference in total 25-OH-D remained significant after control 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.

Key words: 25-hydroxyvitamin D, adverse pregnancy outcome, preeclampsia, vitamin D

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With the resurgence of rickets in the 1990s, the scientific community has focused increased attention on vitamin D.[1] Vitamin D is a steroid hormone that is derived primarily from synthesis in the skin through exposure to ultraviolet 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] 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 approximately 3 weeks.[3] An adequate 25-OH-D level has been determined to be ≥32 ng/mL. Vitamin D insufficiency and deficiency are diagnosed at levels of <32 ng/mL and <20 ng/mL 25-OH-D, respectively.[4] With these criteria, vitamin D deficiency is very common in pregnancy; up to 50% of the women are 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 the result of increased melanin content that prevents adequate exposure to ultraviolet 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.

★ EDITORS' CHOICE ★

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 support associations of vitamin D deficiency and preterm birth, decreased birthweight, 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 pathophysiologic condition of preeclampsia.

Preeclampsia remains poorly characterized with regard to pathophysiologic elements involved in the development of hypertensive disease in pregnancy. Preeclampsia has been described as a 2-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

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disease.[18] Data that suggest an association between preeclampsia and vitamin D deficiency are now developing. In a recent investigation of 25-OH-D levels in pregnancy before the onset of preeclampsia, vitamin D levels that were assessed in early pregnancy were found to be lower among women who eventually experienced preeclampsia. In fact, these investigators noted a 2-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 nulliparous women found that vitamin D intake of 15-20 μg/day, relative to <5 μg/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 the 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 death and several-fold increased risk for neonatal morbidity or death, dependent on 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 control subjects who 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 control subjects who experience a normal pregnancy outcome. This association would further support the significance of vitamin D deficiency in preeclampsia.

Materials and Methods

The institutional review board at the Medical University of South Carolina approved this case-control investigation. Patients who were included in this investigation had to provide consent for the collection of demographic and outcome data and venipuncture for collection of plasma to be 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 have this diagnosis before 34 weeks of completed gestation.[22] Patients with EOSPE were excluded if they also had a diagnosis of chronic hypertension, pregestational diabetes mellitus, renal disease, lupus, or multifetal 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. Control subjects 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, maternal systolic and diastolic blood pressure, and urine protein. Plasma was collected from EOSPE cases at the time of diagnosis. The 2 gestation-matched control samples were also obtained at a similar (within 1 week) gestational age for each EOPSE case. Plasma was collected in a ethylenediaminetetraacetic acid vacutainer tube (BD P100 v1.1; Becton Dickinson Labware, Franklin Lakes, NJ) that contained a protease inhibitor cocktail. Samples were processed and frozen in aliquots within 30 minutes of collection from each subject. The antepartum plasma sample that was collected at the time of diagnosis in EOSPE or matched gestational age for control subjects was assessed for total 25-OH-D in nanograms per milliliter with the use of a double antibody radioimmunoassay (DiaSorin, Stillwater, MN). In our laboratory, this assay has a <10% interassay and intraassay 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] The use of a sample size of 50 patients with EOSPE compared with 100 control subjects would allow detection of a 25% difference in 25-OH-D, with 80% power given an alpha of .05. After delivery, outcome data were collected on both EOSPE cases and control patients that included birthweight, gestational age at delivery, and an assessment of intrauterine growth restriction that was based on <10th percentile birthweight, as assessed by gestational age at delivery.[23]

Results of continuous and categoric variables were reported as median (25 percentile to 75 percentile) and percentage by case or control group, respectively. Bivariable analysis was conducted with the Mann Whitney *U* test for examination of continuous variables (maternal age, prepregnancy body mass index, gestational age at plasma sample collection, gestational age at delivery, mean arterial pressure at sample collection, birthweight, and plasma 25-OH-D levels) by case or control group. Proportions were compared by case or control group with the chi-square test. Unadjusted and adjusted odds ratios and associated 95% CIs 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 with the use of the Hosmer Lemeshow goodness-of-fit test. The area under the receiver operator characteristic curve was used to assess the predictive accuracy of the fitted multivariable model. All statistical tests were 2-sided with the alpha set at .05 to control for type I error. Data analysis was performed with SAS software (version 9.2; SAS Institute Inc,