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Original Research

High early pregnancy serum 25-hydroxy vitamin D level, within a sub-optimal range, is associated with gestational diabetes mellitus: a prospective cohort study

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ABSTRACT

BACKGROUND/OBJECTIVES: Low early pregnancy serum 25-hydroxy vitamin D (25[OH]D) levels can increase gestational diabetes mellitus (GDM) risk, although inconsistent findings related to that association have been reported. This study examined the association of serum vitamin D with GDM and the possible influencers on this association.
SUBJECTS/METHODS: This study included 259 pregnant women within the Seremban Cohort Study (SECOST). Blood samples at < 14 weeks of gestation were drawn to determine serum 25(OH)D levels. GDM diagnosis was made at 24 to 32 weeks of gestation using a standard procedure. Association between serum vitamin D and GDM was tested using binary logistic regression.
RESULTS: Nearly all women (90%) had mild (68.3%) or severe (32.2%) vitamin D deficiency (VDD). Non-GDM women with mild VDD had a significantly higher mean vitamin D intake than GDM women with mild VDD ($t = 2.04$, $p < 0.05$). Women with higher early pregnancy serum vitamin D levels had a greater risk of GDM. However, this significant association was only identified among those with a family history of type 2 diabetes mellitus (T2DM) and in women with a body mass index indicating overweight or obese status.
CONCLUSIONS: The high prevalence of VDD in this sample of pregnant women underscores the need for effective preventive public health strategies. Further investigation of this unexpected association between serum vitamin D level and GDM risk in predominantly VDD pregnant women and the potential effects of adiposity and family history of T2DM on that association is warranted.

Keywords: Vitamin D; gestational diabetes mellitus; vitamin D deficiency; body mass index

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Conflict of Interest

Yvonne Yee Siang Tee and Jacques Bindels are employees of Danone Specialized Nutrition (Malaysia) and of Nutricia Research Foundation (Netherlands), respectively. Eline van der Beek was employed by Danone Nutricia Research at the time of the study was conducted (former employee). None of the authors had any personal or financial conflict of interest.

Author Contributions:

Conceptualization: Mohd Shariff Z, Yong HY; Data Curation: Mohd Shariff Z, Yong HY, Palaniveloo L; Formal analysis: Yong HY, Palaniveloo L; Funding acquisition: Mohd Shariff Z; Investigation: Yong HY, Palaniveloo L; Methodology: Mohd Shariff Z, Yong HY, Loh SP, Mohd Yusof BN, Rejali Z; Supervision: Mohd Shariff Z, Loh SP, Mohd Yusof BN, Rejali Z, Bindels J, Tee YYS, van der Beek EM; Writing - original draft: Yong HY; Writing - review & editing: Mohd Shariff Z, Yong HY, Bindels J, Tee YYS, van der Beek EM.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) shares similar risk factors and pathogenesis with gestational diabetes mellitus (GDM) and is known to be associated with vitamin D deficiency (VDD) [1-3]. However, evidence for a relationship between VDD and GDM has been inconsistent. While several studies reported a non-significant association between serum vitamin D level and GDM [4-8], other studies showed that serum vitamin D was inversely related to GDM risk [9-13], with women with serum 25-hydroxy vitamin D (25[OH]D) < 50 nmol/L having a higher risk of GDM [14,15]. These inconsistent observations could be due to the timing of the serum collection (e.g., early pregnancy, mid-pregnancy, post-GDM diagnosis), the accuracy of vitamin D (and its metabolite) assessment, the selection of the VDD cut-off values, as well as the influences of potential confounders and/or effect modifiers.

Accumulating evidence supports the role of vitamin D in glucose metabolism [16,17], but the underlying mechanism requires further investigation. Vitamin D is thought to be essential in the development of insulin resistance due to its role in gene polymorphisms and metabolic/immune pathways. Gene polymorphisms of the vitamin D receptor, vitamin D-binding protein, and the vitamin D 1-alpha-hydroxylase gene could produce insulin resistance [17-19] and disrupt the production, transportation, and action of vitamin D [17]. Numerous studies have suggested that the association might be due to pancreatic β-cell dysfunction, leading to impaired glucose metabolism, whereby vitamin D affects pancreatic β-cell function, insulin secretion, and insulin resistance, subsequently affecting blood glucose metabolism [13,15]. Additionally, the active form of vitamin D (1,25-dihydroxyvitamin D3; $1,25[OH]_2D_3$) has potent anti-inflammatory properties that could inhibit inflammation and the production of inflammatory cytokines that have a crucial pathogenic role in diabetes by promoting insulin resistance [20,21]. Vitamin D is also involved in immune system development and function. A vitamin D receptor is located on most immunological cells [22], and the active form of vitamin D regulates circulating glucose levels by binding to the vitamin D receptor of pancreatic β-cells and modulating insulin secretion [23,24]. The effects of VDD could increase insulin resistance and subsequently affect blood glucose metabolism, further contributing to increased GDM risk.

With the increasing trend in overweight and obesity incidence among reproductive-age Malaysian women, GDM is becoming a public health concern. The national prevalence of GDM in Malaysian women based on government hospital data, has increased from 8.7% (2010) to 9.3% (2017) [25,26]. However, other small-scale studies have reported GDM in Malaysian women to be in the range of 11.4% to 29.7% [27,28]. Despite the abundance of sunlight, approximately 59.8–90.4% of Malaysian pregnant women appear to be VDD [29,30]. Previous studies showed that VDD is more prevalent among obese women with a higher GDM prevalence [7,8,31], underscoring the importance of exploring the association between serum 25(OH)D level and GDM risk within this population. Other related factors include ethnicity, family history of T2DM, alcohol consumption, smoking status, and physical activity. Knowledge regarding a possible relationship between vitamin D status and GDM risk is important for developing public health actions related to preventive and curative measures. The present study aimed to identify the association between maternal vitamin D status and GDM and the potential influencers of that association.

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SUBJECTS AND METHODS

Study participants

This study included 259 pregnant women from the Seremban Cohort Study (SECOST). Details of the study protocol have been published elsewhere [32,33]. **Fig. 1** provides an overview of the participant selection process. Ethical approval for the study was obtained from the Medical Research Ethics Committee (MREC), Ministry of Health (MOH) Malaysia (KKM/NIHSEC/08/0804/P12-613), and the MREC, Universiti Putra Malaysia (UPM/FPSK/100-9/2-MJKEtika). Prior to data collection, permission and informed written consent were obtained from the Head of Health Office of Seremban district and the respondents, respectively.

Measurements

Biochemical test

Fasting venous blood samples were drawn by clinic nurses on the subject's first prenatal visit (< 14th week of gestation) for determination of serum 25(OH)D level. Blood samples were transported on the same day to the laboratory for ARCHITECT 25-OH chemiluminescent microparticle immunoassay (CMIA) analysis. Subjects were then categorized as severe VDD (< 25 nmol/L), mild VDD (≥ 25 and < 50 nmol/L), vitamin D insufficiency (≥ 50 and <75 nmol/L), or vitamin D sufficiency (≥ 75 nmol/L) [34]. GDM status was diagnosed based on a 75 g oral glucose tolerance test conducted at 24–32 weeks of pregnancy. Fasting venous blood (2 mL) was drawn by clinic nurses before and after (2 hours) ingestion of a standard glucose solution. The GDM diagnostic criteria were fasting plasma glucose (FPG) ≥ 5.6 mmol/L and/or 2-hour plasma glucose (2hPG) ≥ 7.8 mmol/L [35].

Anthropometric measurements

A SECA digital weighing scale and SECA body meter were used to determine subjects' weight and height, respectively. Weight and height measurements at the first prenatal visit were used to calculate body mass index (BMI). Categorization of subjects based on BMI was based on World Health Organization (WHO) cut-off points: 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 (≥ 30.0 kg/m^2) [36].

Vitamin D intake

All women completed a 24-h diet recall. Dietary information was analyzed using Nutritionist Pro Nutrient Analysis Software: Version 1.5 [37] based on the United States Department of

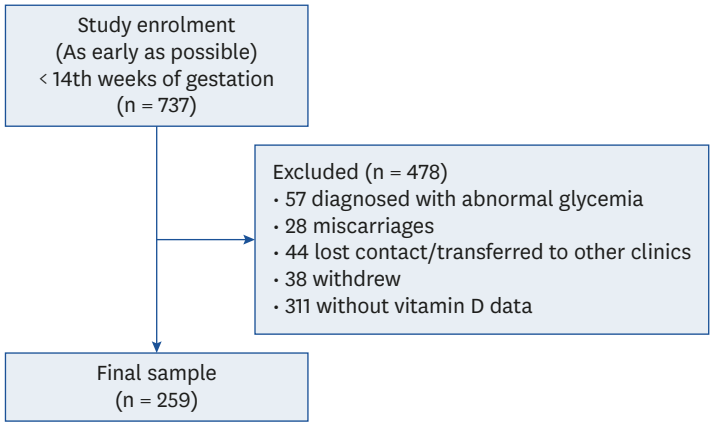

Fig. 1. Overview of the participant selection process.

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Agriculture (USDA) food database (Release 28) [38]. Women were also required to report on the use of dietary supplements during pregnancy. Vitamin D intake from supplements was estimated according to the manufacturers' product information. A subject's total vitamin D intake was estimated by summation of all intakes from food and supplements. Total intakes were divided into 2 categories: below recommendation (< 15 μg/day), above recommendation (≥ 15 μg/day) [39].

Other variables

Other variables included socio-demographic, obstetric, and physical activity information. Weekly energy expenditure was estimated using the Pregnancy Physical Activity Questionnaire (PPAQ) [40] and was expressed in metabolic equivalent (MET) hours per week.

Statistical analysis

Chi-squared test of independence, Fisher's exact test, and independent samples t-test were performed to determine the significance of differences in socio-demographic and obstetrical characteristics, dietary intake, physical activity, serum vitamin D level between GDM and non-GDM subjects, and total vitamin D intake based on early pregnancy serum vitamin D levels, as appropriate.

Binary logistic regression was implemented to examine the covariate-adjusted associations of serum vitamin D level and GDM status. The covariates included in the regression analyses were gravidity, family history of T2DM, early pregnancy BMI, physical activity, and intakes of energy, carbohydrate, and vitamin D. All variables entered in the models were examined for multicollinearity as well as interactions with serum 25(OH)D level and GDM risk. Stratified analyses were conducted if the interaction terms were significant. Results are presented as adjusted odds ratios (AORs) with a 95% confidence interval (CI). SPSS version 25.0 software (IBM Corp., Armonk, NY, USA) [41] was used for data analyses.

RESULTS

Subject characteristics

The characteristics of 223 non-GDM and 36 GDM women are summarized in **Table 1**. For both groups, mean ages were similar, with a mean of 30.39 ± 4.53 years in non-GDM and 31.21 ± 3.62 years in GDM women. Almost all women (91.7–93.7%) were Malay. Most of the women were currently employed (63.9–74.4%) and had a secondary or lower education level (41.7–44.8%). GDM women had a significantly higher percentage of a family history of T2DM (50.0%) and higher gravidity (3.06 ± 1.41) compared with non-GDM women (family history of T2DM = 24.7%; gravidity = 2.40 ± 1.36). While 37.2% and 53.8% of the non-GDM women had a height of 1.55–1.59 m and a normal early pregnancy BMI, most GDM women were overweight (38.9%) and had a height of less than 1.55 m (44.4%). GDM women had a significantly greater mean serum 25(OH)D level (37.65 ± 10.79 nmol/L) than that of non-GDM women (32.05 ± 11.30 nmol/L, $P < 0.05$). None of the women's blood samples indicated vitamin D sufficiency. More than two-thirds of the subjects (68.3%) were categorized as having mild VDD, whereas 23.2% and 8.5% of women were categorized as having severe VDD and vitamin D insufficiency, respectively.

Non-GDM women had a significantly higher mean intake of energy (1,567 ± 434.66 kcal) and carbohydrate (209.99 ± 61.59 g/day) compared with GDM women (energy, 1,390 ± 445.09 kcal/day and carbohydrate, 186.29 ± 64.37 g/day, respectively) (**Table 2**). The mean total

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Table 1. Characteristics of women (n = 259)

Characteristics	Non-GDM (n = 223)	GDM (n = 36)	t/χ^2	*P*-value
Socio-demographic information				
Age (yrs)	30.39 ± 4.53	31.21 ± 3.62	–1.04	0.30
≤ 30	128 (57.4)	15 (41.7)	3.10	0.08
> 30	95 (42.6)	21 (58.3)		
Ethnicity				
Malay	209 (93.7)	33 (91.7)	-	0.64[3]
Non-Malay	14 (6.3)	3 (8.3)		
Employment status				
Unemployed	57 (25.6)	13 (36.1)	1.75	0.19
Working	166 (74.4)	23 (63.9)		
Education (yrs)	13.15 ± 2.47	13.03 ± 2.46	0.28	0.78
Secondary and lower	100 (44.8)	15 (41.7)	0.17	0.92
STPM/matric/diploma/certificate	79 (35.4)	13 (36.1)		
Tertiary and above	44 (19.8)	8 (22.2)		
Monthly household income (unit: MYR)[1]	4,082.76 ± 2,145.87	4,061.11 ± 2,108.66	0.06	0.96
Low (< 3,860)	122 (54.7)	19 (52.8)	0.07	0.96
Middle (≥ 3,860 and < 8,319)	94 (42.2)	16 (44.4)		
High (≥ 8,320)	7 (3.1)	1 (2.8)		
Obstetric information				
Gravidity	2.40 ± 1.36	3.06 ± 1.41	–2.66	0.01*
1	64 (28.7)	5 (13.9)	7.97	0.02*
2	77 (34.5)	9 (25.0)		
≥ 3	82 (36.8)	22 (61.1)		
Medical history				
GDM	21 (9.4)	7 (19.4)	-	0.08[4]
Family history				
Type 2 diabetes mellitus	55 (24.7)	18 (50.0)	9.83	0.01*
Height (m)	1.57 ± 0.06	1.55 ± 0.60	1.80	0.07
< 1.55	72 (32.3)	16 (44.4)	2.19	0.33
≥ 1.55 and < 1.59	83 (37.2)	10 (27.8)		
≥ 1.60	68 (30.5)	10 (27.8)		
Weight at first prenatal visit (kg)	60.07 ± 12.64	62.67 ± 12.89	–1.14	0.26
BMI at first prenatal visit[2]	24.34 ± 4.84	25.99 ± 5.02	–1.89	0.06
Underweight	15 (6.7)	2 (5.6)	4.74	0.19
Normal	120 (53.8)	13 (36.1)		
Overweight	55 (24.7)	14 (38.9)		
Obese	33 (14.8)	7 (19.4)		
Early pregnancy vitamin D status				
Serum 25(OH)D (nmol/L)	32.05 ± 11.30	37.65 ± 10.79	–2.78	0.01*
Severe deficiency (< 25)	57 (25.6)	3 (8.3)	5.95	0.04*
Mild deficiency (≥ 25 and < 50)	149 (66.8)	28 (77.8)		
Insufficiency (≥ 50 and < 75)	17 (7.6)	5 (13.9)		

Values are presented as mean ± SD or number (%).
STPM, Malaysian Higher School Certificate; MYR, Malaysian Ringgit; GDM, gestational diabetes mellitus; BMI, body mass index; 25(OH)D, 25-hydroxy vitamin D.
[1] Economic planning unit, 2014: 1 USD = MYR 4.22 at the time of study; [2]< 14th weeks of gestation; [3]Fisher's Extract Test; [4]Description.
*$P < 0.05$.

vitamin D intake for GDM women (7.10 ± 1.17 μg/day) was lower than that of non-GDM (10.02 ± 0.58 μg/day) women, and a higher proportion of non-GDM women (69.5%) had a total intake of vitamin D below the recommended value (< 15 μg/day).

Vitamin D intake by early pregnancy vitamin D status

There was no significant correlation between vitamin D intake and early pregnancy vitamin D status (r = 0.04, $P > 0.05$). Overall, non-GDM women had a higher mean total intake of vitamin D than that of GDM women, but a significant difference was only observed in women with mild VDD (t = 2.04, $P < 0.05$) (**Table 3**).

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Table 2. Physical activity and dietary intake at the second trimester between non-GDM and GDM women (n = 259)

Variables	Non-GDM (n = 223)	GDM (n = 36)	t/χ^2	*P*-value
Physical activity at the second trimester				
Total physical activity (METs hours/week)	295.19 ± 126.63	287.62 ± 96.14	0.34	0.73
Dietary intake at the second trimester				
Energy (kcal per day)	1,567 ± 434.66	1,390 ± 445.09	2.26	0.03*
Carbohydrate (g per day)	209.99 ± 61.59	186.29 ± 64.37	2.13	0.03*
Protein (g per day)	61.26 ± 21.42	53.51 ± 22.39	2.00	0.05
Fat (g per day)	54.15 ± 20.95	48.40 ± 19.07	1.55	0.12
Calcium (mg per day)	555.10 ± 320.92	534.79 ± 325.94	0.34	0.74
Vitamin D (μg per day)	10.02 ± 0.58	7.10 ± 1.17	2.02	0.05
Food	7.47 ± 1.10	5.71 ± 0.49	1.36	0.17
Supplement	2.91 ± 0.36	1.94 ± 0.67	1.28	0.20
Total vitamin D intake categories[1)]				
Below recommendation (< 15 μg/day)	155 (69.5)	29 (80.6)	1.84	0.18
Above recommendation (≥ 15 μg/day)	68 (30.5)	7 (19.4)		

Values are presented as mean ± SD or number (%).
GDM, gestational diabetes mellitus; MET, metabolic equivalent.
[1)]Vitamin D: 15 μg/day (source: Malaysia Recommended Nutrient Intakes [RNI], 2017).
*$P < 0.05$.

Table 3. Vitamin D intake by early pregnancy serum 25(OH)D among non-GDM and GDM women (n = 259)

Early pregnancy serum 25(OH)D	Non-GDM (n = 223)	GDM (n = 36)	t/χ^2	*P*-value
Severe VDD (n = 60)	10.17 ± 1.09	8.09 ± 1.56	0.43	0.67
Intake below recommendation (< 15 μg/day)	40 (70.2)	2 (66.7)	-	0.67[1)]
Intake above recommendation (≥ 15 μg/day)	17 (29.8)	1 (33.3)		
Mild VDD (≥ 25 and < 50) (n = 177)	9.67 ± 0.65	6.39 ± 1.26	2.04	0.04*
Intake below recommendation (< 15 μg/day)	106 (71.1)	24 (85.7)	2.57	0.11
Intake above recommendation (≥ 15 μg/day)	43 (28.9)	4 (14.3)		
Insufficiency (≥ 50 and < 75) (n = 22)	12.64 ± 2.42	10.50 ± 4.05	0.43	0.67
Intake below recommendation (< 15 μg/day)	9 (52.9)	3 (60.0)	-	0.24†
Intake above recommendation (≥ 15 μg/day)	8 (47.1)	2 (40.0)		

25(OH)D, 25-hydroxy vitamin D; GDM, gestational diabetes mellitus; VDD, vitamin D deficient.
[1)]Fisher's extract test.
*$P < 0.05$.

Association between serum 25(OH)D level and GDM risk

Table 4 shows that women with a higher early pregnancy serum vitamin D level had a significantly higher risk of GDM (AOR = 1.05; 95% CI = 1.01–1.08). Significant interaction effects on GDM risk were detected between family history of DM ($\chi^2 = 19.48$, $P < 0.05$) and BMI ($\chi^2 = 11.80$, $P < 0.05$) with serum vitamin D level, but none of the socio-demographic factors significantly interacted with GDM risk. Stratified analyses showed that the significant positive association between serum vitamin D and GDM was only observed among overweight/obese and those with a family history of T2DM (**Table 5**).

DISCUSSION

Previous studies have reported inconsistent results indicating the relationship between vitamin D status and GDM [4-13]. The present study showed that women with a slightly higher serum vitamin D had an increased risk of GDM, despite all women having sub-optimal vitamin D status. Regardless of whether these results are due to the small sample size for women diagnosed with GDM (n = 36) or the small variance in the serum vitamin D levels, as most (up to 90%) of the women had mild/severe VDD, the detection of a positive association is worthwhile being investigated further, especially as it occurs among predominantly vitamin D deficient women and its interaction with other risk factors. It is worthwhile to note

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Table 4. AOR and 95% CI for the association between serum 25(OH)D and GDM

Variables	GDM risk	
	AOR (95% CI)	*P*-value
Early pregnancy serum 25(OH)D[1)]	1.05 (1.01–1.08)	0.01*
Interaction terms[2)]		
Serum 25(OH)D × family history of DM	1.03 (1.02–1.05)	0.001*
Serum 25(OH)D × BMI	1.01 (1.00–1.03)	0.01*

Non-GDM is the reference group.
AOR, adjusted odds ratio; CI, confidence interval; 25(OH)D, 25-hydroxy vitamin D; GDM, gestational diabetes mellitus; DM, diabetes mellitus; BMI, body mass index; T2DM, type 2 diabetes mellitus.
[1)]Adjusted for gravidity, BMI, family history of T2DM, total vitamin D intake, energy intake, carbohydrate intake and physical activity; [2)] Non-significant interaction terms: age, years of education, monthly household income, employment status, and gravidity.
*$P < 0.05$.

Table 5. The AOR and 95% CI for the associations between serum 25(OH)D with GDM stratified by family history of T2DM and BMI status

Variables	Family history of T2DM[1)]				BMI status[2)]			
	No (n = 186)		Yes (n = 73)		Underweight/normal (n = 150)		Overweight/obese (n = 109)	
	AOR (95% CI)	*P*-value	AOR (95% CI)	*P*-value	AOR (95% CI)	*P*-value	AOR (95% CI)	*P*-value
Serum 25(OH)D	0.99 (0.97–1.01)	0.15	**1.90 (1.01–1.14)**	**0.01***	0.99 (0.98–1.02)	0.16	**1.13 (1.01–1.16)**	**0.01***

AOR, adjusted odds ratio; CI, confidence interval; 25(OH)D, 25-hydroxy vitamin D; GDM, gestational diabetes mellitus; T2DM, type 2 diabetes mellitus; BMI, body mass index.
[1)]Adjusted by gravidity, BMI, vitamin D intake, energy intake, carbohydrate intake and physical activity level; [2)]Adjusted by gravidity, family history of T2DM, vitamin D intake, energy intake, carbohydrate intake and physical activity level.
*$P < 0.05$.

that although the adjusted odds ratio is small (AOR = 1.05), the narrow confidence interval indicates a high degree of certainty associated with the odds ratio [42].

In this study, the unexpected positive association of serum vitamin D level and risk of GDM was only observed in overweight/obese women and those with a family history of T2DM. Indeed, both family history of T2DM and BMI are well-established risk factors for GDM [43,44]. Pregnant women with a family history of T2DM have approximately 2–4.5 times higher risks of developing GDM compared to women without family history of T2DM [45-48]. Increased body fat might increase insulin resistance and subsequently hyperglycemia [49]. Notably, GDM and T2DM share a similar genetic basis, which might be one reason for women with a first-degree family history of T2DM to be at risk for GDM [50]. Similarly, the present study results indicated that, in addition to the serum vitamin D level, family history of T2DM (AOR = 2.85; 95% CI = 1.34–6.05) and early pregnancy BMI (AOR = 1.07; 95% CI = 1.00–1.08) were significant independent risk factors for GDM. The observed positive association between serum vitamin D level and GDM among predominantly vitamin D deficient women with a family history of T2DM and/or overweight/obese BMI status, therefore, deserves further investigation. Regardless, these findings suggest that nutrition- and lifestyle-related approaches to GDM prevention should be implemented as early as possible, particularly for pregnant women with a family history of T2DM and an 'at risk' BMI.

The 91.5% prevalence of early pregnancy VDD (serum 25[OH]D < 50 nmol/L) in our study is similar to that in a local study (90.4%) conducted among pregnant women in Selangor [30], but higher than in studies in Western countries, such as the United States (10.0%) [51], Spain (22.7%) [52] and Netherlands (44.5%) [53]. However, the severe VDD (serum 25[OH]D < 25 nmol/L) prevalence of 23.2% in this study was much lower than in studies conducted in Turkey (45.9%) [54] and China (44.8%) [55]. To date, the "normal" or "optimal" level for serum 25(OH)D remains uncertain. While a serum 25(OH)D level of 50 nmol/L is considered to be acceptable by Institute of Medicine [34], experts of the Endocrine Group suggest a serum

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25(OH)D level of 75 nmol/L for optimum calcium absorption, bone health, and multiple clinical outcomes [56]. Given the high VDD prevalence in Malaysian pregnant women, future studies to determine the optimal serum vitamin D and a safe level of vitamin D intake are urgently needed. It is also essential to develop effective monitoring and intervention strategies to ensure that pregnant women achieve at least a minimum serum 25(OH)D level of 50 nmol/L to prevent potential adverse health consequences in women and offspring.

In the present study, GDM women had a relatively low vitamin D intake but a slightly high mean serum vitamin D level than non-GDM women. This finding should be interpreted with caution, as the mean intake of vitamin D for both non-GDM (10.02 ± 0.58 μg/day) and GDM (7.10 ± 1.17 μg/day) women were below the recommended daily intake [39], which was established for populations with minimal exposure to sunlight and based on an intake level suitable for maintaining an adequate serum 25(OH)D level (> 50 nmol/L) [35]. The low total intake of vitamin D observed in the present study could be related to the limited availability of foods containing a high vitamin D level and the low incidence of vitamin D supplement usage [57]. It is also possible that women could have under-reported their vitamin D intake as the overall percentage of under-reporting was 27.5%, calculated using a cut-off EI/ER of ≤ 0.78 [58], with a greater proportion of under-reporting in GDM women (29.1%) than in non-GDM women (24.3%).

This study has several limitations that need to be taken into consideration. First, the relatively small sample of respondents with GDM (n = 36) and the limited variation in serum vitamin D concentrations could result in estimation bias. Second, as the majority of respondents were Malays and employed, they may did not represent the general pregnant population. Third, the use of percentage body fat as a measure of adiposity may have produced results different from those by BMI assessment. In addition, this study did not measure other diabetes predictors, such as plasma insulin and hemoglobin A1C, or oxidative stress markers, which could be used to explain the contribution of overweight/obesity status to the association between serum vitamin D level and GDM. Furthermore, this study did not measure vitamin D status in the second trimester of pregnancy. Finally, the accuracy of vitamin D intake estimation might be limited as the vitamin D from food sources was determined based on the USDA database and food labels of fortified foods [16]. However, the vitamin D contents of fortified foods in the Malaysian market compared to those in the USDA food database is not expected to vary significantly. Also, the vitamin D intake of supplements was estimated based on the supplement's label value.

Although VDD was prevalent in this sample of Malaysian pregnant women, a slightly higher serum 25(OH)D level within this sub-optimal range was associated with GDM, particularly among overweight/obese women and those with a family history of T2DM. Given the high prevalence of VDD, effective public health strategies aimed at preventing VDD are urgently needed due to the health significance of vitamin D. For women with multiple risk factors (e.g., overweight/obese and family history of T2DM), consultation on vitamin D status concerning the prevention of GDM could include an assessment of overall vitamin D intake (food and dietary supplement). Nevertheless, further investigation is warranted to confirm the relationship between vitamin D status and GDM in this predominantly vitamin D deficient population.

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REFERENCES

1. Lips P, Eekhoff M, van Schoor N, Oosterwerff M, de Jongh R, Krul-Poel Y, Simsek S. Vitamin D and type 2 diabetes. J Steroid Biochem Mol Biol 2017;173:280-5.
PUBMED | CROSSREF
2. Issa CM. Vitamin D and type 2 diabetes mellitus. Adv Exp Med Biol 2017;996:193-205.
PUBMED | CROSSREF
3. Pittas AG, Lau J, Hu FB, Dawson-Hughes B. The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. J Clin Endocrinol Metab 2007;92:2017-29.
PUBMED | CROSSREF
4. Park S, Yoon HK, Ryu HM, Han YJ, Lee SW, Park BK, Park SY, Yim CH, Kim SH. Maternal vitamin D deficiency in early pregnancy is not associated with gestational diabetes mellitus development or pregnancy outcomes in Korean pregnant women in a prospective study. J Nutr Sci Vitaminol (Tokyo) 2014;60:269-75.
PUBMED | CROSSREF
5. Baker AM, Haeri S, Camargo CA Jr, Stuebe AM, Boggess KA. First-trimester maternal vitamin D status and risk for gestational diabetes (GDM) a nested case-control study. Diabetes Metab Res Rev 2012;28:164-8.
PUBMED | CROSSREF
6. Loy SL, Lek N, Yap F, Soh SE, Padmapriya N, Tan KH, Biswas A, Yeo GS, Kwek K, Gluckman PD, et al. Association of maternal Vitamin D status with glucose tolerance and caesarean section in a multi-ethnic Asian cohort: the growing up in Singapore towards healthy outcomes study. PLoS One 2015;10:e0142239.
PUBMED | CROSSREF
7. Rodriguez A, García-Esteban R, Basterretxea M, Lertxundi A, Rodríguez-Bernal C, Iñiguez C, Rodriguez-Dehli C, Tardón A, Espada M, Sunyer J, et al. Associations of maternal circulating 25-hydroxyvitamin D3 concentration with pregnancy and birth outcomes. BJOG 2015;122:1695-704.
PUBMED | CROSSREF
8. Hauta-Alus HH, Viljakainen HT, Holmlund-Suila EM, Enlund-Cerullo M, Rosendahl J, Valkama SM, Helve OM, Hytinantti TK, Mäkitie OM, Andersson S. Maternal vitamin D status, gestational diabetes and infant birth size. BMC Pregnancy Childbirth 2017;17:420-9.
PUBMED | CROSSREF
9. Lacroix M, Battista MC, Doyon M, Houde G, Ménard J, Ardilouze JL, Hivert MF, Perron P. Lower vitamin D levels at first trimester are associated with higher risk of developing gestational diabetes mellitus. Acta Diabetol 2014;51:609-16.
PUBMED | CROSSREF
10. Al-Ajlan A, Al-Musharaf S, Fouda MA, Krishnaswamy S, Wani K, Aljohani NJ, Al-Serehi A, Sheshah E, Alshingetti NM, Turkistani IZ, et al. Lower vitamin D levels in Saudi pregnant women are associated with higher risk of developing GDM. BMC Pregnancy Childbirth 2018;18:86-93.
PUBMED | CROSSREF
11. Wang O, Nie M, Hu YY, Zhang K, Li W, Ping F, Liu JT, Chen LM, Xing XP. Association between vitamin D insufficiency and the risk for gestational diabetes mellitus in pregnant Chinese women. Biomed Environ Sci 2012;25:399-406.
PUBMED | CROSSREF
12. Xu C, Ma HH, Wang Y. Maternal early pregnancy plasma concentration of 25-hydroxyvitamin D and risk of gestational diabetes mellitus. Calcif Tissue Int 2018;102:280-6.
PUBMED | CROSSREF
13. Arnold DL, Enquobahrie DA, Qiu C, Huang J, Grote N, VanderStoep A, Williams MA. Early pregnancy maternal vitamin D concentrations and risk of gestational diabetes mellitus. Paediatr Perinat Epidemiol 2015;29:200-10.
PUBMED | CROSSREF
14. Poel YH, Hummel P, Lips P, Stam F, van der Ploeg T, Simsek S. Vitamin D and gestational diabetes: a systematic review and meta-analysis. Eur J Intern Med 2012;23:465-9.
PUBMED | CROSSREF

15. Wei SQ, Qi HP, Luo ZC, Fraser WD. Maternal vitamin D status and adverse pregnancy outcomes: a systematic review and meta-analysis. J Matern Fetal Neonatal Med 2013;26:889-99.
PUBMED | CROSSREF

16. Burris HH, Rifas-Shiman SL, Kleinman K, Litonjua AA, Huh SY, Rich-Edwards JW, Camargo CA Jr, Gillman MW. Vitamin D deficiency in pregnancy and gestational diabetes mellitus. Am J Obstet Gynecol 2012;207:182.e1-8.
PUBMED | CROSSREF

17. Alvarez JA, Ashraf A. Role of vitamin d in insulin secretion and insulin sensitivity for glucose homeostasis. Int J Endocrinol 2010;2010:351385.
PUBMED | CROSSREF

18. Sung CC, Liao MT, Lu KC, Wu CC. Role of vitamin D in insulin resistance. J Biomed Biotechnol 2012;2012:634195.
PUBMED | CROSSREF

19. Evans KN, Bulmer JN, Kilby MD, Hewison M. Vitamin D and placental-decidual function. J Soc Gynecol Investig 2004;11:263-71.
PUBMED | CROSSREF

20. Eguchi K, Nagai R. Islet inflammation in type 2 diabetes and physiology. J Clin Invest 2017;127:14-23.
PUBMED | CROSSREF

21. Szymczak-Pajor I, Drzewoski J, Śliwińska A. The molecular mechanisms by which vitamin D prevents insulin resistance and associated disorders. Int J Mol Sci 2020;21:6644.
PUBMED | CROSSREF

22. Prietl B, Treiber G, Pieber TR, Amrein K. Vitamin D and immune function. Nutrients 2013;5:2502-21.
PUBMED | CROSSREF

23. Charoenngam N, Holick MF. Immunologic effects of vitamin D on human health and disease. Nutrients 2020;12:2097.
PUBMED | CROSSREF

24. Shymanskyi I, Lisakovska O, Mazanova A, Veliky M. Vitamin D deficiency and diabetes mellitus [Internet]. London: IntechOpen; 2020 [cited 2020 June 1]. Available from: https://www.intechopen.com/books/vitamin-d-deficiency/vitamin-d-deficiency-and-diabetes-mellitus.

25. Jeganathan R, Karalasingam SD. National Obstetrics Registry: 5th Report, Jan 2016–Dec 2017 [Internet]. Selangor Darul Ehsan: Jointly published by the National Obstetrics Registry and the Institute Clinical Research (IRC), Ministry of Health Malaysia; 2020 [cited 2020 May 1]. Available from: http://www.acrm.org.my/nor/doc/reports/5th_NOR_Report.pdf.

26. Jeganathan R, Karalasingam SD. Preliminary Report of National Obstetrics Registry, Jan–December 2010. Kuala Lumpur: Jointly published by the National Obstetrics Registry and the Clinical Research Centre (CRC), Ministry of Health Malaysia; 2013.

27. Logakodie S, Azahadi O, Fuziah P, Norizzati B, Tan SF, Zienna Z, Norliza M, Noraini J, Hazlin M, Noraliza MZ, et al. Gestational diabetes mellitus: the prevalence, associated factors and foeto-maternal outcome of women attending antenatal care. Malays Fam Physician 2017;12:9-17.
PUBMED

28. Tan PC, Ling LP, Omar SZ. Screening for gestational diabetes at antenatal booking in a Malaysian university hospital: the role of risk factors and threshold value for the 50-g glucose challenge test. Aust N Z J Obstet Gynaecol 2007;47:191-7.
PUBMED | CROSSREF

29. Jan Mohamed HJ, Rowan A, Fong B, Loy SL. Maternal serum and breast milk vitamin D levels: findings from the Universiti Sains Malaysia Pregnancy Cohort Study. PLoS One 2014;9:e100705.
PUBMED | CROSSREF

30. Bukhary NB, Isa ZM, Shamsuddin K, Lin KG, Mahdy ZA, Hassan H, Yeop NS. Risk factors for antenatal hypovitaminosis D in an urban district in Malaysia. BMC Pregnancy Childbirth 2016;16:156-66.
PUBMED | CROSSREF

31. Mousa A, Abell SK, Shorakae S, Harrison CL, Naderpoor N, Hiam D, Moreno-Asso A, Stepto NK, Teede HJ, de Courten B. Relationship between vitamin D and gestational diabetes in overweight or obese pregnant women may be mediated by adiponectin. Mol Nutr Food Res 2017;61:1700488.
PUBMED | CROSSREF

32. Yong HY, Mohd Shariff Z, Rejali Z, Mohd Yusof BN, Yasmin F, Palaniveloo L. Seremban Cohort Study (SECOST): a prospective study of determinants and pregnancy outcomes of maternal glycaemia in Malaysia. BMJ Open 2018;8:e018321.
PUBMED | CROSSREF

33. Palaniveloo L, Yong HY, Mohd Shariff Z, Loh SP, Bindels J, Tee YY, van der Beek EM. Vitamin D status is associated with high BMI, working status and gravidity among pregnant Malaysian women. Malays J Nutr 2020;26:129-39.
CROSSREF
34. Institute of Medicine. Dietary Reference Intakes for Calcium and Vitamin D. Washington, D.C.: The National Academies Press; 2011.
35. Ministry of Health Malaysia, Division of Family Health Development. Perinatal Care Manual 3rd Edition [Internet]. Putrajaya: Ministry of Health Malaysia; 2013 [cited 2020 June 1]. Available from: http://fh.moh.gov.my/v3/index.php/pages/orang-awam/kesihatan-ibu.
36. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser 2000;894:i-xii, 1-253.
PUBMED
37. First DataBank. Nutritionist Pro. San Bruno (CA): First DataBank; 2005.
38. U.S. Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Nutrient Data Laboratory. USDA National Nutrient Database for Standard Reference, Release 28. Beltsville (MD): Nutrient Data Laboratory; 2016.
39. Ministry of Health Malaysia, National Coordinating Committee on Food and Nutrition (NCCFN). Recommended Nutrient Intakes for Malaysia: A Report of the Technical Working Group on Nutritional Guidelines. Putrajaya: Ministry of Health Malaysia; 2017.
40. Chasan-Taber L, Schmidt MD, Roberts DE, Hosmer D, Markenson G, Freedson PS. Development and validation of a Pregnancy Physical Activity Questionnaire. Med Sci Sports Exerc 2004;36:1750-60.
PUBMED | CROSSREF
41. IBM Corp. IBM SPSS Statistics 25.0 for Windows, Released 2020. Armonk (NY): IBM Corp.; 2020.
42. Szumilas M. Explaining odds ratios. J Can Acad Child Adolesc Psychiatry 2010;19:227-9.
PUBMED
43. Chiefari E, Arcidiacono B, Foti D, Brunetti A. Gestational diabetes mellitus: an updated overview. J Endocrinol Invest 2017;40:899-909.
PUBMED | CROSSREF
44. Cozzolino M, Serena C, Maggio L, Rambaldi MP, Simeone S, Mello G, Pasquini L, Di Tommaso M, Mecacci F. Analysis of the main risk factors for gestational diabetes diagnosed with International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria in multiple pregnancies. J Endocrinol Invest 2017;40:937-43.
PUBMED | CROSSREF
45. Yang X, Hsu-Hage B, Zhang H, Yu L, Dong L, Li J, Shao P, Zhang C. Gestational diabetes mellitus in women of single gravidity in Tianjin City, China. Diabetes Care 2002;25:847-51.
PUBMED | CROSSREF
46. Yang H, Wei Y, Gao X, Xu X, Fan L, He J, Hu Y, Liu X, Chen X, Yang Z, et al. Risk factors for gestational diabetes mellitus in Chinese women: a prospective study of 16,286 pregnant women in China. Diabet Med 2009;26:1099-104.
PUBMED | CROSSREF
47. Di Cianni G, Volpe L, Lencioni C, Miccoli R, Cuccuru I, Ghio A, Chatzianagnostou K, Bottone P, Teti G, Del Prato S, et al. Prevalence and risk factors for gestational diabetes assessed by universal screening. Diabetes Res Clin Pract 2003;62:131-7.
PUBMED | CROSSREF
48. Erem C, Kuzu UB, Deger O, Can G. Prevalence of gestational diabetes mellitus and associated risk factors in Turkish women: the Trabzon GDM Study. Arch Med Sci 2015;11:724-35.
PUBMED | CROSSREF
49. Castro AV, Kolka CM, Kim SP, Bergman RN. Obesity, insulin resistance and comorbidities? Mechanisms of association. Arq Bras Endocrinol Metabol 2014;58:600-9.
PUBMED | CROSSREF
50. Kwak SH, Kim SH, Cho YM, Go MJ, Cho YS, Choi SH, Moon MK, Jung HS, Shin HD, Kang HM, et al. A genome-wide association study of gestational diabetes mellitus in Korean women. Diabetes 2012;61:531-41.
PUBMED | CROSSREF
51. Flood-Nichols SK, Tinnemore D, Huang RR, Napolitano PG, Ippolito DL. Vitamin D deficiency in early pregnancy. PLoS One 2015;10:e0123763.
PUBMED | CROSSREF
52. Pérez-López FR, Fernández-Alonso AM, Ferrando-Marco P, González-Salmerón MD, Dionis-Sánchez EC, Fiol-Ruiz G, Chedraui P. First trimester serum 25-hydroxyvitamin D status and factors related to lower levels in gravids living in the Spanish Mediterranean coast. Reprod Sci 2011;18:730-6.
PUBMED | CROSSREF

53. Leffelaar ER, Vrijkotte TG, van Eijsden M. Maternal early pregnancy vitamin D status in relation to fetal and neonatal growth: results of the multi-ethnic Amsterdam Born Children and their Development cohort. Br J Nutr 2010;104:108-17.
PUBMED | CROSSREF

54. Ates S, Sevket O, Ozcan P, Ozkal F, Kaya MO, Dane B. Vitamin D status in the first-trimester: effects of vitamin D deficiency on pregnancy outcomes. Afr Health Sci 2016;16:36-43.
PUBMED | CROSSREF

55. Song SJ, Zhou L, Si S, Liu J, Zhou J, Feng K, Wu J, Zhang W. The high prevalence of vitamin D deficiency and its related maternal factors in pregnant women in Beijing. PLoS One 2013;8:e85081.
PUBMED | CROSSREF

56. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CMEndocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011;96:1911-30.
PUBMED | CROSSREF

57. Yong HY, Zalilah MS, Tan CW, Koo SJ. Pre-pregnancy BMI and intake of energy and calcium are associated with the vitamin D intake of pregnant Malaysian women. Fam Med Prim Care Rev 2017;19:417-23.
CROSSREF

58. Huang TT, Roberts SB, Howarth NC, McCrory MA. Effect of screening out implausible energy intake reports on relationships between diet and BMI. Obes Res 2005;13:1205-17.
PUBMED | CROSSREF