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Early-pregnancy maternal vitamin D status and maternal hyperglycaemia

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Abstract

Aims—To estimate the association between serum 25-hydroxyvitamin D concentrations and maternal hyperglycaemia (post-load glucose concentration ≥ 7.5 mmol/l).

Methods—Pregnant women ($n = 429$; 61% black, 36% obese, 45% smokers) enrolled in a cohort study at <16 weeks gestation. Non-fasting blood samples were assayed for serum 25-hydroxyvitamin D at enrolment. At 24–28 weeks gestation, maternal hyperglycaemia was determined using a 50-g 1-h oral glucose challenge test.

Results—A total of 67% of women had 25-hydroxyvitamin D concentrations < 50 nmol/l and 11% had maternal hyperglycaemia. Among smokers, each 23-nmol/l increase in serum 25-hydroxyvitamin D was associated with a reduction in the odds of maternal hyperglycaemia [odds ratio: 0.30 (95% CI: 0.13, 0.68)] after adjustment for parity, race/ethnicity, age, pre-pregnancy BMI, marital status, income, family history of diabetes, and gestational age of gestational diabetes mellitus screening. Among non-smokers, we found no association between early pregnancy vitamin D status and maternal hyperglycaemia.

Conclusions—Smoking status may modify the relationship between poor maternal vitamin D status and maternal hyperglycaemia.

Introduction

Gestational diabetes mellitus, defined as glucose intolerance with onset or first recognition during pregnancy, occurs in 4% of pregnancies [1]. Gestational diabetes is a major risk factor for a variety of pregnancy complications, including macrosomia and birth trauma [2, 3]. Even among women who do not have gestational diabetes, high blood sugar during pregnancy, termed maternal hyperglycaemia, may pose a threat to a healthy pregnancy. Maternal glucose below the threshold of gestational diabetes is positively associated with adverse birth outcomes, such as pre-eclampsia, shoulder dystocia and large-for-gestational age birth [4]. Despite the impact on health, the aetiology of maternal hyperglycaemia remains obscure.

Maternal vitamin D status may be a modifiable factor associated with maternal hyperglycaemia. Vitamin D, a secosteroid obtained through diet and supplement use as well as cutaneous synthesis after sunlight exposure, is required for the secretion of insulin [5].

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Competing interests

None declared.

Results from previous studies relating early pregnancy maternal vitamin D status to risk of gestational diabetes have been inconsistent [6–9], and no work has studied hyperglycaemia as an outcome in a cohort of primarily low-income women. Because maternal hyperglycaemia is associated with poor pregnancy and birth outcomes, studying its association with a modifiable risk factor such as vitamin D status may be of clinical use.

The objective of our study was to determine the independent association between early maternal vitamin D status, as measured by serum 25-hydroxyvitamin D [25(OH)D] and mid-pregnancy maternal hyperglycaemia.

Patients and methods

We used data from the Study of Nutrition and Pregnancy (SNAP). SNAP is a prospective pregnancy cohort study to assess nutrition and infection as contributors to preterm birth, and was conducted among women receiving care in the resident clinics at Magee-Womens Hospital of the University of Pittsburgh Medical Center, an urban academic medical centre in Pittsburgh, PA, USA [10]. The clinics serve primarily low-income women with public insurance, about 50% of whom are African-American. Eligible women had singleton pregnancies and were non-Hispanic black or non-Hispanic white based on self-report. Women were excluded if they had pre-gestational diabetes, vaginal bleeding, thrombophilias, chronic hypertension requiring medication, current or planned cervical cerclage, a compromised immune system, autoimmune diseases, or known use of illegal drugs or controlled substances. Women were enrolled at < 16 weeks gestation. At enrolment, women provided informed, written consent, completed a structured interview that included questions on sociodemographic factors and medical history, and provided a non-fasting blood sample. At 24–28 weeks gestation, women were screened for gestational diabetes as part of routine clinical care. Women were then followed through their pregnancy, and data on post-load glucose concentrations, antenatal and delivery events, and neonatal outcomes were abstracted from medical records after delivery. The study was approved by the University of Pittsburgh Institutional Review Board.

A total of 674 eligible pregnant women were enrolled at the time of this analysis. We excluded women whose pregnancies ended in fetal demise (spontaneous abortion, therapeutic abortion or stillbirth) before gestational diabetes screening ($n = 68$), women who transferred care before gestational diabetes screening ($n = 25$), and women lacking sufficient serum for 25(OH)D assay ($n = 30$). Post-load glucose concentrations were collected as part of clinical care, not as part of the research protocol. Consequently, 121 women were excluded because they were missing post-load glucose values. Lastly, one woman was excluded for whom information was missing on variables required for the final model. Mean post-load glucose concentrations and maternal characteristics did not significantly differ between women included and excluded from the analyses (data not shown). A total of 429 women were included in the final analyses.

A 50-g 1-h oral glucose challenge test was performed at about 24–28 weeks gestation to screen for gestational diabetes. Women with post-load glucose concentration values ≥ 7.5 mmol/l additionally received a 100-g 3-h oral glucose tolerance test. All glucose concentration results were abstracted from medical records. Women were diagnosed with gestational diabetes if they had a post-load glucose concentration ≥ 10 mmol/l, or two or more abnormal 3-h 100-g oral glucose tolerance results [11]. We defined maternal hyperglycaemia as a post-load glucose concentration ≥ 7.5 mmol/l. A total of 39 women, whose healthcare provider classified them as high risk, underwent early gestational diabetes screening (< 24 weeks gestation). We conducted a sensitivity analysis to determine the influence of excluding these women from our analysis and found no significant difference

between the models (data not shown); therefore, women with early gestational diabetes screening were retained in our sample.

Maternal serum samples were stored in aliquots at -80°C until they were analysed in a Vitamin D External Quality Assessment Scheme (DEQAS)-certified laboratory for 25(OH)D [25(OH)D2 + 25(OH)D3] using a DiaSorin radioimmunoassay (DiaSorin Corp., Stillwater, MN, USA). The radioimmunoassay detects 100% of 25(OH)D2 and 100% of 25(OH)D3. The interassay coefficient of variation was 9.5%. The detectable limits for the radioimmunoassay are 3.75–250 nmol/l. None of the samples of 25(OH)D included in our analysis fell outside this range. We defined vitamin D deficiency as < 50 nmol/l and also explored a cut-off of < 40 nmol/l [12].

Women were classified as current smokers if they reported in an interviewer-administered questionnaire smoking any cigarettes during pregnancy and as non-smokers if they did not. In the last year of enrolment, a trained research nurse measured exhaled carbon monoxide (CO) in all study subjects to confirm self-reported smoking status ($n = 122$) [13]. Exhaled CO concentration was measured using a CO breath analyser (Micro CO; Micro Medical Limited; Chatham, UK) that was sensitive to CO concentrations from 1 to 500 ppm (by volume). Participants were asked to hold their breath for 15 s and then exhale slowly with a constant flow into the analyser, and this measurement was recorded.

Maternal demographics and pre-pregnancy weight were obtained by self-report at enrolment, and self-reported family history of diabetes was abstracted from medical records after delivery. Marital status was defined as married or unmarried (single, separated, widowed or divorced). Employment status was defined as unemployed or employed (which included women who worked full time, part time, or occasionally). A family history of diabetes included any reported history of a family member having Type 1 or Type 2 diabetes. Pre-pregnancy BMI was calculated as self-reported pre-pregnancy weight (kg) divided by measured height (m^2) and categorized as underweight (< 18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥ 30 kg/m^2) [14]. The season of blood sampling was categorized as winter (October–March) or summer (April–September).

The Student's *t*-test and Pearson chi-squared test were used to determine the differences in post-load glucose concentration and vitamin D status by maternal characteristics. The relationship of serum 25(OH)D concentration with post-load glucose concentration was assessed using locally weighted regression (locally weighted least squares smoothing plots) [15]. As no meaningful deviations from linearity were found, 25(OH)D was examined as a continuous variable. We also categorized 25(OH)D using recommended cut-off points [12]. Multivariable linear and logistic regression models were used to estimate the association between maternal 25(OH)D and glucose concentrations and the odds of hyperglycaemia, respectively. Risk differences were calculated using the 'margins' command in STATA A. We assessed maternal age, parity, race/ethnicity, smoking status, marital status, annual family income, employment status, education, family history of diabetes, pre-pregnancy BMI, season of 25(OH)D sample and gestational age at gestational diabetes screening as potential confounders. We defined confounding as a $> 10\%$ change in the adjusted vitamin D β coefficient after exclusion of the covariate from the full model. The final model included 25(OH)D, smoking, an interaction term between smoking and 25(OH)D, and the following significant confounders: parity, race/ethnicity, pre-pregnancy BMI, marital status, income, family history of diabetes and gestational age of gestational diabetes screening. Age was included in the final model out of convention. Effect modification by race/ethnicity, pre-pregnancy BMI, and smoking were tested using the Wald test ($\alpha < 0.05$). Because smoking was found to modify the association between maternal vitamin D on maternal glucose

concentrations, we additionally conducted a *post hoc* analysis of the effect modification of exhaled CO values (a biomarker of smoking status) on the relationship between 25(OH)D and maternal hyperglycaemia in a sub-sample of women with exhaled CO values ($n=123$). We used linear regression to assess the effect modification by CO values. Because of the small sample size we adjusted only for race/ethnicity, pre-pregnancy obesity and season. Data were analysed using STATA software version 11.0 (StataCorp, College Station, TX).

Results

The mean (SD) gestational age at enrolment was 9.5 (2.8) weeks. The majority of women were young, unmarried, low-income, multiparous, African-American and high-school educated (Table 1). Nearly half of the women in the cohort smoked during pregnancy and more than one-third were obese before pregnancy. The mean (SD) 25(OH)D concentration was 41.5 (23.7) nmol/l. Approximately 54 and 67% of women had 25(OH)D concentrations < 40 and < 50 nmol/l, respectively. Vitamin D deficiency [25(OH)D < 50 nmol/l] was more prevalent in multiparous, African-American, unmarried, high-school educated, and obese women, as well as women whose blood was drawn in winter months (Table 1). Furthermore, married women and obese women were significantly more likely to have hyperglycaemia than their counterparts. Neither 25(OH)D deficiency nor hyperglycaemia differed by maternal age, smoking status, employment or family history of diabetes.

Women were screened for gestational diabetes at ~26.6 (SD: 4.0) weeks gestation, and the mean (SD) post-load glucose concentration was 5.6 (1.4) mmol/l. In all, 11% of the women ($n=47$) had maternal hyperglycaemia and 2.8% were diagnosed with gestational diabetes. Of the 12 women who had gestational diabetes, nine were vitamin D-deficient and six were smokers. Prevalence of maternal hyperglycaemia did not differ by serum 25(OH)D status (Table 2).

Smoking status during pregnancy modified the association between early pregnancy serum 25(OH)D and maternal hyperglycaemia ($P<0.01$). Among smokers, serum 25(OH)D was lower among women with maternal hyperglycaemia. After adjustment for parity, race/ethnicity, age, pre-pregnancy BMI, marital status, income, family history of diabetes and gestational age of gestational diabetes screening, there was a negative association between 25(OH)D at <16 weeks and the likelihood of maternal hyperglycaemia among smokers (Table 2). The difference in maternal hyperglycaemia risk between 25(OH)D-sufficient women and 25(OH)D-insufficient women was -9.17% (-15.64%, -2.71%; $P=0.005$). Results were similar when we assessed the association of 25(OH)D and continuous post-load glucose concentrations using linear regression (Fig. 1). Each SD increase in 25(OH)D concentration resulted in a 0.34 (95% CI: 0.59, 0.09)-mmol/l decrease in post-load glucose ($P<0.01$). There was no association between maternal vitamin D status at <16 weeks and hyperglycaemia among non-smokers, either before or after adjustment.

The effect modification of the 25(OH)D-glucose relationship by smoking was confirmed when we performed linear regression analyses using exhaled CO as a biomarker for smoking after adjusting for race/ethnicity, pre-pregnancy BMI, and season of blood sample [mean (SD) exhaled CO: 3.2 (4.0) ppm among self-reported non-smokers; 10.4 (6.7) ppm among self-reported smokers (data not shown)].

Discussion

In this cohort of low-income, urban African-American and white pregnant women, the association between maternal serum 25(OH)D and maternal hyperglycaemia varied by maternal smoking status. Among smokers, serum 25(OH)D concentrations in early

pregnancy were inversely associated with glucose. The associations remained statistically significant after adjustment for measured confounders, and was confirmed when a biomarker of self-reported smoking status was used.

We are unaware of any previous study that has tested the modifying effect of smoking on associations between vitamin D and maternal hyperglycaemia; however, an association between vitamin D deficiency and risk of hyperglycaemia is consistent with results from two nested case-control studies. Among 116 women with gestational diabetes and 219 controls, Parlea *et al.* [7] found that women who went on to develop gestational diabetes were 2.3 times (95% CI: 1.1–4.8) as likely to have a serum 25(OH)D < 46.9 nmol/l than women who did not develop gestational diabetes. Similarly, Zhang *et al.* [6] found that women with gestational diabetes were nearly three times as likely to have serum 25(OH)D < 50 nmol/l than women without gestational diabetes. In two other case-control studies, vitamin D status measured early in pregnancy was not significantly associated with gestational diabetes [8, 9]. Cross-sectional studies of vitamin D status in mid to late pregnancy report conflicting results [16–20]. For example, McLeod *et al.* [19] used data on serum 25(OH)D and fasting blood glucose measured contemporaneously at 24–38 weeks among ~400 women participating in the Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study. They found that each SD increase in serum 25(OH)D was related to a modest decrease in fasting blood glucose [0.05 mmol/l ($P = 0.01$)] after confounder adjustment. Many of these studies had a low prevalence of smoking or did not report the prevalence of smoking. Our findings may also differ because we studied hyperglycaemia rather than gestational diabetes owing to low prevalence of gestational diabetes in the cohort. Additionally, over half of women in our cohort were vitamin D-deficient, and were predominantly African-American, low-income, and parous, and nearly half smoked during pregnancy.

We can speculate on the possible mechanisms underlying the difference in our findings by smoking status. It may be that the association between vitamin D and maternal glucose concentration differs in the presence of oxidative stress. Exhaled CO values are not only a biomarker of smoking status, but may also indicate oxidative stress among people with diabetes [21]; therefore, our exhaled CO results suggest that vitamin D lowers glucose concentrations in the presence of oxidative stress. While this has not been elucidated *in vivo*, *in vitro* cancer studies have suggested that metabolites of vitamin D may have antioxidant properties in some cell lines but not in others [22]. Researchers have hypothesized that vitamin D exhibits oxidative properties in some situations and pro-oxidant properties in others, because vitamin D may actually cause a small amount of oxidative stress, stimulating a cell's detoxification mechanisms when challenged with other oxidative stress challenges [22]. More research is needed to test this hypothesis rigorously. Smoking may also trigger an inflammatory response [23] that reduces vitamin D levels [24] and increases glucose concentrations [25]. Unfortunately, biomarkers of systematic inflammation, such as C-reactive protein, were not collected as a part of our study and we were not able to assess this potentially important confounder.

In our cohort, maternal 25(OH)D status did not differ between smokers and non-smokers, but, while some have suggested that smokers have poorer vitamin D status [26, 27], others have found no difference [28, 29]. This is probably attributable to the characteristics of our cohort, as there is some evidence that smoking and vitamin D status are not associated in women of reproductive age but may be negatively associated in older women [29].

Gestational diabetes was rare in our cohort, which may be attributable to the young age of our cohort and the exclusion of women with multiple gestations. We were unable to assess the confounding effects of inflammation, physical activity, dietary intake and water retention as these covariates were not measured in our study, and residual confounding may exist. For

example, in women with undiagnosed diabetes before pregnancy, the kidney may retain water. This, in turn, may artificially dilute concentrations of 25(OH)D, making it appear that low 25(OH)D concentrations are associated with high glucose concentrations, thereby biasing our results away from the null. The majority of women in our cohort were vitamin D-deficient, but the high prevalence of vitamin D deficiency in our population of black and white women living in the northeastern USA is consistent with a number of recent diverse pregnancy cohorts [30]. The sample size was very small for some of our comparison groups, limiting the precision of our estimates. We studied a low-income, urban, predominantly African-American population, a group that has been under-represented in the previous literature. We measured 25(OH)D concentrations early in pregnancy, which supports a temporal relationship between maternal vitamin D status and hyperglycaemia. Lastly, we quantified serum 25(OH)D in a DEQAS-certified laboratory using a DiaSorin radioimmunoassay kit, a rigorous method that detects 100% of 25(OH)D₂ and 25(OH)D₃, and generates comparable results to liquid chromatography tandem mass spectrometry methods [34].

Additional research is needed to confirm or refute our findings that smoking during pregnancy may modify the association between maternal vitamin D status and glucose concentrations. Given the high prevalence of vitamin D deficiency in pregnancy and rising rates of gestational diabetes, understanding this relationship could potentially improve the health of pregnant women.

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What's new?

- Our results suggest that smoking status may modify the relationship between poor maternal vitamin D status and maternal hyperglycaemia.

FIGURE 1.

Scatter plot of post-load glucose (24--28 weeks gestation) and early pregnancy (< 16 weeks) 25-hydroxyvitamin D concentrations among pregnant women who are smokers. Correlation coefficient = -0.09 , $P < 0.01$, $n = 192$.

Maternal characteristics of 429 participants in the study, and early pregnancy (<16 weeks) vitamin D insufficiency (25-hydroxyvitamin D concentration 50 nmol/l) and hyperglycaemia (post-load glucose concentration 7.5 mmol/l) stratified by characteristic

Table 1

Characteristic	Total n (%)	Vitamin D insufficiency group n (%)	P*	Hyperglycaemia group n (%)	P
Maternal age at enrolment					
17–29 years	363 (84.6)	242 (66.7)		37 (10.2)	
30–42 years	66 (15.4)	46 (69.7)	0.63	10 (15.2)	0.24
Parity					
0	86 (20.1)	38 (44.2)		8 (9.3)	
1–7	343 (79.9)	250 (72.9)	<0.01	39 (11.4)	0.58
Race/Ethnicity					
White	167 (38.9)	66 (39.5)		22 (13.2)	
African-American	262 (61.1)	222 (84.7)	<0.01	25 (9.5)	.24
Smoking status					
Smoker	192 (44.8)	129 (67.2)		19 (9.9)	
Non-smoker	237 (55.2)	159 (67.1)	0.98	28 (11.8)	0.53
Marital status					
Married	66 (15.4)	33 (50.0)		14 (21.2)	
Not married	363 (84.6)	255 (70.3)	<0.01	33 (9.1)	<0.01
Annual family income					
< \$10,000	186 (43.4)	130 (69.9)		21 (11.3)	
\$10,000–25,000	148 (34.5)	105 (71.0)		12 (8.1)	
\$25,000–50,000	1 (18.9)	9 (60.5)		13 (16.1)	
\$50,000	14 (3.3)	4 (28.6)	<0.01	1 (7.1)	0.31
Employment status					
Employed	228 (53.2)	150 (65.8)		26 (11.4)	
Not employed	201 (46.8)	138 (68.7)	0.53	21 (10.5)	0.75
Educational status					
High school degree	377 (87.9)	259 (68.7)		38 (10.1)	
College degree	45 (10.5)	27 (60.0)		7 (15.6)	
Post-college degree	7 (1.6)	2 (28.6)	0.05	2 (28.6)	0.17
Family history of diabetes					

Characteristic	Total n (%)	Vitamin D insufficiency group n (%)	P*	Hyperglycaemia group n (%)	P
History of diabetes	162 (37.8)	115 (71.0)		17 (10.5)	
No history of diabetes	267 (62.2)	173 (64.8)	0.19	30 (11.2)	0.81
Pre-pregnancy BMI					
Underweight: <18.5 kg/m ²	12 (2.8)	5 (41.7)		1 (8.3)	
Normal: 18.5–24.9 kg/m ²	167 (38.9)	101 (60.5)		11 (6.6)	
Overweight: 25–29.9 kg/m ²	96 (22.4)	60 (62.5)		9 (9.4)	
Obese: ≥30 kg/m ²	154 (35.9)	122 (79.2)	0.01	6 (16.9)	.03
25(OH)D season sample					
October–March	233 (54.3)	176 (75.5)		21 (10.7)	
April–September	196 (45.7)	112 (57.1)	<0.01	26 (11.2)	0.88

25(OH)D, 25-hydroxyvitamin D.

* Calculated using the chi-squared test.

Table 2

Prevalence of hyperglycaemia (post-load glucose concentration ≥ 7.5 mmol/l) by early pregnancy (< 16 weeks) vitamin D status in the 429 study participants

	Low glucose < 7.5 mmol/l $N=437$	Hyperglycaemia $N=51$	P^1
Total			
Mean (SD) serum 25(OH)D, nmol/l,	42.9 (24.3)	39.1 (17.9)	0.30
Vitamin D status, n (%)			
25(OH)D < 50.0 nmol/l	254 (88.2)	34 (11.8)	
25(OH)D ≥ 50.0 nmol/l	128 (90.8)	13 (9.2)	0.42
Non-smokers			
Mean (SD) serum 25(OH)D, nmol/l	41.1 (23.0)	46.3 (16.3)	0.25
Vitamin D status, n (%)			
25(OH)D < 50.0 nmol/l	142 (89.3)	17 (10.7)	
25(OH)D ≥ 50.0 nmol/l	67 (85.9)	11 (14.1)	0.45
Smokers			
Mean (SD) serum 25(OH)D, nmol/l	45.1 (25.6)	28.4 (15.0)	<0.01
Vitamin D status, n (%)			
25(OH)D < 50.0 nmol/l	112 (86.8)	17 (13.2)	
25(OH)D ≥ 50.0 nmol/l	61 (96.8)	2 (3.2)	0.03

25(OH)D, 25-hydroxyvitamin D.

* Calculated using Students' t -test for serum 25(OH)D and chi-squared test for vitamin D status

Table 3

Association between early pregnancy (<16 weeks) 25-hydroxyvitamin D and maternal hyperglycaemia (post-load glucose concentration ≥ 7.5 mmol/l), stratified by smoking status in the 429 study participants

	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
Non-smokers		
Serum 25(OH)D		
OR reflects 23 nmol/l increase [†]	1.26 (0.85, 1.85)	1.17 (0.73, 1.87)
Vitamin D status		
25(OH)D < 50.0 nmol/l	ref	ref
25(OH)D $\geq$ 50.0 nmol/l	1.37 (0.61, 3.09)	1.18 (0.57, 2.64)
Smokers		
Serum 25(OH)D,		
OR reflects 23 nmol/l increase ²	0.30 (0.14, 0.67)	0.30 (0.13, 0.68)
Vitamin D status		
25(OH)D < 50.0 nmol/l	ref	ref
25(OH)D $\geq$ 50.0 nmol/l	0.16 (0.03, 0.87)	0.14 (0.02, 0.85)

25(OH)D, 25-hydroxyvitamin D; OR, odds ratio.

* Adjusted for parity, race/ethnicity, age, pre-pregnancy BMI, marital status, income, family history of diabetes, and gestational age of gestational diabetes screening

[†] 23 nmol/l is 1 SD increase in serum 25(OH)D.