Original paper

Low Maternal Serum Vitamin D Level at Early Pregnancy and Subsequent Risk of Gestational Diabetes in Women with History of Previous Gestational Diabetes

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Abstract

Background and Objective: GDM is a common condition during pregnancy which is associated with negative short-term and long-term outcomes both for mothers and offspring. Accumulating evidence links vitamin D deficiency with abnormal glucose metabolism. We performed this survey to investigate the predictive value of vitamin D deficiency as risk factor of GDM and, to evaluate the role of its replacement and incidence of development of GDM.

Methods : Cohort study design was conducted in AL -Qadisia City .It included 60 pregnant women with previous history of GDM, and low level of vitamin D at this pregnancy which measured using enzyme immunoassay with cut- off point less than 20 ng\ml . FBS measured by photometric method .Then we divided the study population into : group1 include 30 women that given vitamin D from 16 weeks gestation till delivery. group2 include also 30 women who did not received vitamin .

Result: In our study , low level of vitamin D (MS vitamin D was 11.65+3.23 ng/ml) and normal FBS at 14-16 weeks gestation, the mean age of women was(28.83 +6.03 years). After follow up: group 2 had significantly higher level of FBS than in group 1, 155.77+41.30 versus 110.10+36.86 (P<0.001), and the number and percentage of diabetic patients was also significantly greater in group2 than in group 1, n=22 ,73.33% versus n=6 ,20% (P<0.001).Conclusion: There is a statistically significant positive correlation between vitamin D deficiency and subsequent risk of GDM and in addition, vitamin D replacement significantly reduced the incidence of development of GDM in study population.

Keywords: Vitamin D, Gestational diabetes mellitus.

Introduction

Gestational diabetes mellitus (GDM) is a heterogeneous disorder characterized by intolerance to carbohydrates and hyperglycemia in varied degrees of intensity, with onset or first diagnosis during pregnancy [(1)]. GDM usually manifests in the latter half of pregnancy and is typically diagnosed by an oral glucose tolerance test. If GDM is diagnosed, women will usually be counseled and advised to adopt a healthy lifestyle for the duration of their pregnancy and where it is deemed appropriate, women may also be required to undergo pharmacologic or insulin therapy[(2)]. Gestational diabetes mellitus is one of the most common complication throughout the world that affects 1-14% [(3)] of all pregnancy with recurrent rate reaching 70 % [(1)]. Although GDM become normal

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soon-after delivery, it is resulting with immediate and long-term effects to both mother and child. A woman with GDM may lead to increased risk for preeclampsia [4] cesarean delivery, cardiovascular complications [5] neonatal macrosomia and hypoglycemia. In long term, GDM women are prone (20 – 50%) to develop type 2 diabetes mellitus in five years after delivery [6]. The early detection and adequate treatment reduce the potential complications to both mother and child [7]. Gestational diabetes is a condition that can be effectively controlled, thereby decreasing the associated risks and eventually leading to the delivery of healthy infants. Conversely, the consequences of risk factors in women may predispose them to developing GDM during pregnancy. Identifying women for possibility of GDM is depends on the presence of risk factors. Screening is usually carried out around 24 – 28 weeks of gestational age. But GDM can affect in any stage of gestation, so others advise universal and early screening [8]. The factors that can be influence the pregnant women to develop GDM in all trimesters include advanced maternal age, high BMI, positive family history of diabetes, previous history of GDM, multiparity and irregular menstrual history [9]. Excess weight gain in pregnancy, previous history of macrosomic baby, previous history of stillbirth, previous history of baby with congenital abnormality [10]. These several risk factors for gestational diabetes mellitus are well known and discussed in the literature. Other non-classical factors are still controversial: low birth weight, short stature, smoking, race or ethnicity, physical inactivity, gestational weight gain, socioeconomic factors and vitamin D deficiency [11]. Vitamin D is a fat-soluble vitamin which comes primarily from exposure to sunlight, and is found naturally only in a few foods, such as fish-liver oils, fatty fish, mushrooms, egg yolks, and liver [12]. There are two physiologically active forms of vitamin D collectively called calciferol: D2 and D3. Vitamin D2 (also called ergocalciferol) is synthesized by plants while vitamin D3 (also called cholecalciferol) is subcutaneously produced in humans from 7-dehydrocholecalciferol upon exposure to ultraviolet light B (UVB) radiation [13]. During pregnancy, vitamin D deficiency or insufficiency may develop . This deficiency or resistance is caused by different mechanisms including reduced of vitamin D access due to insufficient dietary vitamin D, fat malabsorptive disorders, and/or lack of photo isomerization, impaired hydroxylation of vitamin D by the liver and kidney to produce 25-OH vitamin and 1,25(OH)2-vitamin D respectively and end organ insensitivity to vitamin D metabolites [14]. Vitamin D supplementation during pregnancy has been suggested to safely improve pregnancy and infant outcomes [15]. Vitamin D deficiency is defined when the level of 25- Hydroxyvitamin D is less than 20 ng/ml (50 nmol/l) [16]. Over recent decades, numerous non-skeletal diseases associated with vitamin D deficiency have been reported including T2DM(type2 diabetes mellitus) [17], GDM and preeclampsia [18] and vitamin D functions are not limited to skeletal health benefits and may extend to preservation of insulin secretion and insulin sensitivity[19]. Vitamin D increases cellular glucose absorption either directly or by increasing insulin sensitivity. Vitamin D may directly or indirectly regulate cell function and secretion by binding 1,25 dihydroxy vitamin D to cell vitamin D receptors and controlling the balance between the extracellular and intracellular cell calcium pools[20]. Data about vitamin D as a risk factor for GDM is spare. Vitamin D deficiency was associated with a 2.66-fold increase in GDM risk and each 5 ng/ml decrease in 25-hydroxy D concentrations was related to a 1.29-fold increase in GDM risk(21).Other studies show vitamin D deficiency in pregnancy was related to the incidence of GDM and serum

25(OH)D was significantly lower in women with GDM than in those with normal glucose tolerance [22].

Materials and Methods

A cohort study was conducted at the outpatient, private and antenatal clinics of Maternity and Pediatrics teaching hospital from 2014 till 2015 in AL _Qadisia city in Iraq. All subjects gave written informed consent for participation in the study which was approved by the local ethics committee. We considered the ethical issues and described to recruited subjects for the study and obtained the consent to take blood samples. From their medical records, we got some information including maternal age, height, pre-pregnancy weight, reproductive and medical histories, and pre-pregnancy body mass index BMI (kg/m2) and entered them in analysis of the data as covariates. Maternal height and weight were measured by standard methods and body mass index (BMI) was calculated by dividing the weight in kilograms by the height in meters to the power of two. Pre-pregnancy weight was obtained by history. Exclusion criteria included normal level of vitamin D(>20ng/ml), pre-gestational diabetes, multiple pregnancy, chronic inflammatory diseases, hypertension, and preeclampsia or active infectious diseases. In our study settings, we include 60 pregnant women at 14–16 weeks of gestation (gestational age was based on the date of last menstrual period and confirmed by first trimester ultrasound scan). All these women with history of gestational diabetes in previous pregnancy and were tested for level of vitamin D in blood, fasting blood sugar, in addition to the standard antenatal tests. All assays were performed in a single private laboratory to increase reliability and minimize the variance between laboratories. Vitamin D level was tested by enzyme immunoassay kit [23]. Maternal fasting plasma samples were collected in10-mL tubes, plasma glucose concentrations were measured in certified clinical laboratories using photometric method [24]. After that we randomly divided the study population into two groups: group 1 include 30 women that given vitamin D in form of ergocalciferol 10 000 IU twice a week from 16 weeks gestation for 4-6 weeks then continue with maintenance dose 1000 IU daily till delivery[25].

group 2 include also 30 women that did not received vitamin D. Then all women in both groups were followed up in the antenatal clinic and underwent fasting blood sugar every two weeks starting from 24 weeks of gestation and till the time of delivery for diagnosis of GDM depending on WHO 2006 criteria [1].

Statistical analysis

Data were analyzed using SPSS version 16 and Microsoft Office Excel 2007. Numeric variables were expressed as mean and SD while nominal variables were expressed as number, percentage and median. Student t-test was used to assess mean difference between two groups while Chi-square test was used to study association between nominal variables. P-value of less than or equal to 0.05 was considered significant.

Results

The study was designed to include 60 pregnant women who were later sub-grouped into two group, 30 patients received vitamin D and the other group was represented by the rest 30 women (no vitamin D was given).

The general characteristics of all women participating in the present study are shown in table 1. Mean age was 28.83 $\pm$6.03 years and range was 20-40 years. Mean BMI was 23.08$\pm$3.03 kg/m2. Median parity was 2 with a range of 1 up to 5. Mean serum vitamin D was 11.65$\pm$3.23 ng/ml with a range of 6.4-

19.00 ng/ml. Mean FBS at 14 weeks gestation was 99.1±12.65 mg/dl with a range of 75-122 mg/dl.

By comparison there was no statistical difference in mean age between the two groups, 28.30+5.96 versus 29.37+6.16 years, P>0.05. Also there was no significant difference in median parity, 2.5 versus 2, P>0.05. Mean BMI was 23.20±3.09 in group 1 and 22.97±3.01 in group 2, also there was no significant difference (P>0.05). There was no significant difference in mean FBS at 14 weeks gestation, 100.07+13.14 versus 98.13+12.3 mg /dl, P>0.05. Serum vitamin D also was not significantly different in the two groups (P>0.05), as shown in table 2.

After 24 weeks gestation mean FBS was significantly higher in group 2 than in group 1, 155.77±41.30 versus 110.10±36.86 (P<0.001), and the number of diabetic patients was also significantly greater in group2 than in group 1 (P<0.001), as shown in table 3.

Discussion

The incidence of gestational diabetes mellitus (GDM) is increasing worldwide. GDM can be responsible for an important proportion of adverse fetal and maternal outcomes during pregnancy, and it is associated with long-term health deterioration for both mother and child. Therefore, it is important to identify potentially modifiable risk factors for GDM(22). Age, obesity and family history of diabetes are well known risk factors for gestational diabetes mellitus. Others are more controversial**.** Currently, strategies for the prevention of GDM include diet and exercise, but these have limited effectiveness. [26]

Table 1. General characteristic of the study sample

Characteristic	N	Mean	SD	Minimum	Maximum
Age	60	28.83	6.03	20.00	40.00
BMI	60	23.08	3.03	19.00	31.00
FBS at 14weeks /mg/dl	60	99.10	12.65	75.00	122.00
Vit .D at14weeks/ng/ml	60	11.65	3.23	6.40	19.00
Parity	2 *			1	5

*median

Table 2. Comparison of age, parity, BMI, serum vit.D and FBS at 14 weeks gestation between group1 and group2

Parameter	Groups	N	Mean	SD	P-value
Age	Group 1	30	28.30	5.96	0.498
	Group 2	30	29.37	6.16	
	Total	60	28.83	6.03	
Parity	Group 1	30	2.5 (1-5)*		0.295
	Group 2	30	2 (2-4)		
	Total	60	2 (1-5)		
BMI	Group 1	30	23.20	3.09	0.769
	Group 2	30	22.97	3.02	
	Total	60	23.08	3.03	
FBS at 14weeks /mg/dl	Group 1	30	100.07	13.14	0.559
	Group 2	30	98.13	12.30	
	Total	60	99.10	12.65	
Vit.D at14weeks ng/ml	Group 1	30	11.79	3.01	0.728
	Group 2	30	11.50	3.48	
	Total	60	11.65	3.23	

*Median (range)

Table 3. Classification of patients after 24 weeks (according to FBS)

	Group 1		Group 2		
DM	**No.**	**%**	**No.**	**%**	**P-value**
No	24	80.00	8	26.67	<0.001*
Yes	6	20.00	22	73.33	
Total	30	100.00	30	100.00	
Mean±SD	110.10±36.86		155.77±41.30		<0.001†

*Chi-square

†T-test

There is increasing interest in the relationship between vitamin D and GDM. Several studies have reported lower vitamin D levels in women with GDM [27,28]**.** This study attempted to identify non classical risk factor for GDM reflected by vitamin D deficiency. vitamin D is a secosteroid hormone that is well-known for its role in maintaining calcium homeostasis and promoting bone mineralization. Moreover, vitamin D has classic skeletal and nonclassic effects that include blood sugar control [29] and regulation of glucose metabolism through influencing insulin sensitivity, although the mechanisms are not fully understood. The pancreatic β cells express both vitamin D receptor and enzyme 1α-hydroxylase which enables them to produce 1,25 $(OH)_2D$ locally [30]. The effect of vitamin D on regulation of pancreatic β cell function and insulin secretion could be mediated through intracellular changes in calcium pool. Vitamin D could also enhance insulin sensitivity by stimulating insulin receptor gene expression thereby enhancing insulin mediated glucose transport [31]. During pregnancy, vitamin D is also essential for maternal health and the prevention of adverse outcome. Normally vitamin D levels increase progressively from the first trimester and are increased by 100% during the third trimester relative to the non-pregnant state [32,33], however vitamin D deficiency or insufficiency is common during pregnancy [14]. In present study, which included 60 pregnant women with previous history of GDM , low level of vitamin D (Mean serum vitamin D was 11.65±3.23 ng/ml), and normal FBS (Mean FBS was 99.1±12.65 mg/dl) at 14-16 weeks gestation, and the mean age of women in the study was 28.83 ±6.03 years. Lowest body mass index (BMI) was 19 kg/m**2** and the highest 31 kg/m**2**, vitamin D deficiency at early pregnancy was significantly associated with an increased risk of GDM which is consistent with results from Maghbooli et al., and Zhang C et al. which demonstrated that maternal serum levels of 25(OH)D during 24-28 weeks of pregnancy were significantly lower in women with GDM compared with controls [27,34]. On the other way, Makgoba [35] and his colleagues did not find an association between first trimester maternal serum 25 (OH)D levels and subsequent GDM development ,this result disagree with our study. Several studies investigated vitamin D supplementation in women with GDM [36]. Rudnicki and Mølsted-Pedersen_ reported that supplementation with an active form of vitamin D (1,25 $(OH)_2D$) was associated with significant decrease of plasma glucose level, possible effect on insulin sensitivity and GDM [37].This result is agree with our result that revealed a supplementary intake of vitamin D was correlated with a significant reduction in risk of GDM. This inconsistency between different studies, in part, could be due to variations in sampling time to measure vitamin D level, especially between levels at early and late gestation. So further research is required to determine the effect of vitamin D on incidence of GDM, and we recommend larger scale studies addressing this issue, with a special concern to the effectiveness of adequate

replacement of vitamin D in preventing GDM.

Conclusion and Recommendation

Gestational diabetes mellitus is a long known condition and its presence has implications for both the mother and the baby. Early diagnosis of gestational diabetes prevents maternal and fetal complications. Controversies still surround the standardized risk factors for this condition all over the world and recently a number of studies illustrated association of various non -classical risk factors with subsequent development of GDM. This study attempted to identify one of the most significant non- classical risk factor for GDM reflected by vitamin D deficiency at early pregnancy. The present study showed that maternal vitamin D deficiency in early pregnancy is an important risk factor for GDM. Also we found that a supplementary intake of vitamin D was significantly associated with a reduced risk of GDM. More evidence is recommended to determine the effect of vitamin D on incidence of GDM . However, we suggest routine testing of all pregnant women, and treatment of women who are found to be vitamin D deficient.

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