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Original Article

Relationship Between Vitamin D Deficiencyand Risk of Gdm In Pregnant Women

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ABSTRACT

Objective: To determine the association between vitamin D status (normal vs deficient) with the risk of Gestational diabetes mellitus among pregnant females of Pakistan.
Study Design: Prospective comparative study.
Place and Duration of Study: Liaquat National Hospital Karachi from April 2021 to April 2022.
Methodology: After approval from Ethical Review Board, total of 120 pregnant patients fulfilling inclusion and exclusion criteria were enrolled in this study. All women had their OGTT performed at mid pregnancy. On the basis of vitamin D levels patients were categorized into Vitamin D sufficient (> 30 ng/ml), insufficient (21-29 ng/ml) and deficient (< 20 ng/ml) group.60 women with vitamin D sufficient level were included in control group , while 60 women with vitamin D insufficient and deficient level were included in study group.
Results: On comparison in control group, Gestational diabetes mellitus found in 18(30 %) cases. In study group, 3(16.7%) cases among vitamin D insufficient while 24(57.1%) cases among vitamin D deficient level had Gestational diabetes mellitus (*p*-value =0.003).
Conclusion: Our observations showed a significant increased risk of gestation diabetes mellitus with vitamin D deficiency as compared to vitamin D sufficient (> 30 ng/ml) and insufficient level (<20ng/ml) in Pakistani pregnant women.

Keywords: Glucose intolerance, Oral glucose tolerance test (OGTT), Vitamin D deficiency.

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INTRODUCTION

Gestational diabetes mellitus (GDM) is one of the most common disorders of pregnancy that is described as any level of glucose intolerance that manifests or is first diagnosed during pregnancy.[1] GDM is also associated with complications for both mother and fetus and it is said to be caused by imbalance between insulin resistance and insulin secretion.[2] Ethnicity, advanced maternal age, history of GDM in previous pregnancy, history of miscarriage and type II diabetes mellitus (T2DM) in first degree relatives, pre gestational overweight and high gestational weight gain are all known risk factors for GDM.[3] The incidence of GDM is becoming more common across the world, affecting 1–25% of all pregnancies, depending on patient demographics, screening methods and criteria for diagnosis.[1,3] GDM is linked to a greater risk of development of type II DM later in life in women.[4] In pregnancy, vitamin D deficiency is highly prevalent particularly in South Asia.[5] Vitamin D has a potential direct impact on glucose metabolism, required for optimal insulin secretion, moreover adequate vitamin D supplementation improves insulin secretion and sensitivity but there is also a knowledge gap about the best dose for pre-existing vitamin D insufficiency, as well as the best gestational age to begin supplementation.[1,6] It has been observed that physically active women are least likely to have glucose intolerance and may have greater vitamin D levels because of increased sunshine exposure and physical activity.[7] Insulin resistance increases by 50–60% during pregnancy, regardless of pre-pregnancy levels and is aggravated by significant gestational weight gain.[8] Recent data suggests that vitamin D receptors expressed in many cells, including those that regulate metabolism of glucose, such as pancreatic beta cells and muscles.[1] Vitamin D has extra skeletal effects, its deficiency may cause dysfunction of glucose metabolism through impairing insulin sensitivity and deteriorating pancreatic beta cells functioning.[9]

Deficient vitamin D level enhances the risk of GDM are biologically acceptable because of the following mechanisms.To begin with the active form of vitamin D, modulates blood glucose levels by attaching to the pancreatic beta-cell's vitamin D receptor. Second, 1,25(OH)2D3 improves insulin functioning by increasing insulin receptors expression and increase production for glucose transport.

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Moreover, vit D modulates the equilibrium of calcium level, which is necessary for insulin-mediated activities. Chronic activation of this modulation system by high glycemic levels and subsequent insulin resistance causes pancreatic secretory competence to be exhausted, causing serum insulin level to be altered, resulting in dysregulation of glucose metabolism and even type II DM.[1,3]

A lot of research work has been done in last decade to see the association between vitamin D status and risk of gestational diabetes mellitus but no authentic data available in Pakistan. This study was undertaken with the aim to determine the association between vitamin D status (normal vs deficient) with the risk of GDM among pregnant women in Pakistan, a country where obesity, vitamin D deficiency, and GDM are all common.

METHODOLOGY

A prospective comparative study conducted in 120 patients younger than 45 years of age attending antenatal clinic at Liaquat National Hospital enrolled from Apr 2021 to Apr 2022. Approval from Hospital's Ethical Review Board was taken (App #0634-2021 LNH-ERC). Sample size was calculated by WHO Software for sample size, taking prevalence of developing GDM in vitamin D insufficient and deficient cases P1= 65.8, in comparison women with optimal vitamin D level P2= 17 %, power of test is 80 %.[10] Calculated sample size was 24 patients (12 patients from each group) at 95% CI, we included 120 patients (60 patients from each group) to follow the assumption of normality. The sampling technique was non-probability consecutive sampling.

Inclusion Criteria: All pregnant patients attending outpatient clinic with singleton pregnancy, history of GDM in previous pregnancy , history of macrosomic baby, history of unexplained IUD baby and patients with family history of type I or II DM in first degree relatives were included in the study.

Exclusion Criteria: Patients with history of type I or II DM, chronic hypertension, chronic renal disease or any autoimmune disease , present history of vitamin D supplements if taken less than 3 months, fat malabsoption, gastric bypass surgery, previous surgery of parathyroid glands, patients taking steroids or any drug that interfere with glucose metabolism were excluded.

All females presenting to Obstetrician clinic of LNH meeting the inclusion criteria enrolled in this study after taking informed consent. Data were collected using validated questionnaire. The questionnaire included demographic details, socioeconomic status, parity, family and medical histories, anthropometric and obstetric characteristics. A detailed history and physical examination that includes height, weight and BMI taken with complete privacy maintained throughout. The gestational age was determined in weeks based on the last date of the menstrual cycle and validated by ultrasonographic measures. A trained phlebotomist collected venous sample and maternal serum vitamin D concentration were determined by ELISA method using radioimmunoassay kits, serum separated and stored at -70 degree centigrade until analysis. The concentration of 25 hydroxy vitamin D level measured in ng/ml.

On the basis of vitamin D level women were categorized into: Vitamin D deficiency (vitamin D level <20ng/ml, Vitamin D insufficiency (vitamin D level between 21-29ng/ml) and optimal vitamin D (vitamin D level between 30-50 ng/ml). Patients were divided into two groups based on vitamin D status, group A (control group with optimal vitamin D level) and group B (study group with vitamin D insufficient or deficient level). All pregnant women had their OGTT performed at mid pregnancy (24 to 28 weeks), a screening test to assess GDM status using IADPSG (International Association of Diabetes and Pregnancy Study Group).Fasting blood glucose level of > 5.1 mmol/L (92mg/dl), 60 min blood glucose level of >10 mmol/L (180mg/dl) and 120 min blood glucose level of > 8.5 mmol/L (153mg/dl). The acquired data was assembled, tabulated, and evaluated using proper statistical tests in order to meet the study's objectives. Patient's data compiled and analyzed through statistical package for Social Sciences (SPSS) Version 25. Frequency and percentage computed for qualitative variables. Mean± SD calculated for quantitative variable. Chi-square or/and fisher exact test was applied to assess the association between categorical variables. *p*-value <0.05 was considered as significant.

RESULTS

We recruited one hundred and twenty pregnant women in our study. The mean age of the patients was 28.43±4.50 years in control and 28.08±5.08 years in study group. The mean height, weight and body mass index was noted as 5.41±0.15 inches, 59.51±8.28 kg and 29.11±5.08 kg/m² in controls while 5.36±0.13 inches, 56.13±8.76 kg and 28.14±5.09 kg/m² in study group respectively. We observed 24(40%) women were obese in controls while 17(28.3%) in study group. The mean gravida and parity was found as 3.03±1.55 and 1.43±1.25in controls and 3.07±1.83 and 1.50±1.46 in study group respectively. Family history of diabetes mellitus was found in 24(40%) controls and 29(48.3%) study group. The history of gestational diabetes mellitus was noted in 16(26.7%) controls and 15(25%) in study group. The gestational diabetes mellitus was observed among 18(30%) in controls while 27(45%) in study group.

Table-I: Frequency Distribution of the Pregnant Women Among Vitamin D Level (n=112)

	Vitamin D level		*p*-value
	Control group	Study group	
Age in years	28.43±4.50	28.08±5.08	0.691
Age group			
≤30 years	33(55.0)	33(55.0)	1.000
>30 years	27(45.0)	27(45.0)	
Height in inches	5.41±0.15	5.36±0.13	0.053
Weight in kilogram	59.51±8.28	56.13±8.76	0.033
BMI	29.11±5.08	28.14±5.09	0.298
Obese			
Yes	24(40.0)	17(28.3)	0.178
No	36(60.0)	43(71.7)	
Gravida	3.03±1.55	3.07±1.83	0.914
Parity	1.43±1.25	1.50±1.46	0.789
Education			
Matric	3(5.0)	5(8.3)	0.616
Intermediate	24(40.0)	29(48.3)	
Graduate	20(33.3)	17(28.3)	
Masters	13(21.7)	9(15.0)	
Surgical History			
Yes	7(11.7)	5(8.3)	0.543
No	53(88.3)	55(91.7)	
Family History of Diabetes Mellitus			
Yes	24(40.0)	29(48.3)	0.358
No	36(60.0)	31(51.7)	
History of Gestational Diabetes Mellitus			
Yes	16(26.7)	15(25.0)	0.835
No	44(73.3)	45(75.0)	
Gestational diabetes mellitus			
Yes	18(30.0)	27(45.0)	0.090
No	42(70.0)	33(55.0)	

According to vitamin D level women were categorized as women with optimal level included in control group while women with insufficient and deficient levels were included in study group. Their vitamin D level were distributed as 60 (50%) women had normal, 18(15%) had insufficient and 42(35%) had deficient level of vitamin D. The gestational diabetes mellitus is highly significantly associated with family history of diabetes mellitus (p<0.001) and history of gestational diabetes mellitus in previous pregnancy (p<0.001).

On comparison among 60 vitamin D sufficient cases, the prevalence of gestational diabetes mellitus was found to be 18(30%). On the other hand, out of 18 vitamin D insufficient cases gestational diabetes mellitus observed in 3(16.7%) and out of 42 vitamin D deficient, 24(57.1%) had gestational diabetes mellitus. We observed significant association among vitamin D levels with the gestational diabetes mellitus (p=0.003). It was observed that women with vitamin D deficient level (<20ng/ml) showed marked increased risk for developing GDM as compared to women with optimal and vitamin d insufficient level.

DISCUSSION

In the past decade, there has been a lot of research done to see if there is a link between maternal serum vitamin D level and the risk of developing GDM, profound association seen. Our study showed that vitamin D level inversely related to risk of developing GDM. It has been observed that GDM is significantly associated with family history of diabetes mellitus (p<0.001) and history of gestational diabetes mellitus in previous pregnancy (p <0.001). Our study showed that vitamin D level inversely related to risk of developing GDM. GDM is prevalent in 57.1 % of women with vitamin D deficiency (24 out of 42 cases) and 16.7 % with vitamin D insufficient level(3 out of 18 cases).

Our observations are comparable with findings observed in prior studies that GDM is highly prevalent among women with vitamin D deficient women. Wei and colleagues.[11] observed that 25(OH)D levels < 50nmol/L among pregnant women is a significant increase in odds of GDM (crude OR 1.38, 95 % CI).Similarly, on the basis of 10 studies meta-analysis, Aghajafari F and colleagues.[12] observed that 25(OH)D levels <75nmol/L were significantly co related with odd of GDM OR 1.49 (95 % CI, 1.18 to 1.88). Maghbooli *et al.*[13] studied association between deficient Vit D level and gestational diabetes mellitus over 741 women in Iran at 24–28-weeks gestation. Consistent with our findings they also found significant decreased levels of 25(OH)D in women

Table-II: Association Of Demographic and Clinical Findings with The Vitamin D Levels and Gestational Disbetes Mellitus (n=112)

	Vitamin D level			*p*-value	Gestational diabetes mellitus		*p*-value
	Normal	Insufficient	Deficient		Yes	No	
Age group							
<30 years	33(55)	11(61.1)	22(52.4)	0.824	21(46.7)	45(60)	0.155
>30 years	27(45)	7(38.9)	20(47.6)		24(53.3)	30(40)	
Obese							
Yes	24(40)	4(22.2)	13(31)	0.326	16(35.6)	25(33.3)	0.804
No	36(60)	14(77.8)	29(69)		29(64.4)	50(66.7)	
Education							
Matric	3(5)	1(5.6)	4(9.5)		5(11.1)	3(4)	
Intermediate	24(40)	9(50)	20(47.6)	0.87	15(33.3)	38(50.7)	0.139
Graduate	20(33.3)	6(33.3)	11(26.2)		14(31.1)	23(30.7)	
Masters	13(21.7)	2(11.1)	7(16.7)		11(24.4)	11(14.7)	
Surgical History							
Yes	7(11.7)	1(5.6)	4(9.5)	0.919	1(2.2)	11(14.7)	0.030*
No	53(88.3)	17(94.4)	38(90.5)		44(97.8)	64(85.3)	
Family History of Diabetes Mellitus							
Yes	24(40)	5(27.8)	24(57.1)	0.072	14(31.1)	53(70.7)	<0.001*
No	36(60)	13(72.2)	18(42.9)		31(68.9)	22(29.3)	
History of Gestational diabetes mellitus							
Yes	16(26.7)	2(11.1)	13(31)	0.271	22(48.9)	9(12)	<0.001*
No	44(73.3)	16(88.9)	29(69)		23(51.1)	66(88)	

with GDM compared to control group. Zhang *et al.*[14] investigated among 953 pregnant women in Tacoma, reported maternal 25-hydroxyvitamin D examined (at 16 weeks) was markedly lower in GDM women, hypovitaminosis D observed in 33% of glucose intolerant women compared to 14% with normal glucose level. Lacroix *et al.*[15] concluded that women with decreased vitamin D level showed 1.48 times higher rate of developing GDM, moreover optimal vitamin D level is more effective in maintaining good glycemic control in pregnancy. Clifton-Bligh *et al.*[16] examined the association between serum 25-hydroxyvitamin D and glucose metabolism among 307 pregnant women in Australia. In this study, 48% women had vit D deficient level, while glucose intolerance was evident in 32% of women, the overall findings were constant with the hypothesis that suboptimal vitamin D level is a risk factor for glucose intolerance in pregnant women. Soheilykhah *et al.*[17] conducted a case-control study in Iran, demonstrated that 83% of women with GDM had 25hydroxy vitamin D levels of 50 nmol/L (p=0.003), in contrast our study showed the prevalence of GDM is 57.1% in women with vitamin D level <20 ng/ml.Poel *et al.*[18] observed significant higher rate of GDM with maternal vitamin D insufficiency (< 50 nmol/L) an odds ratio of 1.61.

Many studies also investigated the effect of vitamin D supplementation in women with GDM. Asemi *et al.*[19] investigated the effect of vitamin D supplementation on 56 Iranian women with GDM found a significant reduction in fasting glucose levels with adequate vitamin D supplementation. Rudnicki and Mølsted-Pedersen.[20], 1997 demonstrated fasting glucose level fell with vitamin D supplementation. Roth *et al.*[21] concluded a significant beneficial role for vitamin D in alleviating the GDM risk in 2,643 pregnant women. Lau *et al.*[22] conducted a studyon 147 pregnant Australian women with GDM, demonstrated that vitamin D level inversely related to FBG, OGTT and HbA1c level, moreover in patients with established GDM, suboptimal vitamin D level associated with inappropriate glucose control. Loy *et al.*[23] reported inverse relationship between vitamin D and FBG. Similarly, Hu *et al.*[24] showed 39% increased risk of GDM observed among vitamin D insufficient women. Contrary to our findings, Farrant *et al.*[25] conducted a cross sectional study on 599 women from south India at the 30th week gestational age among

vitamin D deficient women but no association was found between GDM and vitamin D deficiency.

On the basis of previous studies, it has been concluded that vitamin D deficiency is highly prevalent and independent risk factor for GDM, although some confounding bias may play a role in assessing the relationship between serum vitamin D and the risk of GDM due to the multifactorial pathophysiology of GDM. Moreover assessment of vitamin D level may contribute the early detection of GDM risk. Reduced maternal vitamin D availability during pregnancy might be a factor in the development of insulin resistance, which leads to glucose intolerance. Given the widespread vitamin D deficiency among Pakistani pregnant women, vitamin D might be a promising choice for the prevention and management of GDM, with no significant hazards if administered in physiological doses. However, it must be integrated into wider approaches that include other characteristics that might successfully impact the multifactorial nature of the disease.

Table-III: Association of Gestational Diabetes Mellitus with The Vitamin D Levels (n=112)

	Vitamin D level			*p*-value
	Normal	Insufficient	Deficient	
Gestational diabetes mellitus				0.003*
Yes	18(30)	3(16.7)	24(57.1)	
No	42(70)	15(83.3)	18(42.9)	

LIMITATIONS OF STUDY

Some limitations merit discussion and considerations in our study:

Our study is single center, results need to be confirmed by large multicenter studies.

Second, the impact of some of significant co factors that affect the relationship between vitamin D deficiency and GDM rendering skin color, weight gain in pregnancy and seasonal variation were not evaluated.

CONCLUSION

Our observations on prevalence of GDM and maternal vitamin D levels showed a significant increased risk of GDM with vitamin D deficiency as compared to vitamin D sufficient level in Pakistani females. Such evidence is valuable in view of limited prospective data, however well designed randomized controlled trials are needed to find the exact effect of vitamin D deficiency on prevalence of GDM, till then adequate supplementation should be considered to women who are at risk of vitamin D deficiency. As adequate vitamin D supplementation during pregnancy may benefit by decreasing the risk of GDM.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

MM & ZN: Data acquisition, data analysis, critical review, approval of the final version to be published.

MAS & AT: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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