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Vitamin D Status in Patients of Gestational Diabetes Mellitus in Comparison to That of Normal Pregnancy

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ABSTRACT

Background & objective: Although the role of vitamin-D in calcium metabolism and bone health is undisputed, other long-term health consequences of low vitamin-D are still debated. Observational studies have recently indicated that vitamin-D deficiency may be a modifiable risk factor for gestational diabetes mellitus (GDM), although several experimental studies have failed to establish such an association. The present study was undertaken to test the hypothesis that vitamin-D insufficiency or deficiency is associated with GDM.

Methods: The present case-control study was conducted in the Department of Obstetrics and Gynaecology, Rajshahi Medical College (RMC), Rajshahi, Bangladesh, over a period of 1 year between July 2019 to June 2020. Patients with confirmed GDM (case) and normal pregnant women (control) attending in the above-mentioned place during the study period were the study population. A total of 18 cases and 54 controls were consecutively included in the study based on predefined eligibility criteria. The exposure and outcome variables were serum vitamin-D insufficiency/deficiency and GDM respectively. Vitamin D insufficiency was considered when serum level 25(OH)D ranges from ≥ 15 to < 30 ng/ml and deficiency was termed if 25(OH)D level lies below 15 ng/ml. Crosstab analysis with Odds Ratio (OR) was done to find the association between vitamin-D and GDM and the risk of developing the outcome (GDM) due to vitamin-D insufficiency or deficiency.

Result: In the present study age, residence, socioeconomic status and season at data collection were almost identically distributed between case and control groups. However, the study demonstrated occupation, pre-pregnancy obesity, family history of type-II diabetes, polyhydramnios, level of hemoglobin and serum vitamin-D insufficiency/deficiency to be associated with GDM. Majority (83.3%) of the GDM patients had insufficient or deficient serum vitamin D level (< 30 ng/mL) as compared to 57.4% of the control group. The risk of having GDM in pregnant women with insufficient or deficient serum vitamin-D was estimated to be almost 4-fold (95% CI = 1.1 – 14.3) higher (p = 0.047) than that in the pregnant women with normal serum vitamin-D level.

Conclusion: The study concluded that pregnant women with GDM are associated with insufficient or deficient serum vitamin-D with risk of having GDM in pregnant women with insufficient or deficient serum vitamin-D is much greater than the pregnant women with normal serum vitamin-D level.

Key words: Vitamin D, gestational diabetes mellitus, pregnancy etc.

INTRODUCTION:

Gestational diabetes mellitus (GDM) is a common pregnancy complication, defined as glucose intolerance with onset or first recognition during pregnancy, in women without prior history of diabetes.[1,2] During the last 20 years the prevalence of GDM has increased worldwide and it is expected to further rise along with the increase in pre-conception

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obesity and pregnant women affected by obesity.[3] Gestational diabetes affects approximately 15% of all pregnancies, depending on population characteristics, and this prevalence may in fact be higher under the new diagnostic criteria.[4] It is associated with an increased risk of maternal and infant morbidity, including macrosomia, large for gestational age (LGA), cesarean section delivery and preterm birth. It is also considered to be a risk factor for long-term complications, such as type-2 diabetes mellitus in the mother and their off-springs.[5-8] The etiology of GDM is multifactorial and has not completely been established yet.

Although several GDM risk factors like advanced maternal age, obesity, family history of diabetes and ethnicity have been identified, how these risk factors predispose women to GDM remains an illusive area of scientific inquiry. In recent years, vitamin-D deficiency has been increasingly recognized as a potential contributor to several pregnancy outcomes including fetal growth, hypertensive disorders and gestational diabetes mellitus (GDM).[9-10] Two factors have made vitamin D intriguing to perinatal investigators studying GDM. First, vitamin D has been shown to improve pancreatic exocrine function and insulin sensitivity in animal models. Second, vitamin D status, like most micronutrients, is easily modified by dietary supplementation.[11]

While epidemiologic studies have shown a fairly consistent link between vitamin-D deficiency and a higher risk of type-2 diabetes, and obesity is strongly associated with both GDM and vitamin-D deficiency, it remains unclear whether vitamin-D deficiency contributes to the development of GDM.[12] Several observational studies have found an association between low vitamin D level and increased risk of GDM. Aghajafari and associates[13] showed vitamin-D deficiency to associate with altered glucose homeostasis during pregnancy. Interestingly, a decrease in glucose and increase in insulin levels was noted after vitamin-D supplementation. In a matched, case-control study of 54 Iranian women with GDM and 11 non-GDM controls, Soheilykhah et al[14] found that maternal vitamin-D concentrations at 24-28 weeks of gestation were significantly lower in women with GDM. Clifton-Bligh & colleagues studied 264 pregnant women in Australia and found that nearly one-third (32%) of women with GDM had significantly lower vitamin-D levels. The data also revealed that maternal 25(OH)D, concentrations were inversely realted to fasting glucose.[15] Likewise, in a nested case-control study in the United States maternal vitamin-D levels at 16 weeks of gestation were 20% lower among women who later developed GDM.[16] A meta-analysis of 20 independent observational studies provided strong evidence of association between vitamin-D deficiency and an increased risk of gestational diabetes.[17]

Sharply contrasting to these findings, an Indian study of 559 pregnant women, did not find any association between second trimester vitamin-D levels and GDM.[18] Likewise, a case-control study (with 90 cases and 158 controls) in the United Kingdom reported no association between vitamin-D level in first trimester blood samples & subsequent development of GDM.[19] As there are conflicting evidences, further studies in different population may help establishing the association between these two variables of interest. The present study was therefore, conducted to find the association between serum vitamin D and GDM.

METHODS:

This case-control study was conducted in the Department of Obstetrics and Gynaecology, RMCH, Rajshahi, Bangladesh, over a period of 1 year between July 2019 to June 2020. Pregnant women with confirmed GDM and normal pregnant women at their 2nd and 3rd trimesters (above 12 weeks of gestation) were the cases and controls respectively. A total of 18 cases and 54 controls were consecutively included in the study based on predefined eligibility criteria. However, pregnant women with pre-gestational diabetes mellitus, multiple pregnancies, pregnancy with comorbidity (severe cardiac disease, uncontrolled DM, HTN, renal disease) were excluded from the study. Approval for the study was obtained from the Institutional Review Board (IRB) of Rajshahi Medical College, Rajshahi. The exposure and outcome variables in the present study were serum vitamin-D and GDM, The confounding variables were grouped as demographic variables (age, residence, occupation, socioeconomic status and season at sample collection), BMI, obstetric and reproductive characteristics (gestational age, gravida, parity, age at menarche, age at first pregnancy), pertinent past history (pre-pregnancy obesity, family history of Type-II diabetes), current obstetric history (UTI and polyhydramnios) and biochemical variables (level of haemoglobin, serum calcium and serum creatinine).

Collected data were processed and analyzed using SPSS (Statistical Package for Social Science), version 23.0 available. The test statistics used analyze the data were descriptive statistics, Chi-square Test (for categorical variables) and Unpaired t-test (for continuous variables). The Odds Ratio (OR) of vitamin-D insufficiency or deficiency was calculated to estimate the risk of developing GDM due to this variable. The level of significance was set at 5% and p-value < 0.05 was considered significant.

RESULTS:

Over half of the cases and controls were 30 or > 30 years old with mean age of the cases and controls being 30 and 29.5 years respectively (p = 0.511). Housewives were more likely to be associated with cases than the other occupants (p = 0.045). Neither residence nor socioeconomic class was found to be associated with cases (p = 0.148 and p = 0.959 respectively), although urban residents tend to be associated with GDM more often than rural and slum dwellers. GDM was not found to be associated with season at data collection (p = 0.629) (Table I). Both cases and controls were predominantly overweight or obese with no significant inter-group difference in terms of BMI (p = 0.470). None of the obstetric and reproductive characteristics (gestational age, parity, gravida, age at menarche and age at first pregnancy) was observed to be associated with cases (p = 0.466, p = 0.574, p = 0.514, p = 0.294 and p = 0.346 respectively). Two-thirds (66.7%) of the cases were obese before pregnancy as opposed to 38.9% of the controls (p = 0.014). Type II diabetes in first degree relations was significantly common in case group (66.7%) than that in control group (35.2%) (p = 0.019) (Table II).

Urinary tract infection (UTI) was almost identically distributed between cases and controls (p = 0.367). Polyhydramnios was more likely to be associated with case group (GDM) than with their control counterparts (p = 0.046) (Table III). Level of haemoglobin was significantly lower in the case group than that in the control group (p = 0.021). Serum calcium and serum creatinine were no different between the study groups (p = 0.443 & p = 0.736 respectively). The mean serum vitamin D was much lower in the case group than that in the control group (p=0.040) (Table IV). Analysis of association between level of vitamin D and GDM revealed that majority (83.3%) case group had insufficient or deficient serum vitamin D level (< 30 ng/mL) compared to 57.4% of the control group. The risk of developing GDM in pregnant women with insufficient/deficient serum vitamin D is nearly 4-fold (95% CI=1.1-14.3) higher (p=0.047) than those pregnant women with normal vitamin D level (Table V).

Table I: Demographic characteristics between case and control groups

Demographic characteristics	Group		p-value
	Case (n = 18)	Control (n = 54)	
Age# (years)			
< 30	8(44.4)	26(48.1)	
≥ 30	10(55.6)	28(51.9)	0.511
Mean ± SD	30.0 ± 2.8	29.5 ± 3.3	
Residence*			
Urban	11(61.1)	23(42.6)	
Rural	4(22.2)	26(48.1)	0.148
Slum	3(16.7)	5(9.3)	
Occupation*			
Housewife	12(66.7)	18(33.3)	
Service-holder	4(22.2)	26(48.1)	0.045
Others (business, labor)	2(11.1)	10(18.6)	
Socioeconomic status*			
Poor	2(11.1)	7(13.0)	
Lower middle class & middle class	14(77.8)	42(77.8)	0.959
Upper middle class & rich	2(11.1)	5(9.3)	
Season at sample collection*			
Winter	3(16.7)	10(18.5)	
Spring	2(11.1)	11(20.4)	0.629
Summer	13(72.2)	33(61.1)	

*Data were analyzed using **Chi-squared (χ^2) Test;** figures in the parentheses denote corresponding %. #Data were analyzed using **Unpaired t-Test** and were presented as **mean ± SD.**

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Table II: Distribution of obstetric, reproductive & metabolic variables between groups

Variables	Group		p-value
	Case (n = 18)	Control (n = 54)	
Obstetric & reproductive characteristics			
Gestational age# (weeks)	30.1 ± 3.7	30.8 ± 1.9	0.466
Parity#	0.7 ± 0.2	0.5 ± 0.1	0.574
Gravida#	1.6 ± 0.7	1.5 ± 0.5	0.514
Age at menarche# (years)	12.9 ± 0.4	12.8 ± 0.3	0.294
Age at first pregnancy# (years)	26.3 ± 3.6	25.5 ± 1.9	0.346
Metabolic variables			
BMI* kg/m2			
≥ 25	16(89.9)	50(92.6)	0.470
< 25	2(11.1)	4(7.4)	
Obesity before pregnancy**	12(66.7)	21(38.9)	0.014
Type II DM in first-degree relatives**	12(66.7)	19(35.2)	0.019

Data were analyzed using **Unpaired t-Test** and were presented as **mean ± SD**.

*Data were analyzed using **Fisher's Exact Test**; figures in the parentheses denote corresponding %.

Data were analyzed using **Chi-squared (χ^2) **Test**

Table III: Comparison of current obstetric history between case and control groups

Current obstetric history	Group		p-value
	Case (n = 18)	Control (n = 54)	
UTI*	2(11.1)	3(5.6)	0.367
Polyhydramnios*	3(16.7)	1(1.9)	0.046

*Data were analyzed using **Fisher's Exact Test**; figures in the parentheses denote corresponding %.

Table IV: Comparison of investigations between case and control groups

Biochemical variables	Group		p-value
	Case (n = 18)	Control (n = 54)	
Level of haemoglobin# (mg/dl)	9.6 ± 2.2	11.0 ± 1.2	0.021
Serum calcium# (mmol/L)	10.2 ± 1.2	10.5 ± 1.3	0.443
Serum creatinine# (mg/dl)	0.9 ± 0.1	0.8 ± 0.1	0.736
Serum Vitamin D# [25(0H)D] (ng/ml)	19.8 ± 9.0	24.8 ± 8.7	0.040

#Data were analyzed using **Unpaired t-Test** and were presented as **mean ± SD**.

Table V: Association between vitamin D level and GDM

Vitamin D# (ng/mL)	Group		Odds Ratio (95% CI of OR)	p-value
	Case (n = 18)	Control (n = 54)		
< 30	15(83.3)	31(57.4)	3.7(1.1 – 14.3)	0.047
≥ 30	3(16.7)	23(42.6)		

Data were analyzed using **Chi-squared** (χ^2) **Test**; figures in the parentheses denote corresponding %.

DISCUSSION:

In the present study several factors (occupation, pre-pregnancy obesity, history of type-II diabetes in the first-degree relatives, polyhydramnios and level of haemoglobin) including vitamin-D insufficiency /deficiency were found to be associated with GDM. The study demonstrated that over 80% of GDM patients had insufficient or deficient serum vitamin-D level (< 30 ng/mL) as compared to 57.4% of the control group. The risk of having GDM in pregnant women with insufficient/deficient serum vitamin-D was estimated to be nearly 4-fold (95% CI=1.1-14.3) higher (p=0.047) than that in the pregnant women with normal serum vitamin D level.

Ten observational studies have been recently conducted to study the association of vitamin-D with GDM. Arnold et al[20] conducted a nested case-control study in the United States among pregnant women and reported an inverse relationship between vitamin-D status in early pregnancy and risk of gestational diabetes. A 5 ng/ml increase in vitamin D3 levels was associated with a reduction in GDM risk by 14%. Similar effects were reported by Lacroix and colleagues[21] in a prospective observational study in Canada Lithy et al[22] in a cross- sectional observational study in Arab women. Burris and associates[23] in their study found 25(OH)D levels < 25 nmol/L in 4.0% women with normal glucose tolerance, 5.7% women with impaired glucose tolerance and 13.2% women with GDM. Analyses, adjusted for sociodemographics, season, maternal BMI, gestational weight gain and dietary factors, suggested that women with 25(OH)D levels < 25 vs. ≥ 25 nmol/L may have higher odds of GDM [2.2 (95% CI = 0.8, 5.5)]. Glucose levels after the glucose challenge test were inversely associated with 25(OH)D levels (p < 0.01).[23] These study findings are fairly comparable with findings of the present study. On the contrary, several studies failed to establish the role of vitamin-D in the prevention of GDM.[24] The lack of consistent findings calls for large-scale prospective studies to evaluate the role of vitamin-D in GDM.

To test the effectiveness of vitamin-D supplementation in the prevention or reduction of risk of GDM, many randomized controlled clinical trials have been conducted. Six RCTs have been conducted in this regard from January 2014 onwards. Asemi et al[25] performed a randomized placebo-controlled trial in Iranian pregnant women and found positive impact of vitamin-D and calcium supplementation on the metabolic profiles of GDM patients with decrease in free plasma glucose, serum insulin, HOMA–IR, LDL cholesterol and total cholesterol. Few other studies, on the contrary, reported no beneficial effects of vitamin-D supplementation on GDM outcome.[26,27] To compare and contrast the efficacy of different dosing patterns of vitamin-D on GDM, recently two clinical trials were conducted; Yap and colleagues[28] conducted a study in women with 25(OH)D levels <32 ng/ml before 20 weeks and randomized them to receive oral vitamin D3 at 5,000 IU daily or 400 IU daily from 14 weeks until delivery, and found no difference in the outcomes. Mojibain et al[29] randomized pregnant women with 25(OH)D < 30 ng/ml to receive 400 IU daily or 50,000 IU every 2 weeks until delivery, and found improved outcomes with high dose vitamin-D supplementation. The difference in the outcomes could be attributed to different dosages of vitamin-D used for intervention, as well as the varying dosing schedules in the two studies. Two recently published meta-analyses of RCTs[30,31] however, showed same incidence of GDM with and without vitamin-D supplementation.

Pregnancy is a state in which the mother undergoes physiological insulin resistance, which helps the fetus absorb more nutrients. Our findings for increased risk of gestational diabetes with vitamin-D deficiency are biologically plausible. Firstly, 1,25(OH)2D3, the active form of vitamin-D, regulates circulating glucose levels by binding to vitamin-D receptor of pancreatic β-cell and modulating insulin secretion.[32,33] Secondly, 1,25(OH)2D3 promotes insulin sensitivity by stimulating the expression of insulin receptors and enhancing insulin responsiveness for glucose transport.[34] Lastly, 1,25(OH)2D3 regulates the balance between the extracellular and intracellular calcium pools in β-cell, which is essential for insulin-mediated intracellular processes in insulin-responsive tissues.[35]

Vitamin-D supplementation for GDM seems to ameliorate different metabolic markers including blood glucose levels, insulin resistance and inflammatory biomarkers.[36,37] Supplementation with 50,000 International Units (IU) twice monthly has been shown to improve insulin resistance significantly,[37] while 5000 IU daily has failed to improve glucose levels in another trial.[38]

Emerging evidence suggests that Vitamin-D administration can improve insulin sensitivity and glucose tolerance, but whether vitamin-D supplementation can prevent GDM is unknown. Observational studies provide conflicting evidence as to whether low serum 25-hydroxyvitmain-D (25(OH)D) levels are associated with GDM. Two recent systematic reviews concluded that vitamin-D deficiency is associated with a higher risk of GDM. However, these reviews are limited by the observational and diverse nature of the included studies. Of greatest concern is the inability to understand how important confounding variables such as age, race/ethnicity and adiposity might affect the association.[39] On the other hand, the meta-analysis made in 2012 indicated a significant inverse relation of vitamin-D and the prevalence of GDM from 07 observational studies.[40]

Summarization of the findings of the present study and the observational studies conducted in different parts of the world suggest an association between vitamin-D blood levels and risk of GDM, despite heterogeneity of results across studies. However, the evidence from clinical trials is inadequate to draft any definitive conclusion regarding its supplementation.[41] Like any other scientific studies, the present study has several limitations, which deserve mention before concluding the findings of the present study.

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Limitations:

1. Although several factors other than vitamin D were found to be associated with GDM, the small sample size limits the conduction of regression analysis to find the independent predictors of GDM.

2. The study was contemplated with a case-control design. In terms of strength of the observational studies, cohort design is better, although it was not designed so because of time constraint and apprehension of loss to follow up.

CONCLUSION:

From the findings of the study, it appears that GDM patients are more likely to have insufficiency or deficiency of serum vitamin-D level than the pregnant women without GDM with risk of having the condition in the former group was much greater than that in the latter group. Although, adjustment for other factors (using regression analysis) to find the independent predictors of GDM was not possible due to small sample size than required for the regression analysis, vitamin-D seems to play role in the causation pathway of GDM.

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