First-Trimester Circulating 25-Hydroxyvitamin D Levels and Development of Gestational Diabetes Mellitus

Mahlatse Makgoba, mbchb[1]
Scott M. Nelson, mrcog[2]
Makrina Savvidou, md[1,3]
Claudia-Martina Messow, phd[4]
Kypros Nicolaides, mrcog[3]
Naveed Sattar, frcp[5]

OBJECTIVE—To investigate the association between first-trimester maternal serum levels of 25-hydroxyvitamin D (25-OH-D) as measured by liquid chromatography-tandem mass spectrometry and development of gestational diabetes mellitus (GDM).

RESEARCH DESIGN AND METHODS—We conducted a case-control study involving 248 women in the first-trimester of pregnancy, 90 of whom developed GDM and 158 remained normoglycemic.

RESULTS—Although booking 25-OH-D levels correlated negatively with 2-h glucose post-oral glucose tolerance test and positively with HDL cholesterol, as well as with ethnicity, obesity, and smoking (all $P < 0.05$), there were no statistically significant differences in baseline maternal mean 25-OH-D levels between those who subsequently developed GDM, 18.9 ng/mL (SD 10.7) and those who remained normoglycemic, 19.0 ng/mL (10.7) ($P = 0.874$), even after adjustment for possible confounders including sampling month ($P = 0.784$).

CONCLUSIONS—Our large and well-phenotyped prospective study did not find evidence of an association between first-trimester maternal levels of 25-OH-D and subsequent development of GDM.

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Gestational diabetes mellitus (GDM) markedly increases risk of type 2 diabetes in later life (1). Lower 25-hydroxyvitamin D (25-OH-D) concentrations have been inversely associated with maternal glycemia (2), insulin resistance (3), and increased risk of GDM (4). However, further studies are needed to examine the relevant associations, given its topicality and potential for clinical impact. This is even more so the case given that the nonpregnant arena results of observational studies and trials of 25-OH-D in diabetes conflict, with eight trials showing no effect of 25-OH-D supplementation on glycemia or incident diabetes (5).

Using a well-phenotyped population of first-trimester women (6), we recently demonstrated that GDM can be predicted from simple clinical and laboratory parameters. We subsequently measured 25-OH-D on available samples and sought to examine the relationship of first-trimester 25-OH-D levels with development of GDM.

RESEARCH DESIGN AND METHODS

—We used first-trimester blood samples from 90 women who subsequently developed GDM and 158 control subjects. GDM was defined by at least one abnormal plasma glucose value following the oral glucose tolerance test (OGTT) with normal values of <6 and <7.8 mmol/L for the fasting and 2-h postprandial samples, respectively (World Health Organization criteria). Maternal first-trimester serum 25-OH-D_3 and D_2 were measured using an automated solid-phase extraction procedure with liquid chromatography-tandem mass spectrometry (LC-MS/MS) (7). The lower limit of sensitivity was 4 nmol/L for 25-OH-D_3 and 7.5 nmol/L for 25-OH-D_2. Within- and between-assay precision was below 10%. Results are reported as total 25-OH-D (25-OH-D_2 + 25-OH-D_3). A comprehensive description of prospective recruitment and exclusion criteria and the lipid and metabolic parameters measured have previously been reported (6). Variables are summarized as mean (SD), median (quartiles), or *n* (%) per category; groups have been compared using *t* tests, Wilcoxon tests, or Fisher exact tests as appropriate and using logistic regression analyses adjusting for different variables. Linear regression analysis has been used to assess the association between log-transformed 25-OH-D and demographic and medical history variables. Associations of glucose, lipid, and blood pressure measures with log-transformed 25-OH-D have also been assessed with linear regression, with and without adjustment for potentially confounding demographic and medical history variables. All analyses have been carried out in R (version 2.11.0) (http://www.R-project.org). *P* values are not corrected for multiple testing and should be considered descriptive.

RESULTS

—Women who developed GDM had a greater BMI, a prior history of GDM, and a family history of type 2 diabetes (Table 1). They also had higher systolic blood pressure, but there were no relevant differences in parity, smoking history, or method of conception. However, booking 25-OH-D levels did not differ significantly between case and control subjects in univariate analyses or after

From the [1]Department of Maternal Fetal Medicine, Imperial College School of Medicine, Chelsea and Westminster Hospital, London, U.K.; the [2]Centre for Population and Health Sciences, University of Glasgow, Glasgow, U.K.; the [3]Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London, U.K.; the [4]Robertson Centre, University of Glasgow, Glasgow, U.K.; and the [5]British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, U.K.
Corresponding author: Naveed Sattar, naveed.sattar@glasgow.ac.uk, or Makrina Savvidou, msavvidou@dsla.ndo.co.uk.
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Table 1—*Characteristics of mothers with GDM vs. control mothers*

	Missing values	Control mothers	Mothers with GDM	$P_{univariate}$	$P_{adjusted1}$	$P_{adjusted2}$
n		158	90			
Maternal age (years)	0/0	33.1 ± 4.7	34.2 ± 4.9	0.104*	0.415	0.415
Maternal BMI at 12 weeks (kg/m^2)	0/0	25.2 ± 4.0	30.0 ± 7.9	<0.001†	<0.001	<0.001
Ethnicity	0/0			0.735‡	0.901	0.901
White		108 (68.4%)	58 (64.4%)			
Black		31 (19.6%)	23 (25.6%)			
Asian		12 (7.6%)	6 (6.7%)			
Other		7 (4.4%)	3 (3.3%)			
Parity	0/0			1.000‡	—	—
Nulliparous		67 (42.4%)	38 (42.2%)			
Parous		91 (57.6%)	52 (57.8%)			
Previous GDM	0/0			<0.001‡	—	—
No		158 (100%)	69 (76.6%)			
Yes		0 (0.0%)	21 (23.3%)			
Family history of diabetes	0/0			<0.001‡	0.037	0.037
No		141 (89.2%)	55 (61.1%)			
Yes		17 (10.8%)	35 (38.9%)			
Smoker	0/0			0.795‡	0.884	0.884
No		148 (93.7%)	83 (92.2%)			
Yes		10 (6.3%)	7 (7.8%)			
Gestational age at booking (days)	0/0	87.5 ± 3.0	87.4 ± 3.6	0.916*	0.886	0.886
Systolic blood pressure (mmHg)	37/20	112.5 ± 15.8	118.5 ± 11.6	0.003*	0.039	0.039
Diastolic blood pressure (mmHg)	37/20	70.2 ± 8.5	71.7 ± 7.2	0.218*	0.167	0.167
Sex	1/0			0.356‡	0.730	0.730
Female		77 (49.0%)	50 (55.6%)			
Male		80 (51.0%)	40 (44.4%)			
Birth weight (g)	1/0	3,403.1 ± 571.4	3,283.6 ± 481.9	0.081*	0.388	0.388
Gestation at OGTT (weeks)	0		28.0 ± 4.6			
OGTT						
Fasting/2-h glucose (mmol/L)	0/3		5.3 ± 1.8/9.1 ± 1.8			
HbA_{1c} (%)	11		5.8 ± 0.9			
Total cholesterol (mmol/L)	0/0	4.62 ± 0.76	4.86 ± 0.90	0.033*	0.780	0.780
HDL cholesterol (mmol/L)^	0/0	1.74 (0.35)	1.58 (0.38)	0.001*	0.009	0.009
Triglyceride (mmol/L)^	0/0	1.20 (0.95–1.56)	1.38 (1.08–2.01)	0.002*	0.423	0.423
25-OH-D (ng/mL)	0/0	19.0 ± 10.7	18.9 ± 10.7	0.874†	0.784	0.784
25-OH-D (nmol/L)	0/0	47.6 ± 26.7	47.2 ± 26.7	0.863†	0.782	0.782
Deficient 25-OH-D (<25 nmol/L)						
No	0/0	122 (77.2%)	72 (80.0%)	0.635‡	0.864	0.864
Yes		36 (22.8%)	18 (20.0%)			
Insufficient 25-OH-D (<50 nmol/L)	0/0			0.502‡	0.742	0.742
No		68 (43.0%)	34 (37.8%)			
Yes		90 (57.0%)	56 (62.2%)			
Months of sampling	0/0	6.4 ± 3.3	6.8 ± 3.2	0.426*	0.314	0.314

Data are means ± SD, median (interquartile range), or *n* (%). $P_{adjusted1}$, logistic regression adjusted for maternal age, BMI, gestational age at sampling, smoking, ethnicity, parity, conception status, and previous GDM; 25-OH-D levels additionally adjusted for month of sampling. $P_{adjusted2}$, women without previous GDM (nulliparous or previous pregnancies without GDM) logistic regression adjusted for maternal age, BMI, gestational age at sampling, smoking, ethnicity, parity, and conception status; 25-OH-D levels additionally adjusted for month of sampling. **t* test. †Wilcoxon test. ‡Fisher exact test. ^Log-transformed for regression analysis.

adjustment for confounders, and inclusion of 25-OH-D did not enhance first-trimester prediction of GDM (data not shown). Restriction of analyses to women with no history of GDM did not alter conclusions, and separate examination by ethnic or BMI groups did not either. There were also no relevant differences in proportions of women who had deficient or insufficient 25-OH-D levels (Table 1).

In univariate association analyses, 25-OH-D levels were positively associated with maternal age (2.7% per year; $P = 0.001$) and negatively with BMI at 12 weeks' gestation (−1.8% per kg/m^2; $P = 0.004$). 25-OH-D was lower in smokers ($P = 0.012$), black and Asian women ($P < 0.001$ and $P = 0.003$, respectively), and women with a family history of diabetes ($P = 0.017$). 25-OH-D was positively associated with HDL cholesterol ($P = 0.004$) and negatively associated with fasting glucose ($P = 0.009$), 2-h glucose ($P = 0.002$), and HbA_{1c} ($P = 0.002$) at 28 weeks' gestation (Supplementary Table 1). After adjustment for booking month, age, BMI, smoking, ethnicity, and family history of diabetes, 25-OH-D levels remained negatively correlated only with 2-h glucose and positively associated with HDL cholesterol in the

entire group and women without prior GDM (Supplementary Table 2).

CONCLUSIONS—Using a very well-phenotyped cohort, we found that first-trimester maternal 25-OH-D levels, despite being associated with 2-h glucose levels (independently of age, obesity, smoking, and ethnicity, etc.), are not significantly associated with the development of GDM. A single study has demonstrated an independent association of 25-OH-D at 16 weeks' gestation with GDM as defined by American Diabetes Association criteria (4); however, 25-OH-D deficiency was much less prevalent and 25-OH-D levels were determined by immunoassay, a methodology subsequently dropped by the Centers for Disease Control in favor of LC-MS/MS as a result of the poor specificity of immunoassays compared with chromatographic methods (8). Whether these differences underlie the differences in findings is unclear. It is also unclear why 25-OH-D levels continue to correlate with 2-h OGTT levels despite lack of baseline difference in 25-OH-D levels in women who do and do not develop GDM. The potential for residual confounding must be borne in mind. However, given that our study was larger (90 incident cases vs. 57 in that of Zhang et al. [4]), used more robust LC-MS/MS, and was conducted about 4 weeks earlier in gestation, lack of difference in first-trimester 25-OH-D is of relevance and suggests a need to caution against recommending greater 25-OH-D supplementation in pregnancy, at least as a mechanism to lessen risk for GDM.

Although there was no evidence of a relation of 25-OH-D with GDM, the prevalence of 25-OH-D deficiency (~20%) within our inner-city multiethnic population was notable. In the early 1990s, 90% of white pregnant mothers in the Avon Longitudinal Study of Parents And Children (ALSPAC) study had 25-OH-D concentrations <50 nmol/L during winter and spring; 28% were seriously deficient (<25 nmol/L), and virtually no one reached 75 nmol/L (considered optimal) (9), with similar estimates found in other comparable pregnancy cohorts (10,11). Since then, despite significant public health efforts to ensure that all pregnant women achieve 25-OH-D intakes of 10 μg/day (400 IU/day) (12), there appears to have been little positive impact on hypovitaminosis D prevalence. That noted, 25-OH-D levels do not appear to have worsened considerably, at least as judged by comparing the present data with the aforementioned ALSPAC findings. This observation suggests that factors other than 25-OH-D deficiency (i.e., rising obesity rates in pregnancy in particular) likely explain rising GDM rates. To resolve uncertainties about vitamin D and pregnancy outcomes, there is a need for well-conducted and adequately powered studies of vitamin D intake in pregnancy. Until such time, the current study goes against a major role for vitamin D deficiency in the pathogenesis of GDM.

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