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Early Pregnancy Maternal Vitamin D Concentrations and Risk of Gestational Diabetes Mellitus

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Abstract

Background—While associations of vitamin D deficiency with Type 2 diabetes have been well demonstrated, investigations of vitamin D and risk of gestational diabetes mellitus (GDM) reported inconsistent findings. We examined associations of vitamin D status with GDM.

Methods—In a nested case-cohort study (135 GDM cases and 517 non-GDM controls), we measured maternal serum Vit-D status (total 25[OH]D and 25[OH]D₃) in early pregnancy (16 weeks on average) using liquid chromatography-tandem mass spectroscopy. GDM was diagnosed according to the ADA guidelines. We calculated adjusted odds ratios (ORs) and 95% confidence intervals (CI) using logistic regression models.

Results—GDM cases had lower mean total 25[OH]D (27.3 vs. 29.3ng/ml) and 25[OH]D₃ (23.9 vs. 26.7ng/ml) concentrations compared with women who did not develop GDM (both P-values<0.05). Overall, 25[OH]D₃ concentrations, but not total 25[OH]D concentrations, were significantly associated with GDM risk. A 5ng/ml increase in 25[OH]D₃ concentration was associated with a 14% decrease in GDM risk (P-value=0.02). Women in the lowest quartile for 25[OH]D₃ concentration had a 2-fold (95% CI 1.15-3.58) higher risk of GDM compared with women in the highest quartile (P-value for trend<0.05).

Conclusions—Early pregnancy vitamin D status, particularly 25[OH]D₃, is inversely associated with GDM risk.

Keywords

vitamin D; case-cohort study; gestational diabetes; pregnancy

Background

In 2011, the Endocrine Society's Community of Clinical Practice released guidelines for the evaluation, treatment, and prevention of vitamin D deficiency that included controversial recommendations for daily allowance of vitamin D that exceed levels indicated in prior guidelines.^{1, 2} The Institute of Medicine (IOM), which had released vitamin D supplementation guidelines earlier that year, contends that the new guideline from the Endocrine Society does not provide adequate evidence for the assertion that higher serum levels of 25-hydroxy vitamin D (25[OH]D) concentrations (≥ 30 ng/mL) are beneficial for at-risk populations (e.g. pregnant women).² In 2012, the Cochrane Collaboration released a review of randomized controlled trials that showed vitamin D supplementation during pregnancy improved women's vitamin D status, but did not prevent pregnancy or fetal complications.³

Research on vitamin D and gestational diabetes mellitus (GDM) is motivated by more than a decade of observational studies which demonstrated a consistent and strong association between vitamin D deficiency and Type 2 diabetes mellitus, a condition that has similar pathogenesis and risk factors to GDM.⁴⁻⁸ A number of studies that included observational studies,⁹⁻¹⁷ and meta-analyses¹⁸⁻²⁰ have examined associations between vitamin D status and GDM. Findings from these studies ranged from inverse associations,⁹⁻¹² to null¹³⁻¹⁶ and positive¹⁷ associations between vitamin D status and risk of GDM. Some of the reasons that were put forth for observed inconsistencies included differences in timing of blood collection (e.g. post disease diagnosis), inaccuracy of vitamin D (and metabolite) measurements, and inadequate assessment of potential confounders or effect modifiers, such as pre-pregnancy body mass index (BMI). Recent evidence supports potential role of vitamin D on subsequent risk for weight gain²¹. However, the role of weight gain during pregnancy, such as one characterized by mid-pregnancy BMI, as mediator of the effect of vitamin D deficiency on GDM is not known.

Using a nested case-cohort study design (that allowed selection of GDM cases and non-GDM controls) and study procedures that address some of these limitations, we investigated early pregnancy maternal 25[OH]D concentrations and subsequent risk of GDM. We hypothesized that lower 25[OH]D concentration is associated with an increased risk of developing GDM. In secondary exploratory analyses, we examined whether pre-pregnancy or mid-pregnancy (18-22 weeks of gestation) body mass index (BMI) modify or mediate, respectively, these relationships.

Methods

Study setting

This study was conducted among participants of the Omega Study, a prospective cohort study (1996-2008) of 4,000 pregnant women designed to examine risk factors of pregnancy complications.²² The study reported in this manuscript was part of nested case-cohort studies to investigate associations of vitamin D status with subsequent risk of GDM, preeclampsia, and depression.

Study population

Study participants were identified among women attending prenatal care clinics at Swedish Medical Center in Seattle, Washington and Tacoma General Hospital in Tacoma, Washington. Eligibility criteria for the Omega study included initiation of prenatal care before completion of 20 weeks of gestation, being 18 years of age or older, speaking and reading English, planning to carry the pregnancy to term, and planning to deliver at one of the study institutions. A complete sample of 195 GDM cases and 750 randomly selected sub-cohort participants were sampled for the present study. The overlap between the randomly chosen sub-cohort and the GDM case group included 47 GDM cases. Sub-cohort members minus the overlapping GDM cases constituted the control group for further analyses.

After exclusion of participants with unknown case status (n=18), gestational age at delivery <24 weeks (9), missing 25[OH]D concentration measurements (n=7), preeclampsia (n=41), mood and/or anxiety disorder (n=54), chronic hypertension (n=27), renal disease (n=5), thyroid condition (n=70), liver disease (n=7), rheumatoid arthritis (n=5), and lupus (n=3), a total of 135 GDM cases and 517 non-GDM control participants remained for analyses. All study participants provided informed consent. Study procedures were approved by the Institutional Review Boards of Swedish Medical Center and Tacoma General Hospital.

GDM diagnosis

As part of perinatal screening procedures, all pregnant women attending perinatal clinics affiliated with our institutes are screened between weeks 24-28 using a 50g 1-hour oral glucose challenge test. Women who failed this screening (glucose ≥ 7.8 mmol/L (140 mg/dl)) underwent a 100g oral glucose tolerance test 1-2 weeks after the first failed screening test. GDM was defined according to the recommendations of the American Diabetes Association (ADA) such that women were diagnosed with GDM if two or more of the following exceeded ADA criteria after a 100g oral glucose tolerance test: fasting ≥ 5.3 mmol/L (95 mg/dl); 1-hour ≥ 10.0 mmol/L (180 mg/dl); 2-hour ≥ 8.6 mmol/L (155 mg/dl); 3-hour ≥ 7.8 mmol/L (140 mg/dl).²³

Data Collection

At the time of enrollment, study personnel collected maternal blood specimens. All blood specimens were processed within 30 minutes, and aliquots were stored at -80°C until 25[OH]D concentrations were measured. Soon after blood specimens were collected, participants completed an interview using a structured questionnaire administered in English by a trained interviewer. Questionnaires were used to gather data on socioeconomic status and reproductive and medical histories, including self-reported pre-pregnancy weight and height for BMI calculations. Participants also completed and returned a food frequency questionnaire. After delivery, maternal and infant medical records were abstracted for information on the course (e.g. mid-pregnancy BMI, from antepartum measures of weight and height taken by clinical staff) and outcome of the pregnancy.

Vitamin D Measurement

Maternal early pregnancy 25[OH]D concentrations were assessed by measuring the following vitamin D metabolites in maternal serum collected at enrollment (at 16 weeks of gestation on average): 25[OH]D₃ and 25[OH]D₂ concentrations. Only a few samples had detectable 25[OH]D₂ concentrations. Therefore, we restricted subsequent analyses to total 25[OH]D and 25[OH]D₃ concentrations. Measurements were conducted using liquid chromatography-tandem mass spectroscopy (LC-MS/MS) methods at ZRT Laboratories (ZRT, Portland, OR). The inter-assay precision coefficients of variation for 25[OH]D₂ and 25[OH]D₃ concentrations were 9% and 6% respectively.

Statistical analyses

We examined distributions of categorical (number and percentage) and continuous (mean and standard deviation) variables among GDM cases and non-GDM controls. Multivariable logistic regression models were used to determine associations between early pregnancy maternal serum 25[OH]D concentrations and GDM using odds ratios (OR) and 95% confidence intervals (CI). Logistic regression has been successfully used in prior similar studies with case-cohort design that did not use time-to-event data.²⁴⁻²⁶

We modeled exposure variables (both total 25[OH]D and 25[OH]D₃ concentrations) in three different ways: 1) as continuous variables, 2) as categorical variables (quartiles), and 3) as categorical variables characterizing vitamin D deficiency status. P-value for trend was computed by assessing linear trend across increasing quartiles. According to previously published criteria, vitamin D sufficiency (≥ 30 ng/ml or ≥ 75 nmol/l), insufficiency (20–30 ng/ml, 50–75 nmol/l) and deficiency (<20 ng/ml or <50 nmol/l) were used to categorize participants according to their 25[OH]D concentrations.²⁷ In addition to *a priori* selected potential confounders, covariates that altered unadjusted odds ratios (ORs) by 10% or more were included in final adjusted models.²⁸

We fit four separate models, unadjusted (Model 1) and three adjusted models (Models 2–4), in these analyses. In the first adjusted model (Model 2), we adjusted for race/ethnicity (non-Hispanic White or other comprised of Asians, Hispanics, and non-Hispanic African Americans), maternal age (years), education, marital status, season of blood draw, parity, smoking status, and peri-conceptional multivitamin use. In the second adjusted model (Model 3), we included all Model 2 adjustment variables, as well as maternal pre-pregnancy BMI (kg/m²). In the last adjusted model, Model 4, we included Model 2 adjustment variables and mid-pregnancy BMI (BMI at 18–22 weeks of gestation). Models 3 and 4 were aimed at evaluating the influences of pre-pregnancy BMI or mid-pregnancy BMI, on the magnitude of associations between maternal early pregnancy vitamin D status and GDM risk.

In secondary analyses, we evaluated possible effect modification of vitamin D status (both total 25[OH]D or 25[OH]D₃ concentrations) and GDM associations by pre-pregnancy overweight/obesity status using stratified analyses and by examining independent and joint effects of total 25[OH]D or 25[OH]D₃ concentrations and pre-pregnancy overweight/obesity status on the risk of GDM.²⁹ In stratified analyses, we examined whether associations of

vitamin D sufficient status (25[OH]D ≥ 30 ng/ml) with GDM risk differ among strata defined by pre-pregnancy overweight/obesity status (pre-pregnancy BMI ≥ 25 kg/m²). We examined whether the joint effect of vitamin D status (total 25[OH]D or 25[OH]D₃ concentrations) and pre-pregnancy overweight/obesity status on risk of GDM was greater than expected given their independent effects. For these analyses, we created a variable that categorized women as (1) vitamin D sufficient and not overweight/obese, (2) vitamin D insufficient/deficient and not overweight/obese, (3) vitamin D sufficient and overweight/obese, and (4) vitamin D insufficient/deficient and overweight/obese. Statistical significance of interactions were determined using P-values (if P-value < 0.05) of interaction terms between vitamin D sufficient status and pre-pregnancy overweight/obese status in multivariable logistic regression models.

We also explored whether mid-pregnancy BMI mediated associations between maternal vitamin D status and GDM risk using two approaches, adjusted for season of blood draw, maternal age, race/ethnicity, family history of diabetes, and pre-pregnancy BMI. The first analysis approach involved an effect decomposition method previously described for multivariate logistic regression models in the setting of case-control studies.³⁰ We estimated the controlled direct effect of decreasing 25[OH]D concentrations (quartiles) on GDM risk and the direct effect of mid-pregnancy BMI on GDM risk by fitting regression models of GDM risk on 25[OH]D concentrations, mid-pregnancy BMI, and adjustment variables. We then estimated the effect of decreasing 25[OH]D concentrations on mid-pregnancy BMI by weighing cases (0.046/0.207) and controls [(1-0.046)/(1-0.207)] using GDM prevalence estimates in the population (4.6%)³¹ and proportion of cases in the current study (20.7%). Finally, we calculated the indirect effect of 25[OH]D concentration mediated through increasing mid-pregnancy BMI by taking the product of the effect of 25[OH]D concentration on mid-pregnancy BMI and the effect of mid-pregnancy BMI on GDM risk. Confidence intervals were estimated using the respective standard errors from both fitted models as described before.³⁰

In the second approach, we approximated the direct effects of decreasing 25[OH]D concentrations (quartiles) on log odds of GDM independent of mid-pregnancy obesity (BMI ≥ 30 kg/m²) by using a marginal structural model (MSM) estimated by inverse probability weights. By estimating probability of exposures and mediators among the controls (in our study, non-GDM members of the randomly selected subcohort), MSM can be employed in case-control settings to estimate causal effects.³²⁻³³ Briefly, for each subject we used multinomial logistic regression to predict the probability of their 25[OH]D concentrations (i.e. the probability of being in each quartile group for 25[OH]D concentrations) using the listed adjustment variables. Similarly, we used logistic regression to predict the probability of mid-pregnancy obesity (BMI ≥ 30 kg/m²) using 25[OH]D concentrations and the confounders. The inverses of these two probabilities were multiplied to generate final probability weights used to fit a logistic regression model of 25[OH]D concentrations and mid-pregnancy obesity on GDM risk.

We conducted sensitivity analyses to assess likelihood of different relationships among subgroups (e.g. restricted among non-Hispanic Whites). Our findings from these analyses were similar to our findings from our primary analyses reported in this manuscript. All

reported CIs were calculated at the 95% level, and all reported P-values are two-tailed. Analyses were performed using Stata 11.0 (Stata, College Station, TX).

Results

Women with GDM were more likely to be older, less likely to be non-Hispanic white, more likely to have a family history of diabetes mellitus or hypertension, to have higher BMI (both pre-pregnancy and at 18-22 weeks of gestation), and to deliver early, as compared with women in the non-GDM control group (Table 1). Early maternal serum total 25[OH]D and 25[OH]D₃ concentrations were lower in women who developed GDM (mean $\pm$ SD, GDM cases vs. non-GDM controls: 27.3 $\pm$ 8.7 vs. 29.3 $\pm$ 8.3 ng/ml, P = 0.01 for total 25[OH]D; and, 23.9 $\pm$ 9.4 vs. 26.7 $\pm$ 8.8 ng/ml, P = 0.002 for 25[OH]D₃). Among GDM cases, 17% of women were vitamin D deficient (total 25[OH]D <20 ng/ml) compared to 11% of women in the comparison group.

A 5ng/ml increase in total 25[OH]D concentration was associated with a 14% reduction in GDM risk (OR 0.86, 95% CI: 0.77, 0.97) (Table 2). Women with total 25[OH]D deficiency had a 1.97-fold increased risk of GDM compared to women who were total 25[OH]D sufficient ($\geq$ 30 ng/ml) (95% CI: 1.12, 3.47) in the unadjusted model. Women in the lower three quartiles for total 25[OH]D concentration had higher risk of GDM compared with women in the highest quartile in unadjusted models (P-value for trend=0.013). However, these associations were attenuated and became statistically insignificant after adjustment for potential confounders. Additional adjustments for pre-pregnancy BMI and mid-pregnancy BMI further attenuated these relationships. In stratified analyses (Table 3), associations of total 25[OH]D insufficiency (<30ng/ml) with higher GDM risk seemed to be present among women who were overweight/obese prior to becoming pregnant, (OR 1.96, 95% CI: 0.90, 4.27) but not among women who were not (OR 1.02, 95% CI: 0.60, 1.70). Women who were both total 25[OH]D insufficient and overweight/obese, had a statistically significant 2.8-fold higher GDM risk (OR 2.80, 95% CI: 1.64, 4.83) compared with women who were both total 25[OH]D sufficient and were not overweight/obese. Although the increase in risk was higher than the joint risk we expected based on the independent associations of each risk factor with GDM risk, the interaction did not meet criteria for statistical significance (P value for interaction= 0.279).

We repeated these analyses using 25[OH]D₃ concentration as our exposure variable. A 5ng/ml increase in 25[OH]D₃ concentration was associated with a 12% reduction in risk of GDM (OR 0.88, 95% CI: 0.76, 0.96) (Table 4). Women who were 25[OH]D₃ deficient had a 1.95-fold increased risk of GDM compared to women who were 25[OH]D₃ sufficient (95% CI: 1.16, 3.29). Women in the lower three quartiles for 25[OH]D₃ concentration had higher risk of GDM compared with women in the highest quartile (P-value for trend=0.010). Women in the lowest quartile for 25[OH]D₃ concentration had a 2-fold (95%CI 1.15-3.58) higher risk of GDM compared with women in the highest quartile. These associations were slightly attenuated but remained statistically significant or marginally significant, after adjusting for pre-pregnancy BMI or mid-pregnancy BMI, respectively. In stratified analyses (Table 5), similar to our findings for total 25[OH]D, association of 25[OH]D₃ insufficiency (<30ng/ml) with GDM risk was stronger among women who were overweight/ obese prior

to becoming pregnant (OR 2.02, 95% CI: 0.85, 4.76), compared with association among women who were not (OR 1.29, 95% CI: 0.75, 2.23). Women who were both 25[OH]D₃ insufficient and were overweight/obese had a statistically significant 3.2-fold higher GDM risk (95% CI: 1.80, 5.83) compared with women who were both 25[OH]D₃ sufficient and were not overweight/obese. Although this increase in GDM risk was higher than the joint risk we expected based on the independent associations of each risk factor with GDM risk, the interaction was not statistically significant (P-value for interaction= 0.487) (Table 5).

In the effect decomposition analyses to assess mid-pregnancy BMI as a mediator of 25[OH]D₃ concentration and GDM risk associations, we found that decreasing quartiles of 25[OH]D₃ concentration were associated with a 0.26 kg/m² higher mid-pregnancy BMI (β 0.26, 95%CI, 0.058, 0.467, P-value=0.012). In addition, each higher unit (kg/m²) of mid-pregnancy BMI mediated an indirect effect of 1% higher GDM risk subsequent to decreasing quartiles of 25[OH]D₃ concentration (OR 1.01, 95%CI, 0.99, 1.03). In the MSM analyses, we found that decreasing quartiles of 25[OH]D₃ concentration were associated with a 31% increased risk of GDM (95%CI, 1.09, 1.58, P-value=0.004) independent of mid-pregnancy obesity amongst a marginal population with equal likelihood of belonging to the same quartile group of 25[OH]D₃ concentration and mid-pregnancy obesity status.

Discussion

In this study, we found that maternal early pregnancy vitamin D status, particularly 25[OH]D₃, was inversely associated with risk of GDM. Women who were vitamin D deficient in early pregnancy, based on 25[OH]D₃ concentrations, had a 1.9-fold higher risk of developing GDM after adjustment for potential confounders. We did not find statistically significant interactions between vitamin D status and pre-pregnancy overweight/obesity status on GDM risk, although inverse associations of vitamin D with GDM risk were found to be stronger among women who were overweight/obese prior to pregnancy. In exploratory analyses, we found that mid-pregnancy BMI mediates only a small proportion of the effect of vitamin D status on GDM risk.

Our findings are similar to some previous studies that investigated vitamin D status and GDM risk,⁹⁻¹² but were different from others.¹³⁻¹⁷ Previously, in a nested case-control study conducted among 57 GDM cases and 114 controls, our research group reported that vitamin D deficiency was associated with a 2.66-fold increased risk of subsequent GDM [95% CI 1.01, 7.02].⁹ Three independent meta-analyses of observational studies reported 38-61% higher risk of GDM among women with vitamin D deficiency (total 25[OH]D<50 nmol/l).¹⁸⁻²⁰ More recently, Lacroix reported that lower first trimester 25[OH]D concentrations were associated with higher risk of developing GDM (OR 1.48 per decrease of one SD in 25[OH]D concentration, P=0.04).¹⁰ However, in other studies, associations of vitamin D status with GDM risk were not observed. Baker et al. reported that women with vitamin D deficiency, in early pregnancy, did not have a significantly higher risk of GDM compared with women who did not have vitamin D deficiency (OR 0.78 [95% CI 0.22, 2.78]).¹³ Similarly, researchers did not observe associations of vitamin D deficiency with risk of GDM in other studies conducted in Korea, North England, and Australia.¹⁴⁻¹⁶ Recently, Zhou et al reported that the prevalence of GDM was higher among women with high

25[OH]D (< 30ng/ml) concentrations compared with women in the low and medium groups (OR 1.02 95%CI 1.00, 1.03).¹⁷ Notably, there have not been randomized control trials that were designed to examine associations of vitamin D status with risk of GDM.

Inconsistency in reported results may be due to, at least in part, timing of vitamin D status measurements, differences in assays used to measure 25[OH]D concentrations, inadequate/inconsistent control for confounding, and differences in criteria used to diagnose GDM. In the current study, we took some steps to address limitations of previous studies. First, 25[OH]D concentrations were measured from samples collected in early pregnancy (<20 weeks gestation), well before the diagnosis of GDM, establishing a relatively clear temporal relationship between vitamin D status and GDM. Second, state-of-the-art LC-MS/MS methods were used to measure maternal 25[OH]D concentrations, enabling us to measure both total 25[OH]D and 25[OH]D₃ concentrations in serum. Third, our well-characterized study population allowed for the collection of relevant data to assess the influences of confounding, effect modification or mediation on estimated associations. For example, we conducted analyses to evaluate effect modification by pre-pregnancy BMI or mediation effects of mid-pregnancy BMI.

Relatively few previous studies have considered the different constituents of total 25[OH]D in relation to disease risk. There are two forms of vitamin D, vitamin D₂ (ergocalciferol), a synthetic form, and vitamin D₃ (cholecalciferol), obtained through diet and exposure of skin to sunlight. Unless otherwise specified, vitamin D status refers to the sum total of D₂ and D₃ concentrations. While both forms of vitamin D utilize the same enzymes in their metabolic pathways, the differences in their side chains (vitamin D₂ contains a double bond between carbons 22 and 23, and a methyl group on carbon 24) result in the production of unique metabolites of differing potencies and bioeffectiveness.³⁴ Active metabolites of vitamin D₂ have a diminished ability to bind to (1) vitamin D binding proteins and (2) vitamin D receptors, compared to metabolites of vitamin D₃.³⁵⁻³⁷ Further, the enzyme 25-hydroxylase converts vitamin D₃ to 25[OH]D₃ (which is an ideal indicator of vitamin D₃ status due to its 3 week half-life) five (5) times as fast as it converts vitamin D₂ to 25[OH]D₂.³⁸⁻³⁹ A 2004 study by Armas et al. compared the time course of serum 25[OH]D concentrations over a 28 day period after a single 50,000 IU dose of either vitamin D₂ or vitamin D₃ administered to 20 healthy men.³⁶ Both produced a similar rise in serum total 25[OH]D concentrations in the first 3 days, however serum total 25[OH]D concentrations of participants who received vitamin D₂ rapidly declined reaching baseline by day 14 and then fell below baseline by day 28. Participants treated with vitamin D₃ had serum 25[OH]D concentrations that continued to rise after day 3, peaking at day 14 and were above baseline at day 28. Moreover, the investigators stated that vitamin D₃ was more than 3 times more potent than vitamin D₂.³⁶ These findings and previous reports support the stronger relationship of vitamin D status with risk of GDM we observed when using 25[OH]D₃ concentrations, compared to using total 25[OH]D concentrations.

Several biological mechanisms have implicated vitamin D insufficiency or deficiency in GDM pathogenesis. First, vitamin D deficiency may contribute to the development of GDM via calcium pool dysregulation in the pancreas. Normally, 1,25[OH]D binds to vitamin D receptors (VDR) in pancreatic beta-cells, regulating the balance between extracellular and

intracellular beta cell calcium pools in the pancreas.^{9, 40-42} Second, vitamin D may contribute to lower GDM risk via its effects on insulin-sensitive tissues. Vitamin D promotes insulin sensitivity by stimulating insulin receptor expression and enhancing insulin responsiveness to glucose.^{4, 43-44} Third, interactions of vitamin D and vitamin D related genetic variations (e.g. VDR) with the insulin like growth factor system influence glucose homeostasis.⁴⁴ Fourth, vitamin D may contribute to lower GDM risk via its role in mitigating inflammation and its effects.⁴ Several studies have shown that systemic inflammation, through pancreatic beta cell dysfunction and apoptosis, is associated with T2DM.⁴⁵⁻⁴⁷ Finally, the close relationship of vitamin D deficiency with other common risk factors, such as obesity, may account, in part, for its association with GDM and other related pregnancy complications. In our study, we observed limited mediation of the effects of vitamin D status on GDM risk by mid-pregnancy BMI. While mid-pregnancy BMI is strongly related to vitamin D and mid-pregnancy obesity is a strong predictor of GDM (OR 2.2, 95%CI 1.39, 3.59, P-value=0.002, in our study), it appears that effect of vitamin D status is largely independent of mid-pregnancy BMI. It should be noted that use of mediation analyses in case-cohort settings, particularly the MSM approach, has not been fully explored and findings should be interpreted with caution.^{30, 32-33}

The prospective study design, measurement of vitamin D metabolites, and assessment of potential mediation of associations by mid-pregnancy BMI are some of the strengthes of the current study. On the other hand, several limitations of our study deserve mention. First, we had a single measurement of vitamin D status which does not allow a time integrated measure reflecting vitamin D status over the course of pregnancy. It also does not enable us to identify a critical period during pregnancy when vitamin D status is particularly relevant in relation to risk of GDM. In addition, the previously reported categories we used to define vitamin D status are not pregnancy-specific and changes in pregnancy-related vitamin D metabolism may limit use of these cutoffs in pregnancy studies. Our quartile-based analyses along with other similar studies may provide valuable insight on appropriate cutoffs for 25[OH]D concentrations to guide analyses of association studies or design supplementation studies.²⁷ Second, we did not measure other related indicators of biological activities of vitamin D such as vitamin D receptors, vitamin D binding protein, and enzymes related to vitamin D metabolism (such as 25-OHase and 1-OHase). Third, though we excluded pregnant women with known Type 1 or Type 2 diabetes, it is possible that a limited number of women may have had undiagnosed pre-pregnancy glucose intolerance or DM at the time of blood collection, which would result in outcome misclassification. Among control participants there were 38 women who had failed glucola and 9 women who failed one of the OGTT tests, but did not meet criteria for GDM diagnosis. We conducted sensitivity analyses to deterrmine whether our findings would be different after excluding these participants. However, we did not observe material differences in our findings from those reported in the current manuscript. Fourth, there may be residual confounding in our adjusted measures of association as well as confounding from unmeasured variables. Fifth, mid-pregnancy BMI may not fully characterize weight gain during pregnancy and the effect of vitamin D on pregnancy weight gain may not be captured by mid-pregnancy BMI measurement. Finally, generalizability in our study is guarded for other populations that have different socioeconomic and ethnic composition. In addition, possible differences in

associations among race/ethnic groups that constitute the “other” group in our study should be explored. However, we were not able to assess this in the current study because of small numbers and limited statistical power. Similarity of findings of reports from studies conducted in different study populations mitigates this concern.

Our study provides modest evidence for associations between maternal early pregnancy 25[OH]D₃ concentrations and subsequent risk of GDM. We also found evidence that this association is mediated, at least in part, by mid-pregnancy BMI. Additional studies are needed to better understand the association between maternal 25[OH]D₃ deficiency and GDM, the biological pathways involved, and the impact of vitamin D supplementation (in terms of dose and timing) on risk of GDM. Confirmation of our results would suggest the possibility of reducing the risk of GDM and related morbidity and mortality through vitamin D supplementation.

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Table 1
 Characteristics of study participants according to gestational diabetes mellitus (GDM) status

Characteristics	GDM Cases (N=135) n (%)	Non-GDM Controls (N= 517) n (%)	P-value §
Maternal Age (years)	33.5 ± 4.6	32.6 ± 4.4	0.03
<35	79 (58.5)	345 (66.7)	0.08
35	56 (41.5)	172 (33.3)	
Marital Status	116 (85.9)	447 (86.5)	0.87
Post-high School Education	122 (90.4)	474 (91.7)	0.86
Non-Hispanic White	96 (71.1)	441 (85.3)	<0.001
Nulliparous	79 (58.5)	320 (61.9)	0.47
Leisure Time Physical Activity	98 (72.6)	393 (76.0)	0.70
Prenatal Vitamin Use	124 (91.9)	477 (92.3)	0.96
Infant Birth Weight (grams)	3479 ± 584	3433 ± 670	0.47
GA at Delivery (weeks)	38.3 ± 1.9	38.7 ± 2.1	0.03
Current Smoking	10 (7.4)	30 (5.8)	0.53
Family History of Diabetes Mellitus	46 (34.1)	65 (12.6)	<0.001
Family History of Hypertension	76 (56.3)	226 (43.7)	0.009
Pre-pregnancy BMI* (kg/m ²)*	25.9 ± 6.7	23.1 ± 4.7	<0.001
18-22 Weeks Gestation BMI (kg/m ²)	28.4 ± 6.5	25.6 ± 4.4	<0.001
GA* at Blood Draw (weeks)	15.2 ± 2.9	15.3 ± 2.8	0.75
Season of Blood Draw			
Spring (March-May)	36 (26.7)	145 (28.1)	0.99
Summer (Jun-Aug)	37 (27.4)	135 (26.1)	
Autumn (Sept- Nov)	35 (25.9)	135 (26.1)	
Winter (Dec-Feb)	27 (20.0)	102 (19.7)	
Total Maternal Serum 25[OH]D (ng/ml)	27.3 ± 8.7	29.3 ± 8.3	0.01
Maternal Serum 25[OH]D ₃ (ng/ml)	23.9 ± 9.4	26.7 ± 8.8	0.002
Maternal Serum 25[OH]D ₂ (ng/ml)	3.6 ± 5.0	2.9 ± 4.4	0.13

§ P-values comparing GDM cases to non-GDM controls

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Mean $\pm$ SD (standard deviation)
* Abbreviations: **BMI**, body mass index; **GA**, gestational age

Table 2

Associations of maternal serum total 25[OH]D concentrations (ng/ml) in early pregnancy with risk of gestational diabetes mellitus

	GDM Cases (N=135)	Non-GDM Controls (N=517)	Unadjusted OR (95%CI)	Adjusted ⁺ OR (95%CI)	Adjusted ⁺⁺ OR (95%CI)	Adjusted ⁺⁺⁺ OR (95%CI)
TOTAL 25[OH]D (continuous)						
Per 5 ng/ml increase			0.86 (0.77-0.97)	0.90 (0.80-1.03)	0.95 (0.83-1.08)	0.96 (0.84-1.10)
TOTAL 25[OH]D (categorical)						
Sufficient (≥ 30 ng/ml)	50 (37.0)	234 (45.3)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Insufficient (20-29 ng/ml)	61 (45.2)	226 (43.7)	1.26 (0.83-1.92)	1.27 (0.82-1.95)	1.12 (0.72-1.74)	1.04 (0.66-1.63)
Deficient (<20 ng/ml)	24 (17.8)	57 (11.0)	1.97 (1.12-3.47)	1.63 (0.89-2.97)	1.38 (0.74-2.57)	1.30 (0.69-2.44)
P for trend			0.023	0.099	0.321	0.481
TOTAL 25[OH]D (ng/ml) (quartiles)						
1 st Quartile (≤ 34.9)	22 (16.3)	129 (25.0)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
2 nd Quartile (29.1-34.8)	33 (24.4)	129 (25.0)	1.50 (0.83-2.71)	1.32 (0.71-2.43)	1.29 (0.70-2.39)	1.29 (0.69-2.39)
3 rd Quartile (23.5-29.0)	34 (25.2)	130 (25.0)	1.53 (0.85-2.76)	1.39 (0.76-2.56)	1.29 (0.70-2.38)	1.20 (0.64-2.23)
4 th Quartile (<23.5)	46 (34.1)	129 (25.0)	2.09 (1.19-3.67)	1.65 (0.92-2.98)	1.43 (0.78-2.62)	1.37 (0.74-2.52)
P for trend	---	---	0.013	0.104	0.284	0.388

Vitamin D deficiency was defined according to the cut-points given by Holick, 2007

⁺ Adjusted for season of blood draw, maternal age, race/ethnicity, family history of diabetes⁺⁺ Adjusted for season of blood draw, maternal age, race/ethnicity, family history of diabetes, Pre-pregnancy BMI⁺⁺⁺ Adjusted for season of blood draw, maternal age, race/ethnicity, family history of diabetes, BMI at 18-22 weeks pregnancy

Table 3

Interaction of pre-pregnancy overweight/obesity status with maternal serum total 25[OH]D concentrations on gestational diabetes mellitus (GDM)

Characteristics	GDM		Stratified model		Joint model	
	Yes (N=135)	No (N=517)	Adjusted OR	95% (CI)	Adjusted OR	95% (CI)
Total 25[OH]D/Body mass index (BMI)						
25[OH]D 30 ng/ml, BMI<25kg/m ²	36 (26.7)	191 (36.9)	Referent	Referent	Referent	Referent
25[OH]D<30 ng/ml, BMI<25kg/m ²	40 (29.6)	206 (39.9)	1.02	(0.61-1.70)	1.02	(0.61-1.70)
25[OH]D 30 ng/ml, BMI 25kg/m ²	14 (10.4)	43 (8.3)	Referent	Referent	1.68	(0.81-3.46)
25[OH]D<30 ng/ml, BMI 25kg/m ²	45 (33.3)	77 (14.9)	1.96	(0.90-4.27)	2.81	(1.64-4.83)
P-value for interaction					0.279	

Vitamin D sufficient, 30 ng/ml; pre-pregnancy overweight/obese, 25kg/m²

Adjusted for season of blood draw, maternal age, race/ethnicity, family history of diabetes

* Numbers may not add up to total number of GDM cases or non-GDM controls due to missing data.

Table 4

Associations of maternal serum 25[OH]D₃ concentrations (ng/ml) in early pregnancy with risk of gestational diabetes mellitus

	GDM Cases (N=135)	Non-GDM Controls (N=517)	Unadjusted OR (95%CI)	Adjusted ⁺ OR (95%CI)	Adjusted ⁺⁺ OR (95%CI)	Adjusted ⁺⁺⁺ OR (95%CI)
25[OH]D₃ (continuous)						
Per 5 ng/ml increase			0.84 (0.75-0.94)	0.86 (0.76-0.96)	0.88 (0.78-0.99)	0.90 (0.79-1.01)
25[OH]D₃ (categorical)						
Sufficient (≥ 30)	33 (24.4)	178 (34.4)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Insufficient (20-29)	53 (39.3)	221 (42.8)	1.29 (0.80-2.08)	1.33 (0.81-2.18)	1.19 (0.72-1.96)	1.13 (0.68-1.88)
Deficient (<20)	49 (36.3)	118 (22.8)	2.24 (1.36-3.69)	1.95 (1.16-3.29)	1.78 (1.04-3.02)	1.64 (0.96-2.81)
P for trend			0.002	0.012	0.034	0.073
25[OH]D₃ (ng/ml) (quartiles)						
1 st Quartile (≤ 32.5)	23 (17.0)	129 (25.0)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
2 nd Quartile (26.4-32.4)	29 (21.5)	130 (25.0)	1.25 (0.69-2.28)	1.14 (0.62-2.12)	1.03 (0.55-1.93)	1.03 (0.55-1.93)
3 rd Quartile (20.6-26.3)	28 (20.7)	129 (25.0)	1.22 (0.67-2.22)	1.21 (0.65-2.26)	1.02 (0.54-1.92)	0.95 (0.50-1.81)
4 th Quartile (<20.6)	55 (40.7)	129 (25.0)	2.39 (1.39-4.12)	2.03 (1.15-3.58)	1.79 (1.01-3.19)	1.68 (0.94-3.00)
P for trend			0.001	0.010	0.034	0.072

Vitamin D deficiency was defined according to the cut-points given by Holick, 2007

⁺ Adjusted for season of blood draw, maternal age, race/ethnicity, family history of diabetes⁺⁺ Adjusted for season of blood draw, maternal age, race/ethnicity, family history of diabetes, Pre-pregnancy BMI⁺⁺⁺ Adjusted for season of blood draw, maternal age, race/ethnicity, family history of diabetes, BMI at 18-22 weeks pregnancy

Table 5

Interaction of pre-pregnancy overweight/obesity status with maternal serum 25[OH]D₃ concentrations on gestational diabetes mellitus (GDM)

Characteristics	GDM		Stratified model		Joint model	
	Yes (N=135)	No (N=517)	Adjusted OR	95% (CI)	Adjusted OR	95% (CI)
25[OH]D ₃ /Body mass index (BMI)						
25[OH] D ₃ 30 ng/ml, BMI<25kg/m ²	23 (17.0)	144 (27.9)	Referent	Referent	Referent	Referent
25[OH] D ₃ <30 ng/ml, BMI<25kg/m ²	53 (39.3)	253 (48.9)	1.29	(0.75-2.23)	1.29	(0.75-2.23)
25[OH] D ₃ 30 ng/ml, BMI 25kg/m ²	10 (7.4)	34 (6.6)	Referent	Referent	1.76	(0.75-4.17)
25[OH] D ₃ <30 ng/ml, BMI 25kg/m ²	49 (36.3)	82 (16.6)	2.02	(0.85-4.76)	3.24	(1.80-5.83)
P-value for interaction	0.487					

Vitamin D sufficient, 30 ng/ml; pre-pregnancy overweight/obese, 25kg/m²

Adjusted for season of blood draw, maternal age, race/ethnicity, family history of diabetes

* Numbers may not add up to total number of GDM cases or non-GDM controls members due to missing