RESEARCH

Early pregnancy vitamin D deficiency and gestational diabetes

Exploring the link

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Background and objective
Diabetes, including gestational diabetes mellitus (GDM), and vitamin D deficiency or insufficiency (VDDI) are recognised public health problems. There is conflicting evidence regarding the relationship between vitamin D deficiency and GDM. The aim of this study was to explore the incidence of VDDI among pregnant women attending a maternity unit in Sydney, Australia, and the relationship between VDDI in early pregnancy and later development of GDM.

Methods
This was a prospective cohort study in which 25-hydroxyvitamin D was measured in pregnant women during 2011–13. Exclusion criteria included pre-existing diabetes, bowel disease and reduced cognitive ability.

Results
There were 785 women enrolled in the study and 42 excluded. Findings from this study did not show an association between VDDI in early pregnancy and development of GDM. Important predictors of GDM remained the well-known risk factors: family history, ethnicity, body mass index and age.

Discussion
Clinical conversations should continue to focus on proven modifiable factors such as weight management and the provision of timely testing appropriate to the risk identified through history-taking.

GESTATIONAL DIABETES MELLITUS (GDM), defined as glucose intolerance with onset or first recognition during pregnancy, carries an increased risk of later progression to type 2 diabetes.[1]

It is increasingly recognised that vitamin D affects more than calcium regulation and bone health, demonstrated by the existence of vitamin D receptors in tissues throughout the body. Low levels of vitamin D correlate with ill health and are implicated in various conditions including malignancies,[2] immune illnesses such as type 1 diabetes, thyroid autoimmunity, schizophrenia[3] and multiple sclerosis.[4]

Epidemiological studies have linked vitamin D deficiency or insufficiency (VDDI) with type 2 diabetes.[5–7] Vitamin D is thought to act directly via receptors on pancreatic beta cells[8] and indirectly through the calcium flux required for insulin release in beta cells.[9] Vitamin D insufficiency may alter insulin release, especially in response to glucose load. Vitamin D supplementation has not been shown to beneficially affect insulin secretion or insulin sensitivity.[10] Studies of any relationship between GDM and VDDI are largely retrospective in nature, and samples are limited to women with a GDM diagnosis.

Studies have shown conflicting results regarding the relationship between low vitamin D levels and developing GDM. While several studies have shown an increased risk of developing GDM with maternal VDDI,[11] an Australian observational study did not show any association between low vitamin D levels and GDM developing; it did, however, find that maternal 25-hydroxyvitamin D concentrations were inversely related to fasting glucose results.[12] A retrospective cohort study did not find any association between VDDI and multiple pregnancy and neonatal outcomes.[13] A large study in Indian women found VDDI was common but did not correlate with an increased incidence of GDM.[14]

The aim of this study was to test the hypothesis that a link between early pregnancy VDDI and GDM exists.

It was considered that the data analysis should explore the possibility that common risk factors for VDDI and GDM may contribute to any association between the conditions.

Methods

Design

The study was a prospective cohort study.

Sample

The study site was an urban hospital that provides birth care for women with pregnancies of more than 34 weeks' gestation with a low-to-moderate risk of developing complications. The hospital serves a highly ethnically diverse district.

All women who booked for pregnancy care through the maternity unit who met the eligibility criteria were suitable for enrolment in the study. Women aged between 16 and 46 years who booked for maternity care between August 2011 and December 2013 and who had initial blood tests prior to 30 weeks' gestation

were targeted for inclusion in the study. Women with pre-existing diabetes or inflammatory bowel disease, those unable to provide consent or whose initial blood tests occurred after 30 weeks' gestation were excluded from the study. A power calculation indicated that least n = 692 study participants were required to have an 80% chance of detecting a 5% difference in the proportion of participants with VDDI developing GDM and not developing GDM at the 0.05 significance level. Enrolment in the study was based on the presence of a study group member or midwife who had been orientated to the study. This was a limitation of the study, although no overt selection bias occurred as women were allocated to clinic midwives randomly with no prior triage.

A total of 785 of 3980 pregnant women were ultimately enrolled. This non-probability sample represented a study penetration rate of 19.7% into the available population for study. Forty-three of the 785 women enrolled were excluded because of incomplete data, loss to follow-up or co-existing medical conditions, leaving a final sample size of n = 742 for analysis. Of these 742 women, 165 (22.2%) ultimately received a GDM diagnosis during the study period.

The sample group was compared with the larger population group (n = 3980) using the variables 'country of birth' (using chi-square analysis) and 'age' (using one-way analysis of variance). These variables were chosen because these criteria were present in both the study database and the district maternity database. Results indicated that there were no differences of note between the two groups in terms of country of birth ($\chi^2 = 3.6$; $P = 0.31$). The mean age in the study group (29.1 years) was slightly older than the mean age of the population group (28.2 years; $F = 27.5$; $P < 0.0001$).

Procedure

Early pregnancy vitamin D levels were measured at each woman's first antenatal clinic attendance. Testing for GDM during pregnancy was conducted according to risk factors; testing timing is described later in this article. The women's characteristics – particularly those associated with GDM and/or VDDI, including skin pigmentation, ethnicity and religious veiling, with or without face covering – were collected at the time of enrolment.

Vitamin D testing was performed by in-house or external laboratories. Women had their first visit with their GPs between 6 and 14 weeks' gestation and first hospital visit between 14 and 18 weeks' gestation, resulting in most women having their vitamin D level checked in the late first or early second trimester and new supplementation initiated in the second trimester. Review of each laboratory's testing methods and reference ranges revealed that the coefficients of variance were sufficiently similar that externally performed tests could be included in the study. Women consented to the collection of demographic and personal descriptors as outlined in Table 1, and for these factors to be assessed against later testing for GDM. Table 2 provides a breakdown of women's characteristics against an ultimate GDM diagnosis. The original seven ethnicity categories were reduced to four because of small sample size counts in African, Aboriginal and Torres Strait and Pacific Islander groups. At the time of their initial pregnancy visit, women were routinely assessed for their risk of developing GDM by the application of a risk algorithm based on factors known to increase the possibility of GDM development. This determined the timing of either single or repeated screening glucose challenge tests for women with minimal risk factors or glucose tolerance tests for women with known risk factors or abnormal challenge testing.

The primary outcome in this study was the diagnosis of GDM at any point in the pregnancy.[15]

The study used vitamin D reference ranges from the position statement produced by the Australian and New Zealand Bone and Mineral Society and Osteoporosis Australia.[16]

Analysis

To explore associations between vitamin D level and other potentially important participant characteristics against the primary outcome of interest (GDM diagnosis), univariate statistical analyses (one-way analysis of variance and chi-squared tests) were conducted. Following this, vitamin D level and potentially important variables identified from the univariate analyses and from the literature were entered into a forward conditional binary logistic regression procedure (SPSS Version 24) to establish an adjusted estimate of the effect of vitamin D level on GDM diagnosis. The choice to include a variable in the regression procedure was guided by statistical significance and adjusted residual values. The two vitamin D–related variables were included regardless of these guides, as they were likely to interact and were integral to the research question. Concordance testing was conducted on the resultant final model.

Ethical approval via the Local Health District Human Research Ethics Committee was given in late 2009; South Sydney West Area Health Service Ethics Review Committee (Royal Prince Alfred Hospital zone): Number X09-0123, Sydney Local Health District number: X13-0237(09-0123) and HREC/09/RPAH/203.

Results

Sample characteristics

On the basis of National Institute for Health and Care Excellence[17] and World Health Organization expert consultations, different BMI category cut-offs were used for the Asian women in the study group.[18] It was found that the Asian women in the study group fulfilled the criteria for the use of lower BMI parameters according to this literature. Women from this group are classified as overweight at a BMI >23 kg/m^2 and obese at a BMI >27.5 kg/m^2.

The data presented in Table 2 indicate that each independent variable tested showed a statistically significant relationship with GDM diagnosis, with the exception of religious veiling, vitamin D supplementation and vitamin D level (which were not found to be significant at $P = 0.41$, $P = 0.067$ and $P = 0.66$, respectively).

By entering all potentially important variables (in addition to vitamin D level and supplementation) in a logistic regression procedure, the researchers

sought to establish any adjusted effect of vitamin D level on GDM. The best predictive model yielded by the procedure (Table 3) purposefully retains vitamin D level and supplementation, but these are shown to be insignificant. Ethnicity, BMI, family history and age were the key predictors. Complexion was not retained by the procedure.

Caucasian women and Middle Eastern women were shown to be one-fifth and a little over one-third less likely to develop GDM than Asian women, respectively. Regarding BMI, overweight status was more predictive of GDM than obese status. Overweight status reflected a sixfold increase in risk when compared with underweight status, and obesity reflected just over a fourfold increase. A 5% increase in the risk of GDM development was established for each year of increased age. Those with primary family history were a little more than twice as likely, and those with secondary family history were 1.5 times more likely, to develop GDM than women with no family history of diabetes. Concordance testing (c-stat) suggested that the overall predictive value of the model was strong at 0.73.

Table 1. Sample characteristics

Characteristics	Study sample (n = 742)
Age (years)	**Mean = 29.1 (SD = 4.9)**
Age category (years)	
<35	n = 636 (85.7%)
≥35	n = 106 (14.3%)
Body mass index (kg/m²)	**Mean = 24.7 (SD = 5.0)**
Body mass index category	
Category 1 (Underweight)*	n = 41 (5.5%)
Category 2 (Healthy weight)†	n = 344 (46.4%)
Category 3 (Overweight)‡	n = 225 (30.3%)
Category 4 (Obese)§	n = 132 (17.8%)
Vitamin D (25-hydroxyvitamin D) level (nmol/L)	**Mean = 43.5 (SD = 21.9)**
Vitamin D (25-hydroxyvitamin D) deficiency status category[17]	
Severely deficient (<12.5 nmol/L)	n = 29 (3.9%)
Moderately deficient (12.5–29.9 nmol/L)	n = 182 (24.5%)
Mildly deficient (30.0–49.9 nmol/L)	n = 246 (33.2%)
Replete (≥50 nmol/L)	n = 285 (38.4%)
Family history of diabetes	
None	n = 407 (54.9%)
Primary	n = 229 (30.9%)
Secondary	n = 106 (14.3%)
Ethnicity	
Asian	n = 363 (48.9%)
Middle Eastern	n = 204 (27.5%)
European/Caucasian	n = 114 (15.4%)
Pacific Islander/Māori	n = 31 (4.2%)
African	n = 25 (3.4%)
Aboriginal/Torres Strait Islander	n = 4 (0.5%)
Other	n = 1 (0.1%)
Veiled/robed = Yes	**n = 250 (33.7%)**
Complexion	
Fair	n = 255 (34.4%)
Medium	n = 425 (57.3%)
Dark	n = 62 (8.4%)
Gestational diabetes diagnosis	**n = 165 (22.2%)**

**<18.5 kg/m² (non-Asian and Asian)*
†18.5–24.9 kg/m² (non-Asian); 18.5–22.9 kg/m² (Asian)
‡25.0–29.9 kg/m² (non-Asian); 23.0–27.4 kg/m² (Asian)
§≥30.0 kg/m² (non-Asian); ≥27.5 kg/m² (Asian)
SD, standard deviation

Discussion

This study did not show an association between VDDI in early pregnancy and the development of GDM after adjustment for possible confounders. The variables that were important in predicting GDM were family history, ethnicity, BMI and age.

The researchers felt that the hypothesis would be well tested in the hospital at which the study took place, as the hospital serves an ethnically diverse population,[19] and ethnicity is a risk factor for GDM.

The global prevalence of VDDI in pregnancy has been highlighted. It is unclear if this is physiological. Although 25-hydroxyvitamin D is measured, it is the free fraction that enters the cells and is converted to the active hormone that has biological effect.[20] The placenta has 1-alpha-hydroxylase enzyme, which converts vitamin D to the active and more potent calcitriol, which has a receptor on the placenta.[21] This relationship may enable the placenta to convert vitamin D to the active form and may result in greater biological availability in pregnancy.

A meta-analysis of randomised controlled trials to assess the effect of vitamin D supplementation in pregnancy has not shown beneficial effects on multiple fetal and maternal outcomes including GDM.[22] As a result of the lack of evidence, current Australian guidelines do not recommend universal screening and treatment of low vitamin D levels. There is a lack of clarity regarding the benefit of supplementing vitamin D. Selective screening for women who are at risk of low

Table 2. Participant characteristics against ultimate gestational diabetes mellitus diagnosis (univariate analysis)

	GDM (n = 165)	No GDM (n = 577)	Test	*P* value
Age	Mean = 29.8 (SD = 5.3)	Mean = 28.9 (SD = 4.7)	ANOVA: F = 4.3	0.039
Age category (years)				
<35	n = 135 (81.8%)	n = 501 (86.8%)	X^2 = 2.6	0.11
≥35	n = 30 (18.2%)	n = 76 (13.2%)		
Body mass index (kg/m²)	Mean = 25.5 (SD = 4.5)	Mean = 24.5 (SD = 5.1)	ANOVA: F = 4.9	0.027
Body mass index category				
Category 1 (Underweight)*	n = 3 (1.8%)‖	n = 38 (6.6%)#	X^2 = 26.8	<0.0001
Category 2 (Healthy weight)†	n = 55 (33.3%)‖	n = 289 (50.1%)#		
Category 3 (Overweight)‡	n = 72 (43.6%)#	n = 153 (26.5%)‖		
Category 4 (Obese)§	n = 35 (21.2%)	n = 97 (16.8%)		
Vitamin D (25-hydroxyvitamin D) level (nmol/L)	Mean = 40.8 (SD = 19.5)	Mean = 44.3 (SD = 22.5)	ANOVA: F = 3.4	0.066
Vitamin D (25-hydroxyvitamin D) deficiency status category[17]				
Severely deficient (<12.5 nmol/L)	n = 54 (32.7%)	n = 231 (40.0%)	X^2 = 3.2	0.36
Moderately deficient (12.5–29.9 nmol/L)	n = 59 (35.8%)	n = 187 (32.4%)		
Mildly deficient (30.0–49.9 nmol/L)	n = 46 (27.9%)	n = 136 (23.6%)		
Replete (≥50 nmol/L)	n = 6 (3.6%)	n = 23 (4.0%)		
Vitamin D supplementation				
Yes	n = 124 (75.2%)	n = 424 (73.5%)	X^2 = 0.19	0.67
No	n = 41 (24.8%)	n = 153 (26.5%)		
Family history of diabetes				
No	n = 69 (41.8%)‖	n = 338 (58.6%)#	X^2 = 18.9	<0.0001
Primary**	n = 73 (44.2%)#	n = 156 (27.0%)‖		
Secondary††	n = 23 (13.9%)	n = 83 (14.4%)		
Ethnicity				
Asian	n = 111 (67.3%)#	n = 252 (43.8%)‖	X^2 = 37.0	<0.0001
Middle Eastern	n = 30 (18.2%)‖	n = 174 (30.2%)#		
European/Caucasian	n = 9 (5.5%)‖	n = 105 (18.2%)#		
Other	n = 15 (9.1%)	n = 45 (7.8%)		
Veiled/robed = Yes	n = 60 (36.4%)	n = 190 (32.9%)	X^2 = 0.68	0.41
Complexion				
Fair	n = 32 (19.4%)‖	n = 223 (38.6%)#	X^2 = 21.2	<0.0001
Medium	n = 115 (69.7%)#	n = 310 (53.7%)‖		
Dark	n = 18 (10.9%)	n = 44 (7.6%)		

**<18.5 kg/m² (non-Asian and Asian)*
†18.5–24.9 kg/m² (non-Asian); 18.5–22.9 kg/m² (Asian)
‡25.0–29.9 kg/m² (non-Asian); 23.0–27.4 kg/m² (Asian)
§≥30.0 kg/m² (non-Asian); ≥27.5 kg/m² (Asian)
‖Adjusted residual value ≤2
#Adjusted residual value >2
***Sibling or parent*
††Other relative (eg cousin, grandparent, parent's sibling)
ANOVA; analysis of variance; GDM, gestational diabetes mellitus; SD, standard deviation

Table 3. Binary logistic regression result: Predicting gestational diabetes mellitus from the data*

Variable	Odds ratio	95% confidence interval	*P* value
Ethnicity			<0.0001
Asian	Ref		
Middle Eastern	0.36	0.23, 0.57	
Caucasian	0.20	0.10, 0.42	
Other	0.71	0.37, 1.37	
Body mass index category			<0.0001
Category 1 (Underweight)†	Ref		
Category 2 (Healthy weight)‡	2.52	0.73, 8.68	
Category 3 (Overweight)§	5.88	1.70, 20.30	
Category 4 (Obese)‖	4.11	1.14, 14.81	
Family history of diabetes			0.002
No	Ref		
Primary	2.10	1.40, 3.17	
Secondary	1.49	0.85, 2.63	
Age	1.05	1.01, 1.09	0.012
Vitamin D (25-hydroxyvitamin D) level (nmol/L)	0.99	0.98, 1.00	0.17
Vitamin D supplementation	0.93	0.60, 1.45	0.76

**Concordance statistic (c-stat) = 0.73 (95% confidence interval: 0.69, 0.77)*
†<18.5 kg/m² (non-Asian and Asian)
‡18.5–24.9 kg/m² (non-Asian); 18.5–22.9 kg/m² (Asian)
§25.0–29.9 kg/m² (non-Asian); 23.0–27.4 kg/m² (Asian)
‖≥30.0 kg/m² (non-Asian); ≥27.5 kg/m² (Asian)
Ref, reference

vitamin D levels and supplementation if levels are <50 nmol/L is recommended.[23]

Limitations of the study

A limitation of the study is that it is based on a non-probability sample and the comparison of the sample against non-participants was limited to two important personal demographics only. Clinic processes were such that there was no triaging prior to first booking; women were allocated to midwives randomly. For this reason, the researchers are confident that 'convenience' did not affect the allocation of women to midwives, as the allocation of women to midwifery clinic midwives (and therefore ultimately the study) was random. The single vitamin D level measurement performed in early pregnancy may not reflect status throughout pregnancy. However, the primary goal of the study was to explore whether early pregnancy VDDI served in any way as a marker for ultimate GDM diagnosis. As previously identified, while VDDI may alter insulin release, especially in response to glucose load, supplementation has not been shown to beneficially affect insulin secretion or insulin sensitivity.[10]

Conclusions

Vitamin D has an important role in maternal and fetal wellbeing in pregnancy and lactation as the main source of vitamin D is breast milk in an exclusively breastfed infant. This study did not find a relationship between vitamin D deficiency and GDM.

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