

Association of gestational diabetes mellitus with vitamin D deficiency among Saudi pregnant women: A case-control study

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ABSTRACT

Background: Prevalence of gestational diabetes mellitus (GDM) and 25-hydroxyvitamin D (vitamin D) deficiency is high in Saudi Arabia. Whether GDM is associated with low vitamin D level or not is still under debate, and the literature regarding this association is deficient in Saudi Arabia. GDM is associated with an adverse pregnancy outcome; therefore, the current study was conducted on Saudi pregnant women to evaluate this relationship.

Subjects and methods: This case-control study was conducted in the antenatal clinic at King Fahad Medical City, Riyadh, from February 2015 till February 2017. The Study included 300 pregnant women, of which 100 were GDM cases, and 200 were controls (i.e., without GDM). Cases and control were matched for age, parity, body mass index, gestational age, family history of diabetes mellitus. Vitamin D levels were obtained between 24 to 28 weeks of gestation along with Oral Glucose Tolerance Test (OGTT).

Results: The levels of vitamin D among pregnant Saudi women were sufficient in 13%, insufficient in 51%, and deficient in 36%. It was evident that Vitamin D deficiency (≤ 25 nmol/L) was associated with 3 times more abnormal OGTT. Patients with vitamin D deficiency had a 2.3 times greater risk for developing GDM than those having normal levels. There was no difference among cases and controls regarding, demographic variables like age parity BMI and previous history of GDM.

Conclusion: An inverse relationship between GDM development and maternal vitamin D deficiency.

Keywords:

Gestational diabetes mellitus; 25-hydroxyvitamin D; Pregnant

INTRODUCTION

Gestational diabetes mellitus (GDM) is a carbohydrate intolerance that causes hyperglycemia, which should be diagnosed between 24-28 weeks of gestation.¹ The prevalence depends on ethnicity, age, and screening methods.² GDM prevalence is increased by many times since 1995, reaching almost 45% worldwide, 36.6% in Saudi Arabia and 17.2% in Pakistan.^{2,4} Mechanism of GDM development is still under evaluation but is linked to several factors like maternal age, socioeconomic position, and ethnicity.⁵ GDM is associated with complications like macrosomia, birth trauma, shoulder dystocia, preeclampsia, and neonatal hypoglycemia.⁶

Vitamin D deficiency is common in Saudi Arabia, in reproductive age group females, it is approximately 50% while, in the rest of the population (male and female) it is around 60%.⁷⁻⁹ Vitamin D deficiency is a global problem in pregnancy with prevalence reaching 40-99.5% in Oman, UK, USA, Kuwait, Turkey,

Pakistan, urban India, Japan and China.¹⁰⁻¹² It is very high in some regions of India (96%) and Pakistan (99.5%).^{11,12} In spite of adequate sunlight exposure, 90% of the cases are due to inactivity, chronic diseases, obesity, genetic factors, and dietary insufficiency.^{13,14} Several epidemiological studies suggest a link between low vitamin D levels and an increased risk of gestational diabetes, type 2 DM, osteoporosis, pre-eclampsia, cesarean section, and fetal growth restriction and other adverse pregnancy and neonatal outcomes.¹³⁻²²

The exact mechanism by which GDM develops is not well established. Vitamin D is needed directly by beta cells of the pancreas for insulin secretion.²³ Vitamin D level indirectly affects peripheral insulin receptor sensitivity.²³ In pregnancy, which is complicated by GDM, if associated with vitamin D deficiency it may either start or exaggerate this process by decreasing insulin secretion and sensitivity.²³⁻²⁵ In literature, it is reported that low vitamin D level is associated with high hemoglobin A1C (HbA1C) levels.²⁶

Numerous studies conducted in from around the globe demonstrated contradictory results regarding the association of vitamin D deficiency and GDM.²⁶⁻³¹ In Saudi Arabia, a study has shown a positive association between low vitamin D levels with GDM.³² Similarly,

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various studies supported the inverse association between low vitamin D levels and prevalence of GDM.³³ On the contrary, other studies prove no association.³³ Therefore, more studies are needed to confirm this causal relationship. The current study aimed to determine the prevalence of vitamin D deficiency among pregnant Saudi women and to find the association between vitamin D deficiency and GDM.

SUBJECTS AND METHODS

The study was conducted after taking approval (approval No. 17-247) from the Institutional Review Board (IRB), King Fahad Medical City Riyadh. This case-control study was carried out at Women's Specialized Hospital, King Fahad Medical City, Riyadh, Saudi Arabia, from February 2015 to February 2017. The study included pregnant women with an age range of 18-45 years.

The total sample size was 300 pregnant women, comprising of 100 subjects with GDM (cases) and 200 subjects without GDM (controls). The estimation of the sample size was carried out using PASS 11 software.³⁴ In a matched case-control study, the probability of exposure among sampled control patients was 0.30, and the correlation coefficient for exposure between matched case and control patients was 0.1. Therefore, a sample of 100 participants (cases) was determined. For each case-patient, a matching sample of 200 participants was also obtained. Which will achieve 80% power to detect an odds ratio of 0.50 versus the alternative of equal odds using a Chi-Square test with a 0.05 significance level.

Three hundred **patient's** health record was retrieved from the electronic record system of the hospital HIM and CORTEX. Saudi Women who visited for routine antenatal followed up during the study period and were tested between 24-28 weeks of gestation both for vitamin D^{21,22} levels and OGTT³⁵, were later recruited in the study.

Data for OGTT (Oral Glucose Tolerance Test) and serum 25-hydroxyvitamin D [25(OH)D] results performed between 24-28 weeks of gestation were recorded. For serum 25(OH)D concentrations assay, the tests performed using the Roche Cobas e601 Immunoassay Analyzer using the Roche Elecsys vitamin D3 assay (Roche Diagnostics, Mannheim, Germany). Reference ranges used in this study were based on Endocrine Society Guidelines. According to which vitamin D deficiency was defined as levels ≤ 25 nmol/L, insufficiency as 25–75 nmol/L, and sufficient as 75–200

nmol/L.²¹⁻²² The least required satisfactory serum level of Vitamin D was 75–80 nmol/L.²¹⁻²²

For OGTT, the one-step method was performed to measure plasma glucose with 8 hours of fasting and then 2 hours after drinking a 75 grams OGTT solution, at 24 to 28 weeks of gestation. The diagnosis of GDM was made according to the American Diabetes Association (ADA) criteria, when any one of the following plasma glucose values were exceeded i.e., **fasting plasma glucose ≥ 5.1 mmol/L (≥ 92 mg/dL) and 2 hours ≥ 8.5 mmol/L (≥ 153 mg/dL).**³⁵

Pregnant women in the study group were matched for age, parity, body mass index (BMI), family history of diabetes mellitus or GDM, and gestational age to the control group on 1:2 ratios. Exclusion criteria included patients with one of the following characteristics: multiple pregnancies, history of diabetes mellitus, history of chronic renal or hepatic disease, autoimmune diseases, and existing malignancies. Study form was completed for every **participant's** electronic data, including the following information: demographic information like (maternal age, parity), previous history of GDM, history of vitamin D supplementation, family history of DM, and BMI.

Continuous demographic and clinical data were summarized by means and standard deviations (SD). Frequencies and percentages analyzed categorical data. The student t-test / Mann–Whitney U test was applied for non-normal data for the comparison between the groups. Chi-square, Fisher's exact test was used to detect the association between groups and several demographic or study outcome variables. Multivariate analysis was utilized to estimate the odds of having GDM among patients concerning vitamin D status and intake. Software SPSS (Version 22) was considered for all analyses. A p-value of ≤ 0.05 was considered statistically significant.

RESULTS

Of the 300 participants, 100 (33.3%) pregnant women had GDM who served as cases while 200 (66.7%) in the control group had no GDM. Among pregnant women with GDM, 34 were less than 25 years of age group, whereas 66 were ≥ 25 years old. Among them, 38 (38%) were obese, and 79 (79%) of the participants were not taking any vitamin D supplements (Table 1). Moreover, vitamin D deficiency was observed in 49 participants, 43 had insufficient levels, while 8 had sufficient vitamin D levels (Table 2). The mean vitamin D level was 32.07 nmol/L among the cases (Table 1).

Table 1. Demographic, diagnostic and clinical characteristics of the study population

Characteristics	GDM n (%)	Non GDM n (%)	p-value*
Age (years)			
< 25	34 (34)	70 (35)	0.71
≥ 25	66 (66)	130 (65)	
Mean ±SD	27.10±4.57	27.16±4.54	0.92
Parity			
Primigravida	41 (41)	88 (44)	0.36
Multigravidas	59 (59)	112 (56)	
BMI (kg/m²)			
<25	46 (46)	23 (11.5)	<0.001
25 - 29.9	16 (16)	80 (40)	<0.001
>29.9	38 (38)	97 (48)	0.08
Mean ±SD	29.81±6.16	30.45±5.51	0.37
Family history of DM	60 (60)	64 (32)	0.20
Previous history of GDM	22 (22)	50 (25)	0.67
Vitamin D intake	21 (21)	72 (36)	0.008
Vitamin D level (nmol/L)			
Mean ±SD	32.07±22.64	44.76±28.04	<0.001
Antenatal OGTT			
Normal	0.0	200 (100)	<0.001
Abnormal	100 (100)	0.0	
GDM results (mmol/L)			
FBS (mean ± SD)	5.25 ± 0.62	4.38 ± 0.38	<0.001
PPBS (median ± IQR)	9.10 ± 1.85	6.00 ± 1.7	<0.001

Abbreviations: BMI: body mass index; DM: diabetes mellitus; GDM: gestational diabetes mellitus; IQR: interquartile range; FBS: fasting blood sugar; PPBS: post-prandial blood sugar; SD: standard deviation

*Chi-square, fisher's exact test was used to calculate p-value for categorical variables while, independent sample t-test were used for quantitative variables. A p-value of ≤0.05 was considered as significant.

Among the control group, 70 (34%) pregnant women were from less than 25 years of age, whereas 130 (65%) were ≥25 years of age group. Among them, 88 (44%) women were primigravida. A total of 128 (64%) women were taking vitamin D supplements (Table 1). Moreover, 60 (30%) pregnant women were from vitamin D deficient group, 110 (55%) participants from vitamin D insufficient group, and 31 (16%) patients were from vitamin D sufficient group, respectively (Table 2). The mean vitamin D level was 44.7 nmol/L among the control population (Table 1).

Comparison of cases with controls showed that demographic features including age, parity, BMI, previous history of gestational diabetes, and family history of the diabetes were not statistically different among them (Table 1). Women who took vitamin D supplementation had higher levels of vitamin D compared to those who did not take it (67.6 nmol/L vs. 28.4 nmol/L p<0.001). (Table 1) The study also demonstrated that mean serum vitamin D was significantly (p=0.001) lower in the cases versus controls (32.07 nmol/L vs. 44.76 nmol/L, respectively) (Table 1).

Out of 300 study subjects, only 39 (13%) had a normal vitamin D level, while 153 (51%) had insufficient levels, and 108 (36%) were deficient. The odds ratio showed that GDM has a significant

association (OR (95% CI) 2.3, p=0.001) with vitamin D deficiency (Table 2). That risk of GDM was 2.3 times higher in the vitamin D deficient group as compared to those who had normal levels. A protective effect of vitamin D supplementation was seen in this study (OR 0.47 (95% CI), p-value=0.009) (Table 2).

DISCUSSION

In this study, only 13% of women had sufficient levels of vitamin D levels while the remaining 87% of women had an insufficient (51%) or frank deficiency (36%). The current study confirmed the previously reported low levels of vitamin D among pregnant women worldwide.⁶⁻¹² vitamin D deficiency was reported in 84% women in some parts of Europe.⁶

Like in Saudi Arabia 50-60%^{7,8}, in Australia, it was 45%¹⁰ in India it was 96%¹¹, in Pakistan 99.5%¹² and in Korea 46%.¹³

Pregnant women with vitamin D level of <25 nmol/L have a 2.3 times greater risk for GDM as compared to those who have vitamin D level of higher than that. This finding coincides with the previously reported association between low vitamin D levels and GDM.³⁶⁻⁴⁰ Another recent trial was done in China, which favors that vitamin D levels <25 nmol/L, has two folds the risk of GDM, and adverse pregnancy outcome development, rather than the insufficient group.⁴¹

Table 2. Association of GDM with vitamin D intake and levels

Characteristics	Total n (%)	GDM n (%)	Non-GDM n (%)	OR (95% CI)	p-value*
Vitamin D intake	93 (31)	21 (21)	72 (36)	0.47 (0.27 - 0.83)	0.009
Vitamin D deficiency (<25nmol/L)	108 (36)	49(49)	60(30)	2.3(1.39 - 3.77)	0.001
Vitamin D insufficiency (25-75nmol/L)	153 (51)	43 (43)	110 (55)	0.62 (0.38 - 1.0)	0.05
Vitamin D sufficiency (>75nmol/L)	39 (13)	8 (8)	31 (16)	0.47 (0.20 - 1.07)	0.06

Abbreviations: OR: odds ratio; GDM: gestational diabetes mellitus; CI: confidence interval

* Pearson's Chi-square test was to calculate p-value. A p-values of ≤ 0.05 was considered as significant.

Literature is deficient for GDM and vitamin D association in the Saudi population. Only one cross-sectional study was done in Saudi Arabia by Al Ajlan et al in 2018. To study Vitamin D and GDM relationship, which used cut off of 50 nmol/L for vitamin D.³² Our study is conducted with a better design and used different cut off levels for a precise outcome to confirm the findings of Al Ajlan and coworkers. It reinforced the evidence that at lesser levels of vitamin D below 25nmol/L is associated with an increased rate of GDM as well as intrauterine growth restriction and preeclampsia.²²

Many recent studies reported undesirable pregnancy complications as a result of low vitamin D levels; the fact that highlights, reassessing the value of prescribing vitamin D supplementation for pregnant ladies.¹⁵⁻²² However, due to data inconsistency, there have not been any clear guidelines for screening and supplementation of vitamin D during pregnancy.²⁷ The current study has shown a positive association between vitamin D intake and its level in the blood, which in turn is inversely related to the development of GDM. For instance, the odds of having GDM among participants taking vitamin D were almost half of those who are disease-free. Therefore, this emphasizes the need for a robust clinical trial to determine the exact role of vitamin D in pregnancy and test its potential integration into routine antenatal care. The results of the study might be limited by the nature of the study population that entailed only healthy pregnant women who did not have any other co-morbidities. Other co-morbidities may be confounding factors in analysis. Another limitation is that vitamin D levels were measured at a single time in gestation between 24-28 weeks, although vitamin D deficient women followed and treated with vitamin D supplements. A complete follow up during the entire pregnancy would provide a better understanding of the deficiency trend.

CONCLUSION

Vitamin D deficiency is highly prevalent in Saudi Arabia. This study concludes the inverse relationship between GDM development and maternal vitamin D levels less than 25 nmol/L. More extensive clinical trials

are recommended for confirmation of this finding. Further studies are needed to prove the role of vitamin D supplementation in reducing GDM development.

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