Original Research Paper

Volume - 10 | Issue - 9 | September - 2020 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Obstetrics and Gynecology

EARLY PREGNANCY MATERNAL VITAMIN D DEFICIENCY AND RISK OF GESTATIONAL DIABETES MELLITUS IN LIBYAN PREGNANT WOMEN

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ABSTRACT **Background** Vitamin D deficiency is a common occurrence, which affects maternal health during pregnancy. Evidence is accumulating for a role of a low level of vitamin D during the early pregnancy as a risk factor for the development of gestational diabetes mellitus (GDM). Our objectives are to describe the patterns of vitamin D levels in early pregnancy in mothers attending main antenatal services in Ajdabiya city, during the first quarter of the year 2017 and to examine the relationship between vitamin D levels and glucose metabolic derangements in pregnant women among the above-described population. **Methods** A cohort study was conducted in healthy pregnant women attending routine antenatal care in Ajdabiya city in 2017. All mothers were screened for serum 25 (OH) D level and glycated hemoglobin (HbA1c) and anthropometric by the time of booking during the first trimester (gestational age "GA" 7-15th week of pregnancy). All women with low 25 (OH) D level were screened for GDM with non-fasting post-challenge blood glucose and confirmed by OGTT according to the American Diabetes Association (ADA) classification of GDM criteria in their 2nd trimester. Data was analyzed by using SPSS, IBM 20.0. **Results** All mothers in the study population were Libyan, their ages ranged from 18-43 years. Parity ranged from nulliparous to P10. More than 60% of mothers were housewives while others were either working or students and considered as having an outdoor lifestyle. In the first trimester, we detected 412 mothers had serum vitamin D3 below normal, the majority of cases had deficient serum 25 (OH) D (391, 94.9%) while 21 (5.1%) women had an insufficient serum 25 (OH) D. Serum 25 (OH) D ranged from 5.9-30.0 ng/ml. In the 2nd trimester, we confirmed 43 (10.99%) pregnant women with GDM out of 391 women with deficient serum 25 (OH) D level. 25 (OH) D deficiency was statistically significant ($p = 0.035$, OR = 0.963, 95% CI = 0.881-0.996) and associated with all GDM cases. **Conclusion** We conclude that 25 (OH) D deficiency was significantly correlated with GDM, as a consequence, the deficiency of 25 (OH) D could act as a risk factor for GDM. This result implies the necessity of focusing on vitamin D3 supplementation for women of childbearing age.

KEYWORDS : Vitamin D deficiency, Pregnancy, Gestational diabetes mellitus

INTRODUCTION

Vitamin D has a crucial physiological role not only to maintain calcium and phosphate levels for bone formation [1], but also has a range of non-calcitropic functions, such as stimulating insulin production and participating in the pathological processes of type 2 diabetes mellitus (T2DM) [2, 3]. In humans, a vast majority of vitamin D is synthesized through photochemical conversion of 7-dehydrocholesterol to pre-vitamin D3 in the skin, and the latter is sequentially metabolized in the liver and kidneys [4].

Gestational diabetes mellitus (GDM) is defined as glucose intolerance with onset or detected during pregnancy [5], which has become a significant health issue. It has been reported that GDM affects 1%-14% of all pregnancies, and that its incidence has been steadily rising [6]. GDM not just increase the risk of adverse pregnancy outcomes, but also has lots of long-term health impact on both mothers and their offspring, including susceptibility to obesity, T2DM and metabolic syndrome in later life [7, 8]. Therefore, early intervention of the risk factors for GDM and early detection may be the key to improve the prognosis. Accumulating evidence has indicated that risk factors for GDM include advanced maternal age, pre-overweight and obesity, and family history of diabetes [9, 10].

Vitamin D deficiency has been defined and recently recommended by the Institute of Medicine as a circulating 25-hydroxy vitamin D (25 (OH) D) concentration below 50 nmol/l (20ng/ml).Vitamin D insufficiency defined as a 25 (OH) D of 21-30 ng/ml and sufficiency as a 25 (OH) D of > 30 ng/ml (11). The deficiency of 25 (OH) D has been considered as an important public health issue in developed and developing countries, and vitamin D deficiency during pregnancy is becoming interestingly common [12]. Research on vitamin D and GDM is motivated by more than a decade of observational studies that demonstrated a consistent and strong association between vitamin D deficiency and T2DM, a condition that has similar pathogenesis and risk factors to GDM [13].

The relationships between 25 (OH) D deficiency and the occurrence of insulin resistance (IR), and GDM are not entirely clear. However, several reports have been published drawing attention to the association between a low level of 25 (OH) D and increased GDM risk [14, 15]. Our study aimed to evaluate the effects of maternal vitamin D3 deficiency in the incidence of GDM in pregnant Libyan women in Ajdabiya city.

MATERIAL AND METHODS

Study population

Study participants were identified among women attending public antenatal service in Ajdabiya city during the year 2017. All mothers at early booking before the 16th week were screened for vitamin D3 concentration and glycated hemoglobin (HbA1c%) assessed. Excluding women with a history of GDM, and women diagnosed with chronic illness (diabetes mellitus, hypertension, cardiac disease, or thyroid disease). A complete sample of 412 cases had serum 25 (OH) D levels below normal were only selected for the present study. All of these women were screened between weeks 24-28th using a 50g 1-hour oral glucose challenge test. Women who failed this screening [glucose ≥ 7.8mmol/L (140 mg/dl)] under-went a 75g oral glucose tolerance test 1-2 weeks after the first failed screening test. Gestational diabetes: any reading on 75gm GTT of any of the following; FBG > 95 mg/dl OR one-hour BG > 180mg/dl, OR two hours BG > 153 mg/dl was defined according to recommendations of the American Diabetes Association [16]. Only pregnant Libyan women aged 18-43 were included and non-Libyan were excluded to have a relatively homogenous cohort. Participants complete an interview using a structured questionnaire at booking. A questionnaire was used to gather medical history data either in current or previous pregnancy for the obstetric conditions (Tables 2 and 3). BMI for the mother was calculated as weight in kilogram divided by height in meters squared (kg/m^2). The gestational age (in weeks) was calculated from the last date of the menstrual cycle and confirmed through ultrasonographic measurements. The study was approved by the Ethics. A formal letter from department of Obstetrics and Gynecology at University of Benghazi was send to every hospital requesting the director of hospital as applicable to allow the researcher conduct the study. The following points were considered during the conduction of the study; informed consent, right to no participation, right to withdraw from the study as well as ensuring confidentiality and privacy of the data and acknowledging Co-investigators and data collectors in the study considered. No intervention nor change in standard care for the sake of research purpose was intended but more frequent visits ordered in addition to routine practice.

Sample analyses

During their first visit, the blood samples were collected. All the samples were processed at laboratory which is a participant in the Vitamin D External Quality Assessment Scheme (DEQAS) and meets all the quality assurance standards. The samples were analyzed for 25 (OH) D levels and HbA1c. Serum 25 (OH) D was determined with a Roche Elecsys modular analytics (Cobas E411) using an electrochemiluminescence immunoassay (Roche Diagnostics, Germany) and commercially available IDS kits (IDS Ltd., UK), according to manufacturer's instructions

Serum glucose and HbA1c% were measured using a chemical analyzer (Kone lab, Finland) Between the gestational age of 24-28th weeks of pregnancy, all mothers with non-fasting post-challenge blood glucose (50 grams of glucose equivalent) were selected. Mothers with a one-hour blood glucose of 140 mg/dl or above after challenge were subjected to oral 75 grams oral glucose tolerance test (GTT). Fasting BG, one-hour BG, and two hours of BG were measured.

Data analysis

Data were analyzed by using the IBM SPSS v25.0. The analysis of data included descriptive statistics of study population characteristics; logistic regression was used for measurement of odds ratio confidence intervals for outcomes for the set of assigned events (GDM at challenge test and GTT). The receiver operating characteristic curve (ROC) was used to evaluate the best predicting serum vitamin D for GDM. The statistical analysis was conducted at the 95% confidence level and p-value < 0.05 was considered statistically significant.

RESULTS

Demographic characteristics

Gestational age at booking was ranged from 4 to 30 weeks. Among mothers in the study population, 64.2% were booked by week 12 and 86.0% by week 16. All the mothers in the study population were Libyan. Age ranged from 18 to 43 years. Parity ranged from nulliparous to P10. More than 60% of mothers in the study population were housewives. Others were either working or students and considered as having an outdoor lifestyle.

Health status determinants and past medical history

Body mass index of the study population ranged between 17.36 to 46.29 kg/m2 with a mean of 27.7 kg/m2, a median of 27.1 kg/m2, and SD of 4.9 kg/m2. The rate of obesity was 27.7%. HbA1c ranged between 3.0% to 7.5% with a mean of 4.56, median of 4.5, and SD of 0.6.

Prevalence of vitamin D deficiency

All the mothers in the study population had serum vitamin D3 levels below normal < 30 ng/ml. The majority of cases had deficient serum 25 (OH) D. Serum 25 (OH) D ranged from 5.9 to 30.0 ng/ml. Out of 412 subjects of our study, 391 (94.9 %) had deficient levels (5.9 - < 10 ng/ml) of vitamin D while the rest 21 (5.1%) was vitamin D insufficient (10 - < 30 ng/ml).

Prevalence of GDM

Out of 412 subjects, 43 were diagnosed as positive for GDM in the second trimester.

Analysis of the association between vitamin D deficiency and GDM

All women who developed GDM were 25 (OH) D deficient (10.99%) while no cases were found in women with serum 25 (OH) D insufficient 0.0% (Table 1). Previous medical history finding showed highly significant between vitamin D deficiency and confirmed GDM, in contrast, the other medical problems showed non-significant relation (Table 2). Analysis of vitamin D status vs GDM incidence, as given in methods, indicated a significantly higher risk for GDM among women who were deficient for vitamin D (OR: 0.963, CI: 0.881-0.996, $p = 0.035$) (Table 3). The risk of development of GDM associated with vitamin D deficiency was analyzed after selecting only the cases with serum 25 (OH) D deficiency to adjust the data for this variable, and to exclude the effect of other risk factors. The risk of GDM among women with deficient vitamin D was increased significantly in comparison with the other risk factors. As shown in Table 3, Serum vitamin D3, BMI, Outdoor lifestyle and PPH were significantly associated with the increased risk of GDM using the additive model (adjusted OR = 0.963, 95% CI = 0.881-0.996 for vitamin D3; adjusted OR = 1.107, 95% CI = 1.028-1.193 for BMI; adjusted OR = 0.250, 95% CI = 0.089-0.701 for Outdoor lifestyle; adjusted OR = 5.188, 95% CI = 1.732-15.535 for PPH*), but not others (maternal age, physical activity, the mother's own history of risk factors of GDM, parity).

Table 1: Serum Vit. D3 and Confirmed GDM

Serum Vit. D3	GDM	Non GDM	Total
Deficiency	43(10.99%)	348(89.0%)	391(94.9%)
Insufficiency	0 (0.0%)	21(100.0%)	21(100.0%)

Table 2: Results of monovariate analysis for medical history findings in relation to confirmed diagnosis.

Factor	P value	Comment
History of bronchial asthma	0.593*	Non-significant
History of allergic disorders	1.000*	Non-significant
History of endocrine disorders	0.377*	Non-significant
History of chronic skin disease	1.000*	Non-significant
Serum vitamin D3 level	<0.001†	Significant

* Fisher exact test, † Mann-Whitney U test, otherwise Pearson's 2 used

Table 3: Summary of multivariate analysis of predictors of diagnosis of GDM

Factor	WaldX^2	P	OR	95%CI	
Serum vitamin D3*	4.428	0.035	0.963	0.881	0.996
BMI*	7.222	0.007	1.107	1.028	1.193
Age >29	0.019	0.891	1.067	0.420	2.714
Null parity	0.137	0.711	1.342	0.282	6.382
Para 2plus	1.289	0.256	0.537	0.183	1.571
Outdoor lifestyle*	6.944	0.008	0.250	0.089	0.701
UTI	0.220	0.639	0.824	0.367	1.849
Polyhydramnios	2.700	0.100	2.320	0.850	6.330
Macrosomia	3.142	0.076	2.522	0.907	7.013
IUFD	2.352	0.125	4.243	0.669	26.903
PPH*	8.654	0.003	5.188	1.732	15.535
Constant	0.030	0.863	1.617		

* Independent predictor for GDM, PPH Postpartum Hemorrhage,GJ IUFD Intrauterine fetus death

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DISCUSSION

Vitamin D deficiency is a common issue all over the world. As a consequence, it is considered as a risk factor for many health problems. Recently, several studies reported the association between low serum vitamin D level and increased the risk of gestational diabetes [15,17,18,19]. In this study, the women participating with low serum 25 (OH) D concentration (deficiency and insufficiency) as a risk group of GDM. Interestingly, only 25 (OH) D deficient cases were associated with GDM while there was no correlation between 25 (OH) D insufficiency and GDM. To adjust any other risk factors of GDM, the previous maternal history of PPH, polyhydramnios, macrosomia, and IUFD are considered. Statistically, we find a significant association between serum vitamin D3, BMI, outdoor lifestyle, and PPH with the increased risk of GDM. In contrast, polyhydramnios, macrosomia, and IUFD show no significant correlation with GDM. Moreover, maternal age, physical activity, parity, show also no significant correlation with GDM. Our findings are similar to some previous studies that investigated vitamin D status and the GDM risk [20-23], and the finding from three separate meta-analyses of published studies [24-26], which reported 38-61% higher risk of GDM among women with vitamin D deficiency [18,19,26]. Recently, Pratibha Dwarkanath et al. have reported that lower vitamin D concentrations in early pregnancy may be associated with a higher risk of developing GDM [21]. Furthermore, a study conducted in Saudi Arabia has concluded the development of GDM among pregnant women having deficient vitamin D status [22]. However, Baker et al. reported that women with vitamin D deficiency, in early pregnancy, did not have a significantly higher risk of GDM compared with women who did not have vitamin D deficiency (OR 0.78, 95% CI 0.22- 2.78) [27]. Similarly, researchers did not observe associations of vitamin D deficiency with the risk of GDM in other studies conducted in Korea, North England, and Australia emphasizes the pivotal role of vitamin D in the perinatal period [20,24,27]. An increase in the risk of GDM, by 40-60% in women with vitamin D deficiency during the 2nd trimester of pregnancy has also been previously demonstrated [18,24,28]. A potentially beneficial role for vitamin D in reducing risk factors of GDM has also been shown by Roth et al. (OR: 0.61, 95% CI 0.34-0.83) in 2,643 pregnant women [29]. Cross-sectional studies at mid-pregnancy (24-28 weeks of gestation) conducted by Clifton-Bligh et al. demonstrate a poor vitamin D status as the risk factor for poor glucose control [30]. The current study shows a significant correlation between the vitamin D concentration and GTT value (Fasting glucose, at 1 and 2 hr.), (90.6% of cases diagnosed by FBG) which is not aligned with the finding of Maghbooli et al. confirming the association of poor vitamin D status and the risk of GDM through a negative correlation between serum vitamin D and fasting plasma glucose [31]. Many factors could confirm the relation between early pregnancy vitamin D status and GDM, for instance, body weight. Analysis of the National Health and Nutrition Examination Survey (NHANES) for the years 2003/2004 demonstrated that vitamin D deficiencies were highly prevalent in overweight and obese American subjects [32].

In this work, as we replace maternal body weight with a BMI in the adjusted analysis, we find that the association between vitamin D concentration and GDM persisted indicating that the women with low vitamin D levels at recruitment had 1.107 odds of having GDM. Also found a history of PPH is a significant independent predictor of diagnosis of GDM in the cases of vitamin D deficiency (p = 0.003, OR:5.188, CI 1.7-15.5). Besides, the outdoor lifestyle also shows a significant finding (p = 0.008, OR: 0.250 CI 0.089-0.701) as an independent predictor in the diagnosis of GDM in the 25 (OH) D deficient cases. Although the outdoor lifestyle shows a significant association with the GDM, all women suffer from 25 (OH) D deficiency.

In conclusion, our study provides data indicating that maternal vitamin D deficiency in early pregnancy (serum 25 (OH) D (5.9 - < 10ng/ml) is significantly associated with elevated risk for GDM in Libyan pregnant women in Ajdabiya city even after adjustment for conventional risk factors for gestational diabetes. Analyzing maternal vitamin D status during first pregnancy trimester as a surrogate of pre-pregnancy state was a strength of this study. We also found evidence that this association is mediated, at least in part, by mid-pregnancy BMI. The results imply the necessity of focusing on guideline implementation for vitamin D supplementation for women in childbearing age and pre-pregnancy care. Besides, we need to design a study to explain the significance of the history of PPH as an independent predictor of diagnosis of GDM in the cases of vitamin D deficiency.

ACKNOWLEDGMENTS

We would like to thank all the staff of antenatal services in Ajdabiya for their skillful technical assistance. Our thanks are extended to all participants for the patience and cooperation that helped us to get results of better quality.

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