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Original Research Article

Maternal and Perinatal Outcome of Elderly Pregnancy and its Correlation with First Trimester Hba1c and Serum Vitamin D Level

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Abstract

Aim: The aim of the present study was to assess the maternal and perinatal outcome of elderly pregnancy and its correlation with first trimester Hba1c and serum vitamin D level.

Methods: An observational cross-section study including 200 pregnant women of more than 35 years in age, in their first trimester, divided into two equal groups. First group consisted of 100 women with established diagnosis of gestational diabetes and the second group with proved normal blood glucose levels. We assessed vitamin D level in serum, fasting blood glucose, serum insulin and glycosylated hemoglobin (HbA1c) levels and we depicted the insulin sensitivity using the Quantitative insulin sensitivity check index (Quicki). The results were collected and statistically correlated.

Results: The fasting plasma glucose level was significantly lower in controls compared to those with gestational diabetes. 38% of cases with gestational diabetes gave history of GDM in previous pregnancies which was also statistically significant (p-value = 0.0001), also family history of type 2 DM seemed more likely in this same group. The majority of the controls and women with GDM suffered from Vitamin D insufficiency rather than deficiency where the mean 25 OHD levels were 45.60 ± 6.08 and 46.24 ± 10.22 respectively. The fasting insulin levels were significantly higher in the group with GDM with a mean of 18.52 ±6.34 compared to 8.90 ± 2.54 in the control group. A significant inverse correlation was found between the HbA1C levels and Vitamin D where the higher the levels of Vitamin D, the lower the HbA1c levels indicating a good glycemic control in women with gestational diabetes. As regards the Vitamin D levels, they negatively correlated with the fasting blood glucose levels, the fasting serum insulin levels and the HbA1c levels, in the whole study population including both groups; women with GDM and controls.

Conclusion: In our study, there was high prevalence of vitamin D insufficiency and deficiency. Considering this we suggest routine testing of all pregnant women, and treatment of women who are found to be vitamin D deficient.

Keywords: maternal outcome, perinatal outcome, elderly pregnancy, serum vitamin D level, Hba1c

Introduction

Vitamin D deficiency during pregnancy is a common public health problem. [1-3] There is increasing interest in several nonskeletal actions of vitamin D deficiency during pregnancy, including its effects on placental function, glucose homeostasis, infection and the inflammatory response. [4-6] Evidence exists for to associations of vitamin D deficiency during pregnancy with perinatal complications such as gestational diabetes mellitus (GDM), preeclampsia, spontaneous miscarriage, preterm labor, and neurodevelopm-ental outcomes. [5,7-12]

Major changes in maternal calcium homeostasis and bone metabolism occur in pregnancy to satisfy the fetus needs. [13] Vitamin D is an important regulator of calcium homeostasis. During pregnancy, vitamin D level starts to increase through the first trimester and continue until delivery, probably due to enhanced renal synthesis and increased extra-renal synthesis in the placenta. [13] For this increment is essential to maintain proper 25-dihydroxyvitamin D levels available, a precursor of vitamin D active form. [14]

The coexistence of insulin resistance and vitamin D deficiency has generated several hypotheses as

worsening insulin resistance. [15] Immense interest persists in vitamin D and its potential effects on several pregnancy outcomes including fetal growth, hypertensive disorders, and gestational diabetes mellitus (GDM). [16] Two factors make 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. [16] Several studies have consistently shown that1,25(OH)2D concentration increases progressively during gestation being twice as high in late pregnancy as in postpartum or in non-pregnant controls. [17,18] The active form 1,25(OH)2D is also produced by the placenta during pregnancy [19] with possible autocrine or paracrine function. [20]

The aim of the present study was to assess the maternal and perinatal outcome of elderly pregnancy and its correlation with first trimester Hba1c and serum vitamin D level.

Materials and Methods

This cross-sectional observational study was conducted at SKMCH, Muzaffarpur, Bihar, India. We approached the pregnant women, in the first trimester, attending the antenatal care clinic of Cairo university hospital during this period, the target age group was more than 35 years of age. We first enrolled 100 pregnant women with established diagnosis of gestational diabetes. Those women were diagnosed as having GDM as depicted by estimating the fasting and 2- hours post- prandial blood glucose levels in previous ante- natal care visit; they were already receiving treatment for their condition, through a collaborative approach, involving the Diabetes Mellitus outpatient clinic and the internal medicine department. We then included a second group; consisting of randomly selected 100 pregnant women, those women had normal fasting and 2- hours post-prandial blood glucose levels blood glucose levels, during their routine antenatal care visits. The need to include a control group emerged when we were faced by the high incidence of vitamin D deficiency among our included cases of the first group. A question was raised; is this deficiency caused by impaired glucose tolerance, or it is a common finding in the population study. We included an equal number to the previously enrolled pregnant diabetic women, in order to obtain statistical equality. Written Informed consents were obtained from each participant prior to enrollment; the consent form was written in Arabic language and followed the world health organization guide- lines (WHO). All consent forms were signed by one of the investigators, and were collected and filed. Patients giving history of type 1 or 2 diabetes mellitus antedating pregnancy were excluded, as well as any medical disorders (such as hypertension or cardiac disease) or medical complications related to pregnancy. All the patients included were subjected to detailed history taking with special focus on maternal age, parity, gestational age at diagnosis of gestational diabetes, previous history or family history of diabetes, history of gestational diabetes in previous pregnancies. Data concerning insulin regimens, insulin types and doses (if diagnosed of having gestational diabetes) were also noted. Body Mass Index (BMI) was calculated for all subjects as follows; weight in kilograms divided by their height in meters squared (18.5 or less: underweight, 18.5-24.9 is normal, 25-29.9: overweight, 30- 39.9: Obese and 40 or greater is extremely obese). The BMI in the control group was matched to that in the GDM group for sakes of statistical adjustment. Laboratory investigation included Vitamin D3 level measured by radio immunoassay. Vitamin D deficiency was defined conservatively as <25 ηmol/L, insufficiency as 25–50 ηmol/L and sufficiency as >50 ηmol/L. HbA1c was measured by radio- immunoassay to assess the glycemic control. The normal level for glycosylated hemoglobin is less than 7%. Diabetics rarely achieve such levels, but tight control aims to come close to it. Levels above 9% show poor control, and levels above 12% show very poor control. Fasting serum insulin (in mIU/L), fasting blood glucose and 2 hours postprandial, interpreted in mg/dL were included within the laboratory investigations. The insulin sensitivity as a reflection of insulin resistance was measured using the Quantitative insulin sensitivity check index (Quicki). This index correlates well with glucose clamp studies (r=0.78), and it has the advantage of that it can be obtained from a fasting blood sample, hence it is the preferred method for several types of clinical research. [21] It is calculated

as {1/(log fasting insulin + log fasting blood sugar). Blood samples were collected from pregnant women with gestational diabetes during pregnancy during routine antenatal care visits and were analyzed. All results were statistically analyzed and tabulated.

Statistical Analysis

Data were statistically described in terms of mean ± standard deviation (±SD), median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student t test for independent samples. For comparing categorical data, Chi square test was performed. Exact test was used instead when the expected frequency is less than 5. P values less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

Results

Table 1: Clinical and biochemical demographic data

	Controls (n 100)	Cases with GDM (n 100)	P-value
Maternal age in years	36.14± 3.72	37.23 ±3.80	0.110
Pre-pregnancy BMI (Kg/m2)	24.32 ± 2.38	25.45 ±2.92	0.614
Parity	1.78 ± 1.07	1.80 ±1.04	0.92
Previous history of GDM	7 (7%)	38 (38%)	0.0001
Family history of type 2 DM	12 (12%)	48 (48%)	0.0001
Fasting blood sugar mg/dl	78.06 ± 7.16	95.07 ± 15.35	0.000
25OHD (nmol/L)	45.60 ± 6.08	46.24 ± 10.22	0.644
HbA1C	4.48 ± 0.52	4.22 ± 1.08	0.119
Fasting insulin	8.90 ± 2.54	18.52 ±6.34	0.000
Quicki	0.3518 ±0.1784	0.4848 ±0.0195	0.000

The fasting plasma glucose level was significantly lower in controls compared to those with gestational diabetes. 38% of cases with gestational diabetes gave history of GDM in previous pregnancies which was also statistically significant (p-value = 0.0001), also family history of type 2 DM seemed more likely in this same group. The majority of the controls and women with GDM suffered from Vitamin D insufficiency rather than deficiency where the mean 25 OHD levels were 45.60 ± 6.08 and 46.24 ± 10.22 respectively. The fasting insulin levels were significantly higher in the group with GDM with a mean of 18.52 ±6.34 compared to 8.90 ± 2.54 in the control group.

Table 2: Maternal Outcomes

	Controls (n = 100)	Cases with GDM (n = 100)	P value
Gestational Age (weeks) (Mean±SD)	38.6 ± 1.4	38.8 ± 1.4	.038
Cesarean section	43	44	
			.614
Premature rupture of membranes	1	2	
			.332
Gestational diabetes	10	12	
			.024
Preeclampsia	2	3	
			.022
Intrahepatic cholestasis	1	2	0.143
Intrauterine infection	2	3	.042
2-h postpartum hemorrhage(ml)	256 ± 149	255 ± 106	.78

Women diagnosed as vitamin D insufficiency had a higher incidence rate of gestational diabetes compared with vitamin D deficiency. The incidence rate of intra- uterine infection, preeclampsia were different among groups but not significant after multiple comparison correction. No associations were found between gestational age (both category and numeric values), cesarean section rate, premature rupture of mem- branes, intrahepatic cholestasis and 2-h postpartum hemorrhage.

Table 3: The correlation between HbA1C and different maternal biochemical variables in women with gestational diabetes

Variables	Correlation coefficient (r value)	P-value
Fasting blood sugar	- 0.388	0.000
Fasting insulin levels	0.334	0.000
Vitamin D levels	−0.490	0.000
QUICKI equation	−0.252	0.001

A significant inverse correlation was found between the HbA1C levels and Vitamin D levels (correlation coefficient r = -0.490, P value <0.05), where the higher the levels of Vitamin D, the lower the HbA1c levels indicating a good glycemic control in women with gestational diabetes. An inverse association was also found with the fasting blood sugar levels which was statistically significant (the correlation coefficient r = - 0.388), as well as with Quicki values (r = - 0.252).

Table 4: The correlation between the Vitamin D levels and the various maternal biochemical variables in women included in the study

Variables	Correlation coefficient (r value)	P-value
Fasting blood sugar	- 0.247	0.000
Fasting insulin levels	0.358	0.000
HbA1C levels	−0.494	0.000
QUICKI equation	−0.148	0.066

As regards the Vitamin D levels, they negatively correlated with the fasting blood glucose levels, the fasting serum insulin levels and the HbA1c levels, in the whole study population including both groups; women with GDM and controls. The P value in all these correlations were <0.05. The Quicki values, however, did not significantly correlate with the Vitamin D levels, the P value being 0.066.

Discussion

Vitamin D plays a great role in bone metabolism and mineral homeostasis. Relevant data identify roles for the active form of vitamin D (1,25(OH)2D3) in many bio- logical processes including regulation of cellular growth, differentiation and metabolic modulations. [22] Vitamin D insufficiency has a known effect on bone density, neo- natal vitamin D and calcium status, and childhood rickets. [23] In several studies, the relation between low vitamin D levels, insulin resistance and impaired insulin secretion was clearly demonstrated. [24] Moreover, specific receptors for 1,25(OH)2D3 were detected in pancreatic ß cells, denoting a probable effect of vitamin D on the insulin secretion process. [25]

Early diagnosis and treatment of GDM can reduce adverse pregnancy outcomes, including stillbirth, neonatal macrosomia, neonatal hypoglycemia, birth trauma, and neonatal respiratory distress syndrome as well as decrease the risk of preeclampsia in the mother. [26] Vitamin D deficiency is closely associated with Gestational Diabetes Mellitus (GDM). Vitamin D induces insulin receptor expression through Vitamin D receptor (VDR), enhancing insulin-dependent glucose transport. Vitamin D is also a potential immunosuppressant, which down-regulates the expression of proinflammation markers, such as TNF-α and IL-2, among pregnant women with GDM. [27] The fasting plasma glucose level was significantly lower in controls compared to those with gestational diabetes. 38% of cases with gestational diabetes gave history of GDM in previous pregnancies which was also statistically significant (p-value = 0.0001), also family history of type 2 DM seemed more likely in this same group. The majority of the controls and women with GDM suffered from Vitamin D insufficiency rather than deficiency where the mean 25 OHD levels were 45.60 ± 6.08 and 46.24 ± 10.22 respectively. The fasting insulin levels were significantly higher in the group with GDM with a mean of 18.52 ±6.34 compared to 8.90 ± 2.54 in the control group. A significant inverse correlation was found between the HbA1C levels and Vitamin D levels (correlation coefficient r = -0.490, P value <0.05), where the higher the levels of Vitamin D, the lower the HbA1c levels indicating a good glycemic control in women with gestational diabetes. An inverse association was also found with the fasting blood sugar levels which was statistically significant (the correlation coefficient r = - 0.388), as well as with Quicki values (r = - 0.252).

Women diagnosed as vitamin D insufficiency had a higher incidence rate of gestational diabetes compared with vitamin D deficiency. The incidence rate of intra- uterine infection, preeclampsia were different among groups but not significant after multiple comparison correction. No associations were found between gestational age (both category and numeric values), cesarean section rate, premature rupture of mem- branes, intrahepatic cholestasis and 2-h postpartum hemorrhage. The possible explanation for such relationship between Vitamin D deficiency and the impaired glycemic control, found in our study could be made attributed to the defect in the important role that Vitamin D plays in glucose homeostasis, and via different mechanisms. The mechanism of action of vitamin D in type 2 diabetes is thought to be mediated not only through regulation of plasma calcium levels, which regulate insulin synthesis and secretion, but it also improves insulin sensitivity of the target cells (liver, skeletal muscle, and adipose tissue). Additionally, Vitamin D enhances and improves β-cell function and protects them from detrimental immune at- tacks, directly by its action on β-cells, but also indirectly by acting on different immune cells, including inflammatory macrophages, dendritic cells, and a variety of T cells. Macrophages, dendritic cells, T lymphocytes, and B lymphocytes can synthesize Vitamin D, all contributing to the regulation of local immune responses. [28]

As regards the Vitamin D levels, they negatively correlated with the fasting blood glucose levels, the fasting serum insulin levels and the HbA1c levels, in the whole study population including both groups; women with GDM and controls. Maghbooli et al 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. [29] More recently, Makgoba and his

colleagues did not find an association between first trimester maternal serum 25(OH)D levels and subsequent GDM development. [30] On the other way round, Clifton-Bligh demonstrated an inverse association between maternal serum 25(OH)D levels and fasting blood glucose, although the association between 25(OH)D and GDM was not statistically significant. [31] Additionally, a recent study of Indian women failed to demonstrate a relationship between maternal vitamin D status and risk of developing GDM. [32] In 2013, a randomized controlled study from a Turkish group, on 234 women with GDM and 168 controls, came to a more specific conclusion; they found a statistical significance, between glycemic control and vitamin D levels, only in women with severe deficiency of 25(OH)D levels. They also concluded that only this group (with severe vitamin D deficiency) is at a higher risk of GDM. [33]

Limitations of the Study

1) This study was conducted in a single hospital; it is not possible to provide an exact, generalizable cutoff for increased GDM risk based on vitamin D levels at this stage. 2) Residual confounding cannot be ruled out, as we did not analyze data regarding vitamin D supplementation, the dietary intake of vitamin D, education levels, social data, physical activities, or family history of disease.

Conclusion

In our study, there was high prevalence of vitamin D insufficiency and deficiency. Considering this we suggest routine testing of all pregnant women, and treatment of women who are found to be vitamin D deficient. We do not know whether adequate vitamin D replacement may contribute to prevention of GDM later in pregnancy, as our study suggests a significant inverse correlation be- tween vitamin D status and glycemic control in all the pregnant women included. We recommend larger scale studies addressing this issue, with a special concern to the effectiveness of adequate replacement of vitamin D in preventing GDM.

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