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Prepregnancy Obesity Predicts Poor Vitamin D Status in Mothers and Their Neonates[1,2]

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Abstract

Obesity is a risk factor for vitamin D deficiency, but this relation has not been studied among pregnant women, who must sustain their own vitamin D stores as well as those of their fetuses. Our objective was to assess the effect of prepregnancy BMI on maternal and newborn 25-hydroxyvitamin D [25(OH)D] concentrations. Serum 25(OH)D was measured at 4–21 wk gestation and predelivery in 200 white and 200 black pregnant women and in their neonates' cord blood. We used multivariable logistic regression models to assess the independent association between BMI and the odds of vitamin D deficiency [25(OH)D <50 nmol/L] after adjustment for race/ethnicity, season, gestational age, multivitamin use, physical activity, and maternal age. Compared with lean women (BMI <25), pregravid obese women (BMI ≥30) had lower adjusted mean serum 25(OH)D concentrations at 4–22 wk (56.5 vs. 62.7 nmol/L; $P < 0.05$) and a higher prevalence vitamin D deficiency (61 vs. 36%; $P < 0.01$). Vitamin D status of neonates born to obese mothers was poorer than neonates of lean mothers (adjusted mean, 50.1 vs. 56.3 nmol/L; $P < 0.05$). There was a dose-response trend between prepregnancy BMI and vitamin D deficiency. An increase in BMI from 22 to 34 was associated with 2-fold (95% CI: 1.2, 3.6) and 2.1-fold (1.2, 3.8) increases in the odds of mid-pregnancy and neonatal vitamin D deficiency, respectively. The rise in maternal obesity highlights that maternal and newborn vitamin D deficiency will continue to be a serious public health problem until steps are taken to identify and treat low 25(OH)D. J. Nutr. 137: 2437–2442, 2007.

Introduction

Maternal vitamin D deficiency is a major public health problem. Staggering rates of poor vitamin D status are found among pregnant mothers throughout the world (1–4). In a recent study, we found that ~3 in 4 African American and 1 in 2 white gravidas living in a northeastern United States city had mid-pregnancy serum 25-hydroxyvitamin D [25(OH)D][6] concentrations <80 nmol/L (5), the level considered "optimal" by experts (6,7). Maternal vitamin D deficiency is associated with preeclampsia (8) and reduced infant birth size (9), as well as adverse offspring health consequences such as rickets, skeletal problems, type 1 diabetes, schizophrenia, and asthma (6,10). Deep skin pigmentation, inadequate exposure to sunlight, winter season, and advanced age are among the strongest negative predictors of 25(OH)D levels (11); each is associated with a reduction in the skin's synthesis of cholecalciferol (D3) through UV B radiation, our most important source of the vitamin (11).

Obesity is another notable risk factor for vitamin D deficiency that may be related to a sequestering of D3 in adipose tissue (12). Although many investigators have demonstrated a difference in 25(OH)D concentrations by overweight status (13–28), we are unaware of any studies that have considered this in the context of pregnancy. Pregnancy is a time of particular susceptibility to vitamin D deficiency, because mothers must sustain their own vitamin D stores as well as those of their fetuses (29). Furthermore, the role of the hormonally active form of vitamin D in placental development and function, inflammation, angiogenesis, immunomodulation, and insulin sensitivity (30–34) points to the potential for vitamin D deficiency to partially mediate several of the well-known adverse pregnancy outcomes related to prepregnancy overweight, including miscarriage, preeclampsia, and gestational diabetes (35). An understanding of the relation between 25(OH)D and prepregnancy BMI may help to focus intervention efforts aimed at identifying and treating maternal and neonatal vitamin D deficiency and its related morbidities.

Our objective was to assess the independent effect of prepregnancy BMI on maternal 25(OH)D concentrations during gestation and on newborn 25(OH)D concentrations at birth.

Subjects and Methods

Data came from a prospective pregnancy cohort study conducted in outpatient clinics at Magee-Womens Hospital in Pittsburgh, Pennsylvania

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[6] Abbreviations used: 25(OH)D, 25-hydroxyvitamin D; D3, cholecalciferol; D2, ergocalciferol.
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and affiliated private practices from 1997 to 2001 (36). Women aged 14–44 y who were carrying singleton infants, free of preexisting medical conditions, and planning to deliver at Magee-Womens Hospital were eligible. After providing informed, written consent, all subjects completed an interviewer-administered questionnaire at enrollment to collect data on sociodemographic factors, medical history, and health behaviors. Nonfasting blood samples were collected at times of usual blood draws for clinical indications and banked. Medical records were abstracted to ascertain self-reported prepregnancy weight and measured height, antepartum and delivery events, and neonatal outcomes. We also collected and banked venous cord serum samples. Following delivery, women completed an interview-administered questionnaire about health habits in the last 3 mo of pregnancy. The study was approved by the University of Pittsburgh Institutional Review Board.

A total of 2211 women enrolled in the study and had complete data on pregnancy outcomes. We selected from this cohort a random sample of 200 white women and 200 black women who were nulliparous (i.e. had no previous pregnancies lasting >20 wk) and had an index pregnancy delivered at term (37–42 wk) with no diagnosis of preeclampsia and an infant whose birth weight was deemed appropriate for its gestational age (≥10th percentile based on Magee-Womens Hospital standards adjusted for gestational age, race, and sex). From each of the 400 women, we sought to select 1 serum sample at <22 wk gestation, 1 predelivery serum sample, and 1 cord serum sample. If a woman had more than 1 sample collected at <22 wk gestation, we randomly selected 1 using a random number generator. Of the 400 women selected, 392 had an available banked serum sample collected at <22 wk, 384 had an available banked serum sample collected predelivery, and 366 had an available banked cord serum sample. Two women were excluded because their only serum sample 25(OH)D level was an extreme outlier (>300 nmol/L), leaving 398 women in the final analysis.

Quantitation of serum 25(OH)D. Maternal and cord serum samples were stored in aliquots at −80°C until they were analyzed for 25(OH)D. Quantitation of serum 25(OH)D [25(OH) ergocalciferol (D2) + 25(OH)D3] was performed using a commercial ELISA from Immunodiagnostic Systems and validated against an HPLC method, as described previously (5). The ELISA could detect 25(OH)D in the range of 5–300 nmol/L. The inter-assay CV for the ELISA was 10.3%. The relationship between serum 25(OH)D concentrations obtained from the ELISA compared with HPLC was as follows: slope = 1.14, intercept = 22, $r = 0.88$. We used this validation study to adjust the 25(OH)D concentrations obtained by ELISA to ensure better agreement with the HPLC data, as suggested by the manufacturer.

The cutoff to define a normal circulating concentration of 25(OH)D is being debated. For our analysis, we classified women and neonates into 1 of 3 groups that defined vitamin D status: vitamin D deficiency (25(OH)D < 50 nmol/L), vitamin D insufficiency (25(OH)D 50–80 nmol/L), and vitamin D sufficiency (25(OH)D > 80 nmol/L) (6,7). The same cutoffs were used for both women and neonates, because experts contend that the ideal healthy level of 25(OH)D is the same in infants as adults (6).

Definition of study variables. Prepregnancy BMI [weight (kg)/height $(m)^2$] was based on measured height and maternal self-report of prepregnancy weight at the first prenatal visit. Prepregnancy BMI was categorized as lean (BMI <25), overweight (BMI 25.0–29.9), and obese (BMI ≥30.0). Race/ethnicity was self-reported as non-Hispanic white or non-Hispanic black. Season of sample collection was defined as winter (December, January, February), spring (March, April, May), summer (June, July, August), and fall (September, October, November). Data were available on marital status (married, unmarried), maternal education (<12, 12, >12 y), and smoking status (smoker, nonsmoker). At enrollment, women self-reported their regular use of multivitamins or prenatal vitamins in the periconceptional period (defined as the 3 mo before and 3 mo after conception), and at delivery, women reported their regular use in the last 3 mo of pregnancy. Women were also asked to categorize their usual amount of time spent watching television in the year before the index pregnancy as 0–10, 11–20, 21–30, or >30 h/wk. Women were asked if they engaged in any leisure-time physical activity in the year before the index pregnancy.

Statistical analysis. Nonparametric data were log-transformed before statistical tests were performed. A Pearson chi-square test was used to determine differences in maternal characteristics and the prevalence of vitamin D deficiency by BMI category. Spearman rank correlation coefficient was used to test for correlations between prepregnancy BMI and serum 25(OH)D levels. We built multivariable regression models to assess the independent association between prepregnancy BMI and 25(OH)D (linear regression) as well as BMI and odds of vitamin D deficiency (logistic regression). To assess the dose-response relation between BMI and vitamin D status, we used published methods (37) to determine the most appropriate specification of BMI in our model. We found the best fit using prepregnancy BMI as a continuous, linear variable in the final linear and logistic regression models.

We fit parsimonious regression models by specifying full models with potential confounding variables: race/ethnicity, maternal age, education, marital status, season, smoking status, preconceptional television watching, preconceptional physical activity, periconceptional multivitamin use, multivitamin use in the last 3 mo of pregnancy (in models for vitamin D status at term and in cord serum only), and gestational age at the time of sample collection (termed gestational age). Effect modification by race/ethnicity was tested using Wald *P*-values in linear regression models ($\alpha = 0.10$) and a likelihood ratio test in logistic regression models ($\alpha = 0.10$). Potential confounders were considered not influential and were removed from the model if their inclusion did not satisfy our a priori change-in-estimate criterion (a >10% change in the coefficient for linear regression or a >10% change in the OR in logistic regression). Race/ethnicity, season, gestational age, multivitamin use, preconception physical activity, and maternal age met our definition of confounding and were included in the final models. A *P*-value of 0.05 was considered significant. Data were analyzed using Stata software version 8.0.

Results

In this cohort of 398 women, 57% were lean, 22% were overweight, and 21% were obese. Non-Hispanic black race/ethnicity was significantly more common in overweight and obese women compared with lean women ($P < 0.01$; **Table 1**). There was a tendency for obese women to use periconceptional multivitamins less frequently than their leaner counterparts ($P = 0.07$), but no other differences by prepregnancy BMI group were found. The majority of women used multivitamins or prenatal vitamins regularly during pregnancy.

Maternal and neonatal vitamin D status varied significantly by maternal prepregnancy BMI (**Table 2**). Compared with lean women, pregravid obese women had significantly lower mean serum 25(OH)D concentrations at 4–22 wk and at term after adjustment for race/ethnicity, season, gestational age, periconceptional multivitamin use, preconception physical activity, and maternal age. Neonates of obese mothers also had significantly lower cord concentrations of 25(OH)D, independent of confounders.

There was a moderate, negative correlation between prepregnancy BMI and serum 25(OH)D at 4–22 wk ($r = -0.22$; $P < 0.0001$), at term ($r = -0.19$; $P < 0.001$), and in cord serum ($r = -0.18$; $P < 0.0001$). **Figure 1** illustrates this negative, linear relation for maternal serum 25(OH)D at 4–22 wk. Plots for maternal serum 25(OH)D at term and cord 25(OH)D were similar (data not shown). After confounder adjustment, a 10-kg/m^2 increase in maternal BMI was associated with lower concentrations of serum 25(OH)D at 4–22 wk [−5.4 (95% CI: −9.2, −1.6) nmol/L, $P < 0.01$], at term [−6.3 (95% CI: −11.0, −1.6) nmol/L, $P < 0.01$], and in cord serum [−4.3 (95% CI: −8.4, −0.2) nmol/L, $P < 0.05$].

Overweight and obese women were more likely than lean women to have vitamin D deficiency at 4–22 wk ($P < 0.01$) and to deliver newborns with vitamin D deficiency ($P < 0.05$)

TABLE 1 Maternal characteristics by prepregnancy BMI[1]

	Prepregnancy BMI <25 kg/m^2	Prepregnancy BMI 25–29.9 kg/m^2	Prepregnancy BMI ≥30 kg/m^2
n	227	88	83
Sociodemographic variables		%	
Maternal race/ethnicity,			
Non-Hispanic white	56.4	44.3	37.4
Non-Hispanic black	43.6	55.7	62.7
Maternal age,			
<20 y	41.4	35.2	36.1
20–29 y	47.1	48.9	51.8
30 y or more	11.5	15.9	12.1
Marital status,			
Married	78.9	75.0	85.5
Unmarried	21.2	25.0	14.5
Maternal education,			
<12 y	25.6	25.0	15.7
12 y	27.3	29.6	33.7
>12 y	47.1	45.5	50.6
Lifestyle variables			
Smoking status in the year before the index pregnancy,			
Smokers	53.7	50.0	53.0
Nonsmokers	46.3	50.0	47.0
Periconceptional multivitamin use at least once per wk,			
Yes	47.1	48.9	33.7
No	52.9	51.1	66.3
Multivitamin use in the last 3 mo of pregnancy,			
Yes	93.7	89.4	96.3
No	6.3	10.6	3.7
Usual preconceptional television watching,			
0–10 h/wk	40.5	42.1	31.7
11–20 h/wk	19.8	22.7	30.5
21–30 h/wk	15.9	14.8	15.9
>30 h/wk	23.8	20.5	22.0
Any preconception leisure-time physical activity,			
No	58.3	60.7	66.7
Yes	41.7	39.3	33.3

[1] $P < 0.01$ (Pearson chi-square test). No other distributions were significantly different at $P < 0.05$.

TABLE 2 Association between prepregnancy BMI and maternal and neonatal vitamin D status

	Prepregnancy BMI <25 kg/m^2	Prepregnancy BMI 25–29.9 kg/m^2	Prepregnancy BMI ≥30 kg/m^2
Maternal serum (4–22 wk gestation)			
n	223	87	82
Adjusted mean 25(OH)D (95% CI),[1] *nmol/L*	62.8 (55.0, 70.4)	58.6 (51.5, 66.8)	55.9 (48.7, 64.2)[2]
Vitamin D status,[3] %			
25(OH)D < 50 nmol/L	36.3	48.3	61.0
25(OH)D 50–80 nmol/L	37.2	35.6	28.0
25(OH)D > 80 nmol/L	26.5	16.1	11.0
Maternal serum (37–42 wk gestation)			
n	219	84	81
Adjusted mean 25(OH)D (95% CI),[4] *nmol/L*	67.3 (58.8, 77.0)	61.2 (52.0, 72.0)	60.2 (51.0, 71.2)[2]
Vitamin D status, %			
25(OH)D <50 nmol/L	26.0	33.3	39.5
25(OH)D 50–80 nmol/L	32.4	34.5	35.8
25(OH)D >80 nmol/L	41.6	32.1	24.7
Cord serum			
n	216	80	70
Adjusted mean 25(OH)D (95% CI),[4] *nmol/L*	56.2 (49.7, 63.6)	53.8 (46.2, 62.8)	49.9 (42.8, 58.2)[2]
Vitamin D status,[3] %			
25(OH)D <50 nmol/L	37.5	45.0	58.6
25(OH)D 50–80 nmol/L	36.1	36.3	31.4
25(OH)D >80 nmol/L	26.4	18.7	10.0

[1] Adjusted for race/ethnicity, season, gestational age at the time of blood sampling, periconceptional multivitamin use, preconception physical activity, and maternal age.
[2] Significantly different from lean women, $P < 0.05$.
[3] Distributions significantly different, $P < 0.01$ (chi-square test).
[4] Adjusted for all variables mentioned above as well as regular multivitamin use in the last 3 mo of pregnancy.

(Table 2). In fact, there was a strong dose-response relation between prepregnancy BMI and the odds of vitamin D deficiency [25(OH)D < 50 nmol/L] in mothers and their neonates (**Fig. 2**). For instance, compared with a woman with a pregravid BMI of 22, a woman with a BMI of 28 was 1.4 times as likely to be vitamin D deficient in early pregnancy (95% CI: 1.1, 1.9) and 1.5 times as likely to have a newborn with vitamin D deficiency (95% CI: 1.1, 1.9), independent of race/ethnicity, season, gestational age, multivitamin use, preconception physical activity, and maternal age. Compared with the same referent, a woman with a BMI of 34 had a 2.1-fold (95% CI: 1.2, 3.6) increase in the odds of vitamin D deficiency in mid-pregnancy and a 2.1-fold (95% CI: 1.2, 3.8) increase in the odds of having a newborn with vitamin D deficiency. Results were similar when we assessed the odds of having a 25(OH)D concentration < 80 nmol/L. BMI and odds of vitamin D deficiency at term tended to be associated ($P = 0.09$).

There was no evidence that any of the effects we observed varied by race/ethnicity. Restricting these analyses to women with BMI values within the 5th to the 95th percentiles did not meaningfully affect the results (data not shown).

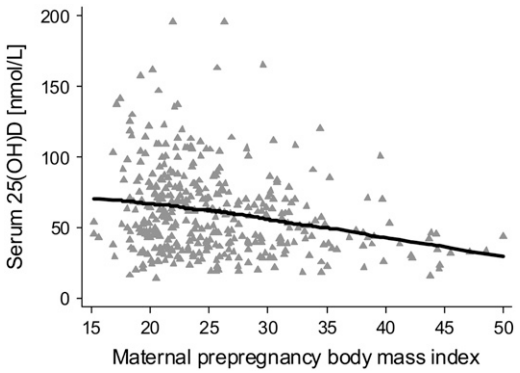

FIGURE 1 Plot of prepregnancy BMI vs. maternal serum 25(OH)D at 4–22 wk gestation. The solid line represents the best fit of this relation ($r = -0.22$; $P < 0.0001$).

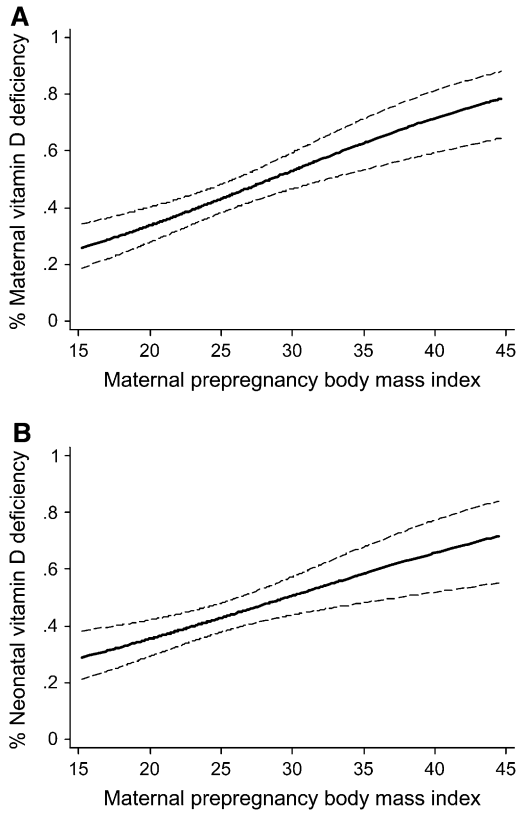

FIGURE 2 Unadjusted association between maternal prepregnancy BMI and the probability of maternal vitamin D deficiency (*A*) and neonatal vitamin D deficiency (*B*). Vitamin D deficiency is defined as serum 25(OH)D $<$ 50 nmol/L. Probabilities were predicted based on results from logistic regression models (BMI effect was significant at $P < 0.05$ in maternal model and $P < 0.01$ in neonatal model). The solid line represents the point estimate and the dashed lines represent the 95% confidence bands.

Discussion

In this cohort of supplemented women, maternal prepregnancy obesity was associated with lower serum 25(OH)D concentrations and higher odds of vitamin D deficiency among mothers in mid-gestation and neonates at birth. Importantly, we found monotonic dose-dependent relations between prepregnancy BMI and maternal and newborn vitamin D status. The associations remained after controlling for race, supplement use, and other measured confounders. The relation was not as strong in mothers at term as it was at 4–22 wk, which may have been due to a longer period (37–42 wk) between BMI estimation and 25(OH)D measurement and/or the lower prevalence of vitamin D deficiency at term. Vitamin D deficiency was probably less common at term because more women were using multivitamins in the last 3 mo of pregnancy than in the periconceptional period.

We are unaware of any other published study to examine the effect of prepregnancy obesity on the vitamin D status of mothers or newborns. Our results are consistent with the numerous studies revealing low 25(OH)D concentrations in obese nonpregnant adults and children (13–28), including several that reported a monotonic decline in 25(OH)D levels as BMI or body fat mass increased (13–15,17,22). For instance, Parikh and colleagues (14) reported a 24% decrease in 25(OH)D concentrations in obese adults (58.8 nmol/L) vs. nonobese adults (77.5 nmol/L) and a strong, negative correlation between 25(OH)D and BMI ($r = -0.4$; $P < 0.0001$) in a predominantly female cohort. In most other studies, correlations were more modest, ranging from −0.14 to −0.27 (15,21,22,27), as we observed. Prior investigations were all cross-sectional (i.e. obesity and 25(OH)D were measured simultaneously). In contrast, our report of prepregnancy BMI in relation to gestational and cord 25(OH)D levels suggests that adiposity around conception may predict pregnancy and neonatal vitamin D status.

There is some evidence that the relation between obesity and 25(OH)D may vary by race/ethnicity. Recently, Looker (17) showed that the negative association between fat mass and 25(OH)D was significantly stronger in white women than in black women. Smaller studies have reported either no association between 25(OH)D and obesity in blacks (16,18) or a similar strong association in whites as in blacks (14). In our study, the relation was similar in blacks and whites. However, our sample size may have limited our power to detect an interaction.

Previously, investigators demonstrated correlations between 25(OH)D and total body fat percentage by whole body dual energy X-ray absorptiometry that were as strong as or stronger than correlations between 25(OH)D and anthropometric measures such as BMI (13–15). These findings highlight that it may be adiposity—not just body mass—that is related to vitamin D status. Indeed, the mechanism explaining the variability in 25(OH)D by obesity status is likely related to the ability of subcutaneous fat to sequester cutaneous synthesized D3, the precursor to 25(OH)D. In an elegant study, Wortsman et al. (12) showed no difference between nonobese and obese individuals in the capacity of the skin to synthesize D3 but a striking 57% reduction in the increase of serum D3 after sun exposure in the obese subjects. Moreover, after providing obese subjects with a pharmacologic oral dose of D2, groups did not differ in peak serum D2 levels. These data suggest that the availability of excessive adipose tissue causes a decrease in endogenously synthesized D_3 to be released into circulation. Their results also indicate that oral intake of D2 may be more bioavailable for obese individuals. Although some researchers thought that lower 25(OH)D concentrations may be due to a negative feedback at the hepatic level from elevated 1,25-dihydroxyvitamin D in the setting of obesity (19), recent reports contradict this theory (14). The lower 25(OH)D levels in obesity are thought to secondarily elevate intact parathyroid hormone concentrations (14,20). High parathyroid hormone levels may enhance calcium uptake into adipocytes, thereby promoting lipogenesis and excess weight gain (38,39). How this endocrine system is altered in pregnancy is not known.

Although a lowering of 25(OH)D concentrations with increasing BMI or fat mass is worrisome for all adults, it is particularly concerning for pregnant women and their fetuses. Not only is poor in-utero and early-life vitamin D status related to long-term negative health effects for the offspring (6,10), but maternal vitamin D deficiency may also increase the risk of adverse pregnancy outcomes (8,9). Importantly, vitamin D insufficiency is an independent risk factor for preeclampsia (8), an outcome that is also more common in obese than normal weight women (40). Our findings suggest that reduced 25(OH)D levels in pregravid obese women may partially mediate the obesity-preeclampsia association. Future studies are needed to explore this intriguing possibility.

We used prepregnancy BMI as a surrogate for prepregnancy fat mass because direct measures were not available. Our reliance on BMI may have led to an underestimation of the association between maternal obesity and 25(OH)D concentrations.

We were also limited by our assay's ability to detect 100% of 25(OH)D3 but only 75% of 25(OH)D2, which would underestimate concentrations of total 25(OH)D in women whose primary source of vitamin D was D2. If obese women were more likely to derive vitamin D from D2, this may have biased our results upwards and away from the null. We did not have detailed data on vitamin D intake to determine whether sources differed by obesity status. Additionally, we used self-reported physical activity and television watching as covariates in our regression models to represent surrogates of sun exposure. A direct measure of sun exposure would have allowed us to definitively rule out that lowered 25(OH)D levels were caused by a greater avoidance of sun by obese individuals, as some have proposed (19). We did not have the resources to measure biomarkers of the vitamin D endocrine system or vitamin D-binding protein concentrations. We also lacked data on parathyroid hormone concentration or other functional indicators of vitamin D status in mothers and neonates.

Our results suggest that pregravid obese women and their newborns are at high risk of vitamin D deficiency, even when mothers regularly use prenatal vitamins. These data illustrate that prepregnancy obesity has a direct impact on the nutritional status of the neonate. Future research should investigate whether obese pregnant women may benefit from serum 25(OH)D screening and high-dose vitamin D supplementation during gestation to improve their own vitamin D stores and that of their infants. The dramatic rise in the prevalence of maternal prepregnancy obesity in the United States (41) highlights that maternal and newborn vitamin D deficiency will continue to be a serious public health problem until steps are taken to identify and treat low 25(OH)D concentrations in clinical and public health settings.

Acknowledgments

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