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Association of Modifiable and Nonmodifiable Factors with Vitamin D Status in Pregnant Women and Neonates in Oakland, CA

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ABSTRACT

There is little information on the contribution of modifiable vs nonmodifiable factors to maternal and neonatal vitamin D status in temperate regions of the United States. The purpose of this cross-sectional observation study conducted between December 2006 and February 2008 was to identify associations between observed and measured maternal characteristics and vitamin D status at term in pregnant women and their infants in a multiethnic community in Oakland, CA. Two hundred seventy-five pregnant women aged 18 to 45 years and carrying a singleton fetus were recruited and data from 210 mother-infant pairs were included in analyses. Analysis of covariance identified predictors of maternal and cord serum 25-hydroxyvitamin D [25(OH)D] in a multivariate model considering vitamin D intake, lifestyle factors, and skin pigmentation. Maternal serum 25(OH)D was significantly associated with season of delivery ($P=0.0002$), average daily D intake ($P=0.0008$), right upper inner arm pigmentation ($P=0.0035$), and maternal pre- or early-pregnancy body mass index (calculated as kg/m^2) ($P=0.0207$). The same factors were significant for cord serum 25(OH)D, which was highly correlated with maternal serum 25(OH)D ($r=0.79$; $P<0.0001$). During the year, 54% of mothers and 90% of neonates had 25(OH)D <30 ng/mL (<75 nmol/L). Of women taking daily prenatal vitamin/mineral supplements (400 IU vitamin D), 50.7% had serum 25(OH)D <30 ng/mL (<75 nmol/L). In conclusion, 25(OH)D <30 ng/mL (<75 nmol/L) was prevalent in mothers and neonates across racial groups and seasons, and vitamin D status was associated with both modifiable and nonmodifiable risk factors.

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During the last decade, there has been growing interest in the prevalence and consequences of vitamin D insufficiency during pregnancy. Despite the fact that pregnant women in most countries are encouraged to take a daily prenatal vitamin/mineral supplement containing vitamin D, a disturbingly high prevalence of hypovitaminosis D has been demonstrated among pregnant women in nearly all populations studied. Reported prevalence of maternal vitamin D deficiency at or near term has ranged from 5% to 20% in light-skinned populations to 30% to 70% among dark-skinned or veiled populations living at various latitudes (1-11).

It is well-established that 25-hydroxyvitamin D [25(OH)D] readily crosses the human placenta and that the vitamin D pool of the fetus depends on that of the mother (12). Early-life adverse outcomes associated with suboptimal in utero vitamin D status in both humans and animal models include rickets, compromised growth, increased incidence of acute lower respiratory infection, and altered brain morphology (13-16). There is some evidence that perinatal vitamin D insufficiency may increase offspring risk for later onset of multiple sclerosis, type 1 diabetes mellitus, schizophrenia, and colorectal, breast, and prostate cancers (17). Vitamin D deficiency during pregnancy has been associated with increased maternal risk of preeclampsia, gestational diabetes, and cesarean section (18-21).

To date, no studies of vitamin D status in pregnancy have taken place in northern California. Despite its temperate and sunny climate, northern California has not been spared from the resurgence in cases of rickets documented around the United States in the past decade (22-24). At Children's Hospital in Oakland, 59 cases of rickets were diagnosed from 2001-2006 (Suruchi Bhatia, MD, August 2006, unpublished data). Although compromised maternal vitamin D status during pregnancy predisposes offspring to clinical and subclinical deficiency, few studies have collected comprehensive data on predictors of maternal 25(OH)D concentrations, including skin pigmentation, clothing coverage, and dietary intake of vitamin D. No pregnancy studies have measured skin

pigmentation quantitatively. The purpose of the present study was to determine associations between risk factors and vitamin D status in pregnant women and their infants at delivery in a multiethnic community in Oakland, CA.

PARTICIPANTS AND METHODS

The University of California, Davis, Children's Hospital and Research Center Oakland, and Alta Bates Medical Center, Berkeley Institutional Review Boards approved the study protocol and all participants provided written informed consent. Recruitment took place between December 2006 and January 2008. No routine vitamin D screening was provided during antenatal care at the clinic or hospital.

Pregnant women were recruited from East Bay Perinatal Medical Associates in Oakland, CA, during a prenatal visit approximately 1 month before their due date. Women who were English-speaking, 18 to 45 years of age, planning to deliver at Alta Bates Medical Center, and carrying a singleton fetus were eligible to participate.

An interviewer-administered questionnaire was used to evaluate intake and lifestyle factors related to vitamin D status. Average daily dietary intake of vitamin D was calculated from food frequency using food composition data from the US Department of Agriculture National Nutrient Database (25). Participants were asked to estimate frequency and quantity of the main dietary sources of vitamin D (fatty fish, milk, breakfast cereals, fortified orange juice, eggs, and meat) consumed in the month before the interview. Questions concerning sun exposure included frequency and time spent in the sun as well as typical clothing cover and sunscreen use in the past month. Body surface area was calculated based on the Mosteller formula and percent of body surface exposed was estimated using the method described by Hall and colleagues (26). Participants were asked about prenatal vitamin/mineral supplement use (type, source, frequency of consumption, point in pregnancy when initiated), as well as frequency and dose of other vitamins, minerals, herbal supplements, or medications taken on a regular basis during the pregnancy. Other items in the questionnaire included smoking habits, racial origins of participant's parents and father of the baby, and height of the participant and father of the baby. Questionnaires were developed based on food frequency questions from a validated calcium and vitamin D block questionnaire and additional vitamin D exposure questions from a study undertaken by Hall and colleagues (26).

Skin pigmentation was measured at the right inner upper arm, right hand dorsum, and mid-forehead with a portable reflectometer (CR-400, Konica Minolta, Ramsey, NJ), which measures skin reflectance (L*) ranging from 0 (perfect black) to 100 (perfect white). Maternal venous blood was collected upon admission to the Alta Bates Medical Center Labor and Delivery Unit and cord blood collected immediately post delivery by ward nurses. Blood samples were kept at 4°C until centrifuged and serum was subsequently stored at −80°C until analysis. Batched samples of serum 25(OH)D were assayed monthly at ARUP Laboratories (Salt Lake City, UT) using the DiaSorin radioimmunoassay (DiaSorin Inc, Stillwater, MN). Medical records were reviewed to ascertain pre- or early pregnancy weight, length of gestation, pregnancy and delivery events, and infant birth weight. Maternal body mass index (BMI) was calculated from reported height and pre- or early-pregnancy weight recorded in the medical file.

STATISTICAL ANALYSES

Because no prior studies of vitamin D status in pregnant women or infants have been undertaken in northern California, a maximal sample size of 196 was calculated based on an estimated prevalence of 50% with α=.05 and δ=.07. Anticipating 25% attrition due to preterm delivery, withdrawal, loss to follow-up, or missed blood collection, 275 women were enrolled. Statistical analysis was performed using SAS software (SAS 9.1, 2003, SAS Institute Inc, Cary, NC). Data are presented as mean± standard deviation. Normality was tested using the Shapiro-Wilk statistic. Maternal BMI, body surface exposed, and cord serum 25(OH)D required log transformation to meet normality criteria. Skin pigmentation measurements at various sites were compared using paired *t* tests with a Bonferroni correction and differences in correlations with maternal and cord serum 25(OH)D were evaluated using Pitman's test for related variables. Analysis of covariance was used to identify significant predictors of maternal and cord serum 25(OH)D in a multivariate model and to adjust seasonal mean 25(OH)D for other variables remaining in the model. Potential confounders were added as independent variables in the model. Path analysis was conducted with sun exposure variables to identify contributors to the effect of season on serum 25(OH)D. Seasonal boundaries were based on sine curve analysis of 25(OH)D response and were defined as January 21 to April 20, April 21 to July 20, July 21 to October 20, and October 21 to January 20. For all tests, $P<0.05$ was considered significant.

RESULTS AND DISCUSSION

Of the 275 pregnant women enrolled between December 2006 and January 2008, 5 withdrew, 3 were lost to follow-up, 2 delivered outside Alta Bates Medical Center, 7 delivered before 37 weeks gestation, and 48 failed to undergo study blood collection at delivery. The main reason for failed blood collection was unfamiliarity of staff or relief nurses with study procedures. The remaining 210 women and their infants were included in analysis. Characteristics of women completing the study are shown in Table 1.

Maternal and cord concentrations of serum 25(OH)D were highly correlated (r=0.79; $P<0.0001$), with cord concentrations on average 61%±18% of paired maternal concentrations. The overall prevalence of 25(OH)D <15 ng/mL (<37.5 nmol/L) was 13.6% in mothers and 49.3% in neonates, and of 25(OH)D <30 ng/mL (<75 nmol/L), 54.4% in mothers and 90.0% in neonates.

Daily average maternal vitamin D intake, estimated from food and prenatal vitamin/mineral supplement frequency data, was significantly correlated with maternal and cord serum 25(OH)D (r=0.26; P=0.0001 and r=0.33; $P<0.0001$, respectively). Overall, 89.5% of study participants reported taking prenatal vitamin/mineral supple-