



Italian Journal of Gynæcology & Obstetrics

September 2019 - Vol. 31 - N. 3 - Quarterly - ISSN 2385 - 0868

Relationship between vitamin D level and gestational diabetes mellitus

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ABSTRACT

Background: Gestational diabetes mellitus (GDM) is a frequent disorder in pregnancy, estimated at around 4.5% in Iran. Recently, several epidemiological studies have reported an association between vitamin D deficiency and an increased risk of type 2 diabetes. Considering the high prevalence of vitamin D deficiency and gestational diabetes in Iran, investigating the relationship between these clinical conditions can help a better understanding of the pathogenesis mechanism involved.

Materials and Methods: This was a case-control study performed on singleton pregnant women at 24 to 28 weeks of gestational age who visited the prenatal care clinic at Kosar Hospital in Qazvin, Iran. All patients were tested for fasting blood sugar (FBS), 1-hour and 2-hour oral glucose tolerance test (OGTT) with 75 g of glucose. Based on GTT results, pregnant women were divided into two groups. Vitamin D level was measured in both groups.

Results: The mean age of participants was 26.4±7.2 years. Vitamin D level in the gestational diabetic group (13.8±5.2) was significantly lower than that found in the normal group (29.7±10.7). The serum levels of 25-hydroxyvitamin D3 had significant negative correlation with FBS ($r = -0.49$, $P = 0.001$).

Conclusion: The present study showed that vitamin D deficiency is significantly associated with high levels of blood sugar. Vitamin D deficiency is a preventable and treatable risk factor. Therefore, paying attention to manageable risk factors such as vitamin D deficiency for gestational diabetes is a highly important medical necessity.

Keywords: Vitamin D; Gestational diabetes; Pregnancy; Glucose Tolerance Test.

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DOI: 10.14660/2385-0868-118

SOMMARIO

Background: il diabete mellito gestazionale (GDM) è un disturbo frequente in gravidanza, stimato in circa il 4,5% in Iran. Recentemente, diversi studi epidemiologici hanno riportato un'associazione tra carenza di vitamina D e un aumentato rischio di diabete di tipo 2. Considerando l'elevata prevalenza della carenza di vitamina D e del diabete gestazionale in Iran, lo studio della relazione tra queste condizioni cliniche può aiutare a comprendere meglio il meccanismo patogenetico coinvolto.

Materiali e metodi: questo è stato uno studio caso-controllo condotto su donne in gravidanza singleton da 24 a 28 settimane di età gestazionale che hanno visitato la clinica di cura prenatale presso l'ospedale Kosar di Qazvin, Iran. Tutti i pazienti sono stati testati per glicemia a digiuno (FBS), test di tolleranza al glucosio orale di 1 ora e 2 ore (OGTT) con 75 g di glucosio. Sulla base dei risultati GTT, le donne in gravidanza sono state divise in due gruppi. Il livello di vitamina D è stato misurato in entrambi i gruppi.

Risultati: l'età media dei partecipanti era di 26,4 ± 7,2 anni. Il livello di vitamina D nel gruppo diabetico gestazionale (13,8 ± 5,2) era significativamente inferiore a quello riscontrato nel gruppo normale (29,7 ± 10,7). I livelli sierici di 25-idrossivitamina D3 avevano una correlazione negativa significativa con FBS ($r = -0,49$, $P = 0,001$).

Conclusioni: il presente studio ha dimostrato che la carenza di vitamina D è significativamente associata ad alti livelli di zucchero nel sangue. La carenza di vitamina D è un fattore di rischio prevenibile e curabile. Pertanto, prestare attenzione a fattori di rischio gestibili come la carenza di vitamina D per il diabete gestazionale è una necessità medica molto importante.

INTRODUCTION

Gestational diabetes is the most common medical complication in pregnancy. Patients with gestational diabetes could be classified in two groups: a) Those in whom diabetes is diagnosed before the beginning of pregnancy period (overt diabetes), and b) those with gestational diabetes which occurs during the course of pregnancy⁽¹⁾. The prevalence of gestational diabetes is 10% in Iran according to a recent report⁽²⁾. Gestational diabetes affects both mother and child and leads to several complications, most commonly fetal macrosomia, injury during natural delivery or cesarean section, polyhydramnios, pre-eclampsia, fetal metabolic disorder (hypoglycemia, hypocalcaemia, or hyperbilirubinemia), and finally late-onset complications such as development of type 2 diabetes in the mother after childbirth⁽³⁾. Therefore, the early diagnosis of gestational diabetes and timely case management play a crucial role in controlling and preventing gestational diabetes-associated complications^(4,5).

Currently, the diagnostic test mostly recommended is the 3-hour oral glucose tolerance test (3-hour OGTT) with the ingestion of 75 g of glucose. Gestational diabetes affects almost 14% of pregnancies in the United States and the trend is on the rise^(5, 6). The findings of several studies indicate that vitamin D may have a place in secretion and functional disorder of insulin. Studies performed on pancreas cells have shown that vitamin D could play a crucial role in insulin secretion⁽⁶⁾.

A currently studied topic is assessing the possible correlation between vitamin D deficiency in pregnant women and the occurrence of gestational diabetes in these mothers. Epidemiological studies have confirmed the presence of a relatively significant association between vitamin D deficiency and the high risk of type 2 diabetes⁽⁷⁾. Considering the high prevalence rates for both vitamin D deficiency and gestational diabetes in Iran, investigating the possible correlation between these two medical complications could help in gaining a better insight into the interactions involved in the pathogenesis of these diseases. Therefore, the present study attempted to detect the level of vitamin D deficiency in pregnant women to further prevent the unpleasant outcomes of gestational diabetes in this group of patients.

MATERIALS AND METHODS

1. Study design and sample

This was a case-control study conducted on 300 eligible singleton pregnant women of 24-28 weeks of gestational age referred for prenatal care to the prenatal clinic at Kosar Hospital in Qazvin, Iran.

2. Methods

All pregnant women were initially tested for FBS and later, the 1-hour and 2-hour OGTT was determined following the ingestion of 75 g of pure glucose solution. The results obtained for three measurements were separately placed into normal and diabetic groups and further evaluated. Values higher than 92 mg/dl for FBS, 180 mg/dl for 1-hour GTT, and 153 mg/dl for 2-hour GTT were put in the gestational diabetic group, while those with lower values were placed in the normal group. Vitamin D level was measured for all participants. The BMI, age, physical activity, fish consumption, and vitamin D intake of both groups were also recorded.

3. Measuring tools

Demographic and laboratory findings for each patient were collected in a checklist and all anthropometric indices and gestational age were measured by a gynecologist. The height was measured in the barefoot standing position using a wall-mounted Seca stadiometer to the nearest 1 mm. Weight was also measured using Seca scale (Vogel and Halke, Hamburg, Germany) to the nearest 100 g. BMI was calculated as weight (kg) per height (m) squared, and gestational age was measured by LMP (last menstrual period).

4. Laboratory measurements

According to Williams' Endocrinology (2014 edition)⁽⁸⁾, the glucose level in pregnant women before and after OGTT with 75 g of glucose should normally be ≤ 92 mg/dl in fasting blood sugar (FBS), ≤ 180 mg/dl (after one hour), and ≤ 153 mg/dl (after 2 hours). Based on these cut-off values, the diagnosis of GDM was made if at least one value out of three venous plasma glucose concentrations was equal to or exceeded the thresholds of 92, 180, and 153 mg/dl (for fasting, one-hour, and 2-hour post-glucose load, respectively). This test should be performed following overnight fasting (minimum and maximum fasting times of 8 and 14 h, respectively), three days of unlimited diet (with 150 g of carbohydrate per day or higher), and unlimited daily activity.

Vitamin D serum level was determined by Elecsys assay and values less than 25 U/ml were considered as vitamin D deficiency.

5. Ethical considerations

The study protocol was approved by the Ethics Committee of Qazvin University of Medical Sciences (ID number: IR.QUMS.REC.1394.75). Moreover, participants gave their written informed consent.

6. Inclusion and exclusion criteria

The inclusion criteria were singleton pregnancy and gestational age of 24-28 weeks. Exclusion criteria were overt diabetes, being hospitalized to be checked for blood sugar before 24 weeks of gestational age, and having hypertension or other underlying diseases.

7. Data Analyses

Kolmogorov-Smirnov test was used to

examine the normality of variables of interest. Quantitative variables were described as mean±standard deviation (SD) and categorical variables were described as percentage. Quantitative variables were compared with t-test. Furthermore, Pearson's correlation coefficient was used to determine the relationship between two quantitative variables. P-values less than 0.05 were considered as significant and further analyzed statistically by SPSS 23 using chi-square test and Student's t-test.

RESULTS

The mean age of the sample was 25.6±5.1 years with the range of 18 to 35 years (Table 1).

Table 1.

Demographic characteristics of participants

		control N=153	diabetic N=147	p.value
	Age*	25.1±5.3	26.1±4.9	0.1
	Gestational age*	25.3±1.3	25.4±1.3	0.5
	Body mass index*	27.1±3.0	26.8±3.1	0.421
Occupation**	Labor	8(5.2)	4(2.7)	0.231
	Employee	14(9.2)	21(14.3)	
	Housewife	131(85.6)	122(83.0)	
Physical exercise**	5>sessions of 30 min duration per week	12(7.8)	22(15.0)	0.059
	5-8 sessions of 30 min duration per week	131(85.6)	110(74.8)	
	8<sessions of 30 min duration per week	10(6.5)	15(10.2)	

*Data are presents as Mean±SD

**Data are presents as N(%)

The evaluation of vitamin D level in patients showed that vitamin D concentration was significantly lower in the group with gestational diabetes (13.8±5.2 U/ml) than the normal group (29.7±10.7 U/ml). Moreover, 34 (22.2%) in the control group and 139 (94.6%) in the gestational diabetes group had a vitamin D level of less than 25 mg/dl. More details about mean of FBS, 1&2&3 hour glucose exist in Table 2

Table 2.

Distribution of blood glucose levels between two groups of gestational diabetes and normal.

	Control (mean± SD)	Gestational diabetes (mean± SD)
FBS*	78.93± 6.13	94.17±10.57
GTT** 1h	137.42± 19.63	180.1± 17.14
GTT 2h	117.78± 16.56	146.02±14.24
GTT 3h	90.3±17.04	105.31± 20.47

*fasting blood sugar

**glucose tolerance test

Furthermore, 144 (98%) in gestational diabetic group and 147 (96.1%) in the control group had a history of consumption of vitamin D, and this difference was not significant (P=0.5).

In addition, 81 (55.1%) in the group with gestational diabetes and 66 (44.9%) in the control group reported fish consumption but the observed difference was not significant (P=0.16).

Women with GDM had a 60-time higher (95% CI, 27.1-136.4) risk of 25-hydroxyvitamin D3 deficiency (<25 ng/mL) compared with the normal group. The serum levels of 25-hydroxyvitamin D3 had a significant moderate negative correlation with FBS (r =-0.49, P=0.001), 1-hour OGTT (r =-0.31, P=0.001), 2-hour OGTT (r=-0.57, P=0.001). Values did not change much after adjustment based on age and BMI.

The results of logistic regression analysis showed a significant relationship between GDM and serum vitamin D level in both unadjusted and adjusted (for mother's age, BMI, gestational age, and vitamin D intake) models, where an increase in vitamin D reduced the risk of gestational diabetes by 30% (P<0.001).(Table 3).

Table 3.
Comparison of the vitamin D status in gestational diabetes and normal.

variables	OR	(95%CI)		pvalue
		Unadjusted model	Adjusted model**	
Level Vit D	0.69	(0.64 , 0.75)	(0.63 , 0.74)	<0.001

** adjusted OR for Age, BMI, GA, VitD Use

DISCUSSION

There are increasing numbers of reports concerning the role of vitamin D in regulating the normal level of glucose in plasma. Gestational diabetes is associated with insulin resistance and several studies indicate that vitamin D deficiency could, through insulin resistance, expose pregnant women to the risk of gestational diabetes.

In the present study, 300 pregnant women referred to the prenatal care clinic at Kosar teaching hospital were investigated. The major finding of this study was the inverse correlation between the plasma levels of vitamin D and blood sugar in singleton pregnant mother at 24-28 weeks of gestational age following the performance of OGTT with 75 g of glucose.

The correlation between vitamin D level and gestational diabetes is still a matter of controversy. Similar to Makgoba et al. and inconsistent with our study, Farrent et al. found no association between vitamin D level and gestational diabetes during the second trimester^(9, 10). On the contrary, studies by Poel et al. and Clifton et al. showed results similar to our findings^(11,12). As vitamin D level may be indicative of proper diet, possible interfering factors may include the mother's BMI and consumption of a vitamin D-containing diet such as fish. The mentioned interfering factors were modified in Farrent et al.'s study, similar to our study, yet the results were quite the opposite compared to the results of the present study. In a recent study by Makgoba et al., no correlation was found between vitamin D level and gestational diabetes within the first trimester⁽¹⁰⁾. However, similar to our findings, an inverse correlation was observed between the level of vitamin D and 2-hour OGTT during the second trimester. Therefore, it could not be concluded that the patients' behaviors such as a change in diet may explain these differences, as the level of vitamin D was measured in a time period before confirming the occurrence of gestational diabetes and establishing a proper diet.

Soheilykhah et al. concluded that 83% of pregnant women with gestational diabetes showed vitamin D levels less than 50 U/ml⁽¹³⁾. Also, Maghbooli et al. reported that gestational diabetes was significantly higher in pregnant women with vitamin D levels lower than 35 U/ml⁽¹⁴⁾. Similar to our study, Clifton et al. observed that those with a higher level of blood sugar had a lower level of vitamin D⁽¹⁵⁾. Burris et al. also reported similar findings which are comparable with the present study but with the threshold of 25 U/ml for vitamin D deficiency⁽¹⁵⁾. Finally, Zhang et al. found a similar pattern but, in their study, vitamin D level was tested at 16 weeks of gestational age⁽¹⁶⁾.

In our study, the threshold level for vitamin D was 25 U/ml and, for this value, an inverse correlation was observed between vitamin D and FBS and 1-hour and 2-hour OGTT levels. There is still controversy over the clinical importance of different concentrations of blood glucose in the diagnosis and screening of gestational diabetes. It seems that the differences found in various studies could

be associated with the difference in the method by which gestational diabetes was investigated. For instance, Zhang et al. used OGTT by the ingestion of 100 g of glucose and found no correlation between vitamin D deficiency and blood sugar level, whereas using OGTT with 75 g of glucose produced results quite similar to those found in our experiments⁽¹⁶⁾. As described earlier, the threshold level for vitamin D deficiency has been set differently in various studies which could somehow explain the inconsistency in the results obtained by various authors.

In our study, contrary to several other studies, a higher BMI showed no association with gestational diabetes or a low level of vitamin D^(17, 18, 19, 20). This could indicate that vitamin D deficiency, independently of any type of interfering factor such as BMI and nutrition, is linked to an abnormal blood glucose concentration. In the present study, comparable with some cross-sectional studies, the low level of vitamin D at 24-28 weeks of gestational age was associated with an abnormal FBS concentration. The results of two studies from India were quite the opposite^(9, 11). The authors speculate that the level of vitamin D might have been checked at a time when gestational diabetes was developed.

The season for sampling is another possible interfering variable as vitamin D is mostly produced in the skin when it is exposed to ultraviolet light. This could possibly link the level of vitamin D to the season in which the study is conducted. In our study, all samplings were performed in the same season, thus ruling out the confounding effect of the season of sampling on changes in vitamin D level. In three studies in which the season was deleted as an interfering factor, the authors found no relationship between vitamin D level and blood glucose concentration, a finding in disagreement with our result^(9, 13, 21).

The strengths of our study were a large sample size, racial and sex similarity, and considering the role of interfering factors such as nutrition and BMI. The limitations of the present study were: (a) a failure to investigate the physical activity of the study sample because the authors were unaware whether the pregnant women were employed or homemakers; (b) the cross-sectional design of the study; (c) determining vitamin D levels on the same samples used for

diabetes screening test; although the samples were collected before making a definitive diagnosis for diabetes, impaired OGTT may have nevertheless occurred before the samples were taken and, thus, the correlation observed in our study cannot certainly justify the condition; and (d) the single measurement of vitamin D level; as a single determination cannot accurately reflect the level of vitamin D during the entire period of pregnancy, further studies are needed to clarify this association.

1. Limitations of the study

The present study had some limitations, including the time of blood sampling, i.e. in the 24-28 weeks of gestational age.

CONCLUSION

Vitamin D deficiency is a preventable and treatable risk factor commonly seen in pregnancy and leading to complications such as preeclampsia, infantile rickets, and other short-term and long-standing medical problems^(22, 23). Two million adults (7.7%) aging 25 to 64 years had diabetes in Iran in 2008. Also, 4.4 million (16.8%) Iranian adults had impaired fasting glucose⁽²⁴⁾. Considering the growth of GDM and its complications, it is wise to remove the modifiable risk factors of gestational diabetes such as vitamin D deficiency⁽¹⁶⁾. Regarding the findings of the present study and other similar works, the consumption of vitamin D-containing supplements may clinically prove useful in preventing gestational diabetes. However, further large-scale clinical studies are required to investigate the vitamin D level in all three trimesters of pregnancy to confirm this recommendation.

CONFLICT OF INTEREST

None.

ACKNOWLEDGMENTS

This research was supported by a grant from the research department of Qazvin University of Medical Sciences. The authors would like to thank the participants involved in this study, the department of research of Qazvin University of Medical Science, and the Clinical Research Development Center of Kowsar Hospital for assisting us in this research project.

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