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Serum Vitamine D3 Level in Women with Gestational Diabetes Mellitus

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Authors' contributions

This work was carried out in collaboration among all authors. Author RME *designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors* AAEIS *and* HAM *managed the analyses of the study. Author* AEM *managed the literature searches. All authors read and approved the final manuscript.*

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ABSTRACT

Background: Vitamin D3 is synthesized in skin and sequentially metabolized in liver and kidney in humans. It is well known for its function in maintaining calcium and phosphorus homeostasis and promoting bone mineralization. The primary objective of this study was to evaluate vitamin D3 level in pregnant women who were suffering from gestational diabetes mellitus and comparing it with the control groups.
Materials and Methods: This case control study was conducted on 100 pregnant women who were attending the inpatient and outpatient clinics of Obstetrics department, Tanta University Hospital, who were divided into two equal groups.Group A (control group): Fifty apparently healthy pregnant women at 24th-28th weeks of gestation .Group B (study group): Fifty pregnant women had gestational diabetes.
Results: There is significant increase between the two studied groups according to HbA1c, also there is decrease between the two groups as regards VIT D. Mean HbA1c % was statistically significant higher in the study group versus control group. There was statistical significant difference noted between mean serum level of vitamin D among the two studied groups. A statistically significant negative correlation was observed between serum 25 OH vitamin D and

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HbA1c among our cases (r=- 0.745) (p ≤ 0.001). Mean serum vitamin D was significantly lower in cases with complications than those with normal outcome.
Conclusion: Vitamin D deficiency may have a positive relationship with gestational diabetes mellitus.

Keywords: Serum Vitamine D3; gestational; diabetes mellitus.

1. INTRODUCTION

Vitamin D3 is synthesized in skin and sequentially metabolized in liver and kidney in humans. It is well known for its function in maintaining calcium and phosphorus homeostasis and promoting bone mineralization.

However, in the last ten years studies found that vitamin D3 deficiency may cause the development of type II diabetes mellitus (T2DM), the main pathophysiology is unclear [1].

The prevalence of GDM is expanding, reached almost 15% - 20% [2]. Unmanaged gestational diabetes elevates the risk of developing T2DM after pregnancy and predisposes the offspring to obesity and T2DM later on [3].

Recent studies found that decreased vitamin D3 has a role in the pathogenesis of insulin resistance and insulin release disturbances.

The coexistence of insulin resistance and decreased vitamin D3 has generated several hypotheses as worsening of insulin resistance [4].

Great interest persists in vitamin D3 and its possible consequences on pregnancy outcome as gestational diabetes mellitus (GDM) [5].

Vitamin D3 deficiency in pregnancy reach up to 40% - 100% [6-8]. It is related to altered glucose homeostasis during pregnancy [6-10]. Although active type of vit D3 [1.25 (OH) D] was accounted to diminish glucose and increase insulin levels [11], other reports documented no obvious contrasts in vitamin D3 status between females with GDM and NGT [12,13].

Recent studies suggest that vitamin D3 supplementation may increase insulin sensitivity and glucose tolerance [14]. In spite of the fact that, vitamin D3 insufficiency is associated with a higher risk of GDM, conflicting evidence is provided as to whether low serum 25-hydroxyvitmainD (25 (OH) D) levels are associated with GDM. The primary objective of this study was to evaluate vitamin D3 level in pregnant women who were suffering from gestational diabetes mellitus and comparing it with the control groups.

2. SUBJECTS AND METHODS

This case control study was conducted on 100 pregnant women who were attending the inpatient and outpatient clinics of Obstetrics department, Tanta University Hospital, who were divided into two equal groups. Group A (control group): Fifty apparently healthy pregnant women at 24th-28th weeks of gestation. Group B (study group): Fifty pregnant women had gestational diabetes mellitus.

Inclusion criteria: From 18 to 40 years. BMI from 25 to 30 kg/m^2. Singleton pregnancy. Gestational age between (24th-28th) week.

Exclusion criteria: Cigarette smoking. Previous history of obstetric complications. Abnormal liver function. Impaired kidney function. Thyroid & parathyroid dysfunction. Patients who received medications known to affect calcium and vit D metabolism. Patients refused to participate in the study. All pregnant women were subjected to the following:

- Full history taking including detailed personal history including (name, age, weight, height, occupation, residency and special habits including smoking).
- History of present pregnancy including detailed history of symptoms of diabetes, abdominal cramps, vaginal discharge.
- Obstetric history: detailed gravidity and parity, consanguinity, and history of maternal and neonatal complications (history of previous abortions, sudden IUFD, preterm delivery, delivery of a macrosomic fetus), contraceptive history,
- Menstrual history: 1st day of LMP and calculation of gestational age using Naegele's rule provided that she had regular cycles for the last six months before she got pregnant and was sure of her date.

- Past history of previous GDM, medical disorders, drug allergy and blood transfusion.
- Family history of any inherited conditions.
- Thorough general and abdominal examination, calculation of body mass index (BMI).
- Ultrasonographic examination to determine gestational age, viability of the fetus and exclude major fetal anomalies.
- Routine investigations including CBC, AST, ALT, Serum creatinin, Blood urea, Random blood sugar, HbA1c and urine analysis.
- Serum vit D3 assay by ELISA technique.

Serum 25 hydroxy vitamin D using ELISA techniqu **:**The kit uses double-antibody sandwich enzyme linked immunosorbent assay (ELISA). It relies on competitive binding to assay the level of Vit D3 in samples (VD3). Vitamin D3 was added to monoclonal antibody enzyme well which is pre-coated with human vitamin D3 monoclonal antibody, incubation; then, vitamin D3 antibodies labeled with biotin, and combined with Streptavidin-HRP are added to form immune complex; then carried out incubation and washing again to remove the uncombined enzyme. The reagents were kept at room temperature (22-28°C) for at least half an hour. After we ended the test, keep promptly reagents at 28°C. We avoided prolonged exposure to room temperature. Unused coated microwell strips ought to be delivered safely in the foil pocket containing desiccant and put them at 2-8°C. To prevent either microbial or chemical contamination, unused reagents ought to be never returned to its first vials. As it is essential to do the determination in duplicate to get more accurate results. We prepared two wells for every point of the calibration curve (C0-C5), two for each sample, two for each.

2.1 Statistical Analysis

The sample size was calculated using Epi-Info software statistical package created by World Health organization and center for Disease Control and Prevention, Atlanta, Georgia, USA version 2002. The criteria used for sample size calculation (n>33) were 95% confidence limit, 80% power of the study.

Analysis of data were performed by SPSS v25 (SPSS Inc., Chicago, IL, USA). Quantitative parametric variables (e.g. age) were presented as mean and standard deviation (SD). Pearson's rho coefficient of correlation (r) was used to calculate the degree of correlation between 2 variables. P value < 0.05 was considered significant.

3. RESULTS

As regards demographic data there is no significant difference between the two studied groups as regards age, BMI, gestational age and gravidity (Table 1). There is significant increase between the two studied groups according to HbA1c, also there is decrease between the two groups as regards VIT D. Group A: HbA1c ranged from 4.2 to 5.9% with a mean of 4.86± 0.41. According to Statistical analysis of HbA1c and vitamin D in the studied groups there is Mean HbA1c % was statistically significant higher in the study group versus control group as shown in Table 2. According to Mean HbA1c % was statistically significant higher in the study group versus control group as in Fig. 1.

According to serum level of vitamin D There was statistical significant difference noted between mean serum level of vitamin D among the two studied groups Fig. 2.

Table 1. Demographic data in the studied groups

		Range			Mean	±	S. D	t. test	p. value
Age	**Control**	18	–	40	26.94	±	6.71	1.111	0.269
	Study	18	–	40	28.24	±	4.84		
BMI	**Control**	25	–	29.9	26.77	±	1.16	1.319	0.190
	Study	25	–	30	27.15	±	1.73		
GA	**Control**	24	–	27	25.18	±	1.00	1.641	0.104
	Study	24	–	28	25.58	±	1.40		
Gravidity	**Control**	1	–	4	1.98	±	1.08	1.451	0.150
	Study	1	–	7	2.42	±	1.85		

Table 2. Statistical analysis of HbA1c and vitamin D in the studied groups

		Range			Mean	±	S. D	t. test	p. value
HbA1c	**Control**	4.2	–	5.9	4.86	±	0.41	16.556	0.001*
	Study	5.5	–	7.3	6.66	±	0.65		
VIT. D	**Control**	15	–	20.7	17.60	±	1.80	12.781	0.001*
	Study	5.7	–	19.3	11.40	±	2.92		

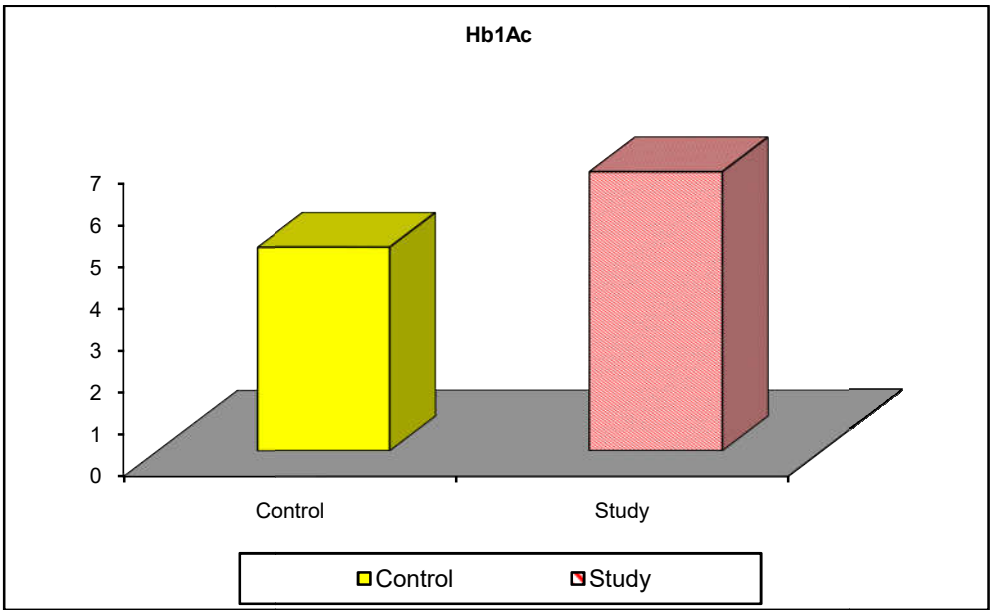

Fig. 1. Statistical analysis between the two studied groups according to HbA1c %

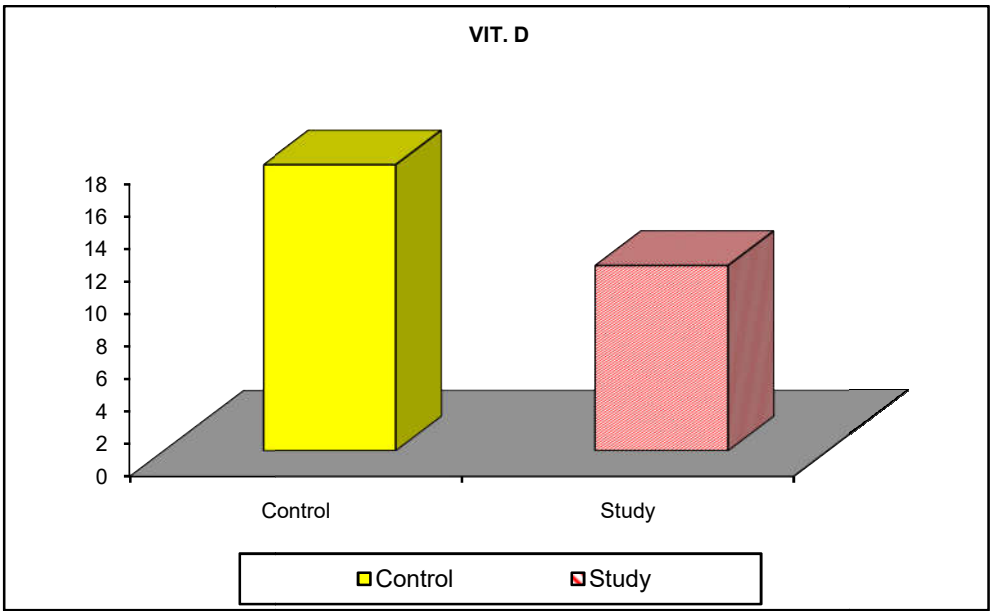

Fig. 2. Statistical analysis between the two studied groups according to 25 OH vitamin D

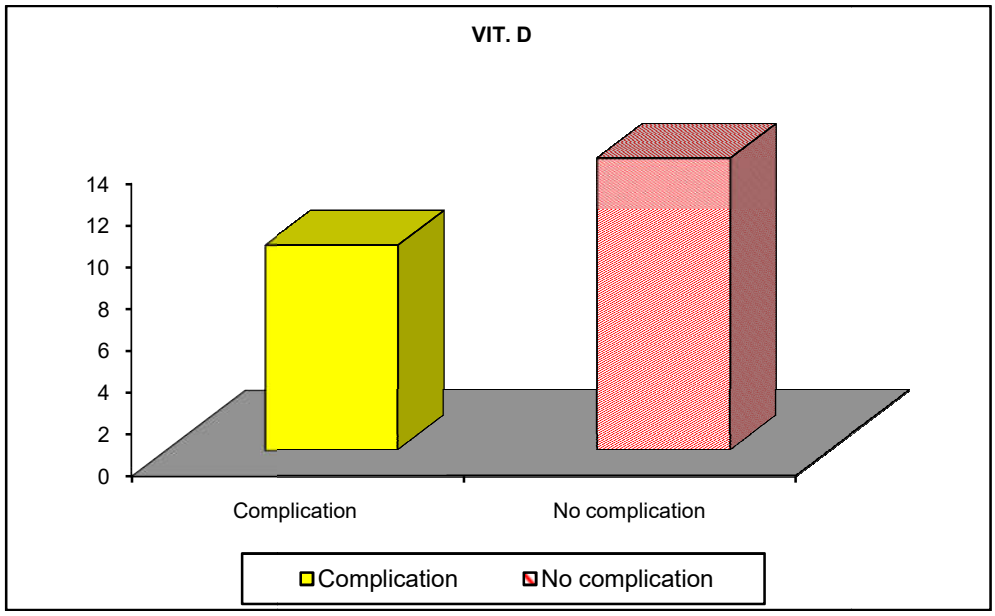

Fig. 3. Correlation between Vitamin D and occurrence of complications among study group

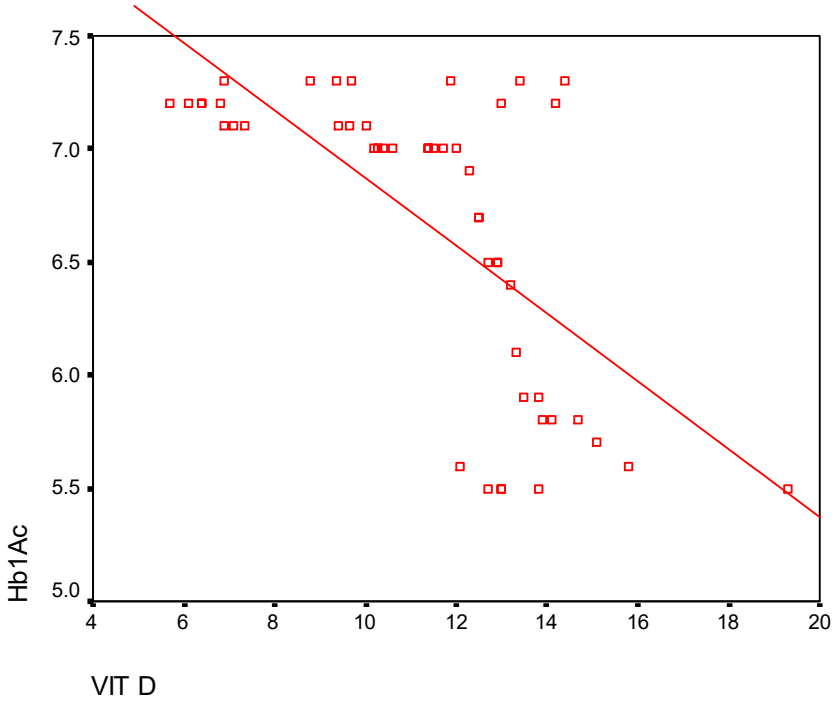

Fig. 4. Correlation between 25 OH vitamin D and HbA1c

According to Serum vitamin D ranged from 5.7 to 13 with a mean of 9.82 ±2.36 in cases with complications while in cases without complications, it was found that vitamin D ranged from 11.4 to 19.3 with a mean 13.98 ± 1.60. Mean serum vitamin D was significantly lower in cases with complications than those with normal outcome (Fig. 3). According to Correlation between 25 OH vitamin D and HbA1c (%) in study group (gestational DM) there is A statistically significant negative correlation was observed between serum 25 OH vitamin D and HbA1c among our cases (r=- 0.745) ($p \leq 0.001$) (Fig. 4).

4. DISCUSSION

Gestational diabetes mellitus (GDM) is considered as an early marker of glucose intolerance, associated with both insulin resistance and impaired insulin secretion also elevated risk of maternal and fetal complications during pregnancy [15].

The non-classical functions of vitamin D are gaining attention due to closer associations between vitamin D deficiency and T2DM, heart disease, autoimmune diseases and certain types of cancers [16]. The aim of this study was to evaluate serum vitamin D3 level in pregnant women who were suffering from gestational diabetes and comparing it with the control groups. This case control study was conducted on 100 singleton pregnant female at gestational age between (24th-28th) weeks, who were divided into two equal groups, group (A) which included 50 apparently healthy pregnant women as control group and group (B) which included 50 pregnant women suffering from gestational diabetes.

Also, Mean HbA1c % was statistically significant higher in cases versus control group and serum vitamin D3 level was lower in case group as regards the control group. Moreover, we found that Mean serum vitamin D was significantly lower in cases who developed complications than those with normal outcome**.**A negative correlation between serum 25 OH vitamin D and HbA1c was detected (r=- 0.745) ($p \leq 0.001$). These complications were as follow; 8% of them had preterm labour, 12% developed polyhydramnios, also 12% delivered a macrosomic baby, 4% had fetus with congenital anomalies and 1% of them was IUFD.

In addition, Dwarkanath et al., in 2019, aimed to determine the association between maternal vitamin D concentrations in early pregnancy and the risk of gestational diabetes mellitus (GDM), included 392 cases with GDM, the mean age was slightly younger than our documented age of GDM cases and BMI was less than the documented BMI of GDM cases [17]. In agreement to this study, El-Sagheer et al., in 2016, a study included 40 cases of GDM, the mean age of GDM cases was nearly similar to our results but BMI was slightly higher than our results [18]. The increase in the prevalence of GDM in this study can be attributed to increased BMI, as high maternal weight is associated with a substantially higher risk of GDM. This can be attributed to their dietary habits [19].

There is a complex relationship between vitamin D and obesity. While this study and other different studies reported an inverse relation between vitamin D levels and BMI to the extent of considering it as a strong predictor of vitamin D. Few studies found no significant association between vitamin D and BMI [20]. This was declared by Torloni et al., meta-analysis in that risk of GDM is positively associated with pre-pregnancy BMI. We found an inverse association between serum 25OHD and BMI in patients with GDM [21]. Similar results were declared by Farrant HJ et al., in 2009, when a study was conducted on 559 pregnant females in India to study the effect of vitamin D deficiency on the glycemic parameters and they concluded that the lower serum level of vitamin D, the higher in HbA1c concentrations. However, they didn't correlate with the occurrence of gestational diabetes [22].

Moreover, Clifton B et al., conducted another study in Australia 2008 on 307 pregnant female based on the hypothesis that vitamin D affects peripheral insulin resistance at the level of muscle, liver and adipose tissue as previously mentioned, when they measured serum 25 OH vitamin D in mid gestation period (period of maximum glucose intolerance is expected), they found that there was significant negative correlation between maternal serum vitamin D and HbA1c [23]. These results were similar to the results declared by our study.

Inconsistent with our study, Baker et al., conducted another study in USA in 2015 on more than 4000 pregnant women where it was concluded that vitamin D deficiency was not associated with the occurrence of gestational diabetes [24]. This was declared due to different confounding factors affecting blood glucose levels as age, ethnicity and body mass index.

A recent study published in April 2018 conducted in Norway on more than 700 multiethnic pregnant female concluded that vitamin D deficiency can't considered as a risk factor for GDM or any glucose intolerance despite its high prevalence after adjustment for confounding factors, in particular BMI, ethnicity and smoking [25].

Also, Cho et al., conducted an interesting study in 2013 to illustrate the cause of vitamin D deficiency in pregnancy and found that 85% of his pregnant females were vitamin D deficient and this was explained by the fact that 25(OH)D is hydroxylated by CYTP27B1 to the bioactive

1,25(OH)D form, and CYP24A1 catabolizes both 25(OH)D and 1,25(OH) D to the inactive metabolites, respectively, their data indicated that the elevated activity of CYP24A1 in the placenta may play a role in the development of vitamin D deficiency in pregnancy [26].

The high frequency of maternal hypovitaminosis D is consistent with findings in other studies [27]. South Asians, both in their country of origin and after migration to Europe or the USA, have lower serum 25(OH)D concentrations as compared to white Caucasians (Goswami et al. 2011; Hamson et al. 2003) due to skin pigmentation, covered up-clothing (especially common in women) and low dietary vitamin D intake [28].

In agreement with our study, Zhang MX conducted a meta-analysis on more than 9200 Chinese female and it showed that women with vitamin D deficiency experienced a significantly increased risk for developing GDM [29].

Our results disagree with another Indian study conducted in 2015 on more than 70 pregnant female concluded that despite the relationship observed between vitamin D deficiency and occurrence of GDM, it can't be justified to screen routinely for vitamin D deficiency in pregnancy and supplementation didn't improve any glycemic parameters during this period [30]. The inconsistency of findings may be attributed to small sample size, lack of physical activity and less sun exposure. In harmony with our study, Maghbooli et al., studied the relation between vitamin D and gestational diabetes in cross-sectional study conducted on more than 700 pregnant lady in 24-28 week gestation and reported lower levels of maternal serum 25 OH vitamin D compared to euglycemic controls [30].

Studying the relation between vitamin D and glucose intolerance during pregnancy, an English study was conducted in 2011 on around 250 pregnant female half of them were diagnosed with GDM while the other half were with normal glucose tolerance and Makgoba et al., declared that there was no significant difference between the two groups as regards mean serum vitamin D level and hence, its deficiency was not associated with subsequent development of GDM [31].

In addition, in agreement with our study, Zhang C et al., studied the relationship between maternal serum 25 OH vitamin D and the risks of development of GDM in 2008 on 900 pregnant lady and the team declared that vitamin D deficiency in early pregnancy is an established risk factor for the occurrence of gestational diabetes even after controlling other risk factors including maternal age, family history of type 2 diabetes, race, ethnicity and BMI [32].

Similar results were concluded by Mousa and his team who conducted a study in 2017 on more than 100 pregnant female and suggested that lower maternal vitamin D level can be a risk factor for subsequent development of GDM [33]. In agreement with our study, in 2013, Wei el al., studied the relation between vitamin D deficiency and different pregnancy outcomes, concluded that lower maternal vitamin D levels in pregnancy may be associated with an increased risk of preeclampsia, GDM and preterm birth [34].

Moreover, Rodrigues K et al. in 2019 study documented that the most important outcomes documented among pregnant women were frequency of preeclampsia, hospitalization and cesarean delivery [35].

5. CONCLUSION

Vitamin D deficiency may have a positive relationship with gestational diabetes mellitus.

CONSENT AND ETHICAL APPROVAL

As per international standard or university standard guideline participant consent and ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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