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Studying the Correlation Between Serum Level of 25-hydroxyvitamin D and Glucose Metabolism During Pregnancy

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ABSTRACT

There are conflicting ideas concerning the correlation between serum levels of 25-hydroxivatmin D and side effects of pregnancy. The present research seeks to study the correlation between lack of this vitamin and glucose metabolism in pregnancy. In this Cross-sectional research, as many as 330 women aging 18 to 35 in the 24th to 28th week of their pregnancy and fully aware of the process entered this project after their consent was gained. They underwent public screening for diabetes through 50-gram oral glucose challenge test (GCT). The serum level of HbA1C and 25-hydroxyvitamin D and analysis of urine for glucose were measured at the same time when the level of blood sugar was assessed. As for those people whose blood sugar 1 hour after receiving 50 g oral glucose was equal to or more than 140 mg/dl, the two-hour OGTT diagnosis test was carried out with 75 grams of glucose. The average levels of Vitamin D and HbA1C were compared with one another among the participants. Variables such as mother's age, parity, family history of diabetes, and BMI of mother were recorded in the checklists. Data was analyzed by SPSS20 software using T-test, Correlation, and K2 statistical methods. The average age of the mothers participating in this research and their average level of parity were 26.78 ± 4.5 and 1.89 ± 0.92 respectively. There were 48 cases (14.5%) with pregnancy diabetes, while 282 cases (85.5%) had no sign of diabetes. The serum level of vitamin D was above 30 ng/dl in 9 subjects (2.7%), while this level was below 20 ng/dl in 321 people (93.7%). A reverse significant correlation was observed between the serum level of vitamin D and average levels of HbA1C (p=0.006 and r=0.15). a significant difference was observed in Glucosuria between the diabetic and non-diabetic people (p=0.001) but it had no significant correlation between the level of vitamin D. Prevalence of vitamin D deficiency in this research is really high. The routine assessment of this vitamin before pregnancy and the necessity of correcting its deficiency and prescription of vitamin d supplements and its effect on OGTT results,needs more researches.

Keywords: 25-hydroxivitamin D, gestational diabetes, Glucose Metabolism.

INTRODUCTION

Lack of vitamin D is a common phenomenon among people suffering from type 2 diabetes and pregnant women. It may act as a dangerous factor for metabolic syndrome in these people and replacing vitamin D would reduce resistance to insulin[1]. In patients suffering from gestational diabetes and especially those with type 2 diabetes, the concentration of D during pregnancy

will remain less than what is observed in healthy women. As deficiency of vitamin D, diabetes and gestational diabetes are common in Iran, studying the correlation of these diseases with one another can help identify its pathogenesis particularly because no clear link has been established yet between deficiency of vitamin D and glucose tolerance and insulin resistance during pregnancy. As one of the main characters of gestational diabetes is resistance to insulin and people are exposed to type 2 diabetes, studying the patients suffering from diabetes can provide us with a good sample for the comprehensive study of diabetes. Taking these issues into consideration, the present research seeks to study the correlation between the serum level of 25-hydroxivitamin D and glucose metabolism during pregnancy. Vitamin D or calciferol and its metabolites are soluble in fat and its metabolism (1- and 25-di hydroxyvitamin D) depend upon the hemostasis of calcium and the serum level of calcium and phosphor is regulated through Parathyroid hormone. Estrogen, placental growth hormone and prolactin influence the metabolism of vitamin D and result in greater demand for calcium during pregnancy.

There are a few foods that contain vitamin D such as egg and fat fish. The main source of this vitamin is the synthesis inside the skin. Vitamin D_3 (Cholecalciferol) is synthesized when sunlight (UV) reaches 7-di hydrocholesterol inside our skin. It is hydroxylated in liver and then in kidneys and finally turns into the active form of 1- and 25-di hydroxyvitamin D. The extra-skeletal effects of vitamin D are great, it influences our immune and cardiovascular systems, and its deficiency results in muscle weakness and higher risks of affliction with cancer. It has also been studied in metabolic syndrome and diabetes. It is involved in type 1 Mellitus diabetes as it influences the immune system. As for type 2 diabetes, it helps increase the activity of β cells and improve insulin sensitivity. Obesity is usually accompanied with lower concentrations of 25OHD. The risk of affliction with type 2 diabetes among those women who have sufficient levels of vitamin D was reported to be much less in several researches[2,3].

Various researches have shown these complications in 25OHD serum level to be less than 20 ng/ml (50 nmol/l). Prescription of vitamin D supplements is regulated based on the patient[4]. As for those with high risks of fracture or falling and 25OHD levels below 20 ng/ml of vitamin D, 50000 oral units are prescribed weekly for 6 to 8 weeks. As for pregnant women, the weekly dose of 50000 for 6 to 8 weeks is not reliable and a daily dose of 600 to 800 units is prescribed[5].

Deficiency of vitamin D results in various effects including pregnancy complications: pregnancy diabetes, preeclampsia, infections and limited growth of the fetus. Various studies have failed to come up with a clear definition for deficiency of vitamin D during pregnancy, but they have shown that deficiency of vitamin D within the first trimester results in higher pregnancy complications[6]. Although the favorable supplementary dose of vitamin D is not clear, prescription of vitamin D supplements seems to be a simple yet useful intervention. Deficiency of vitamin D is quite common among pregnant women and it may disrupt glucose metabolism. The extra-skeletal effects of vitamin D is an interesting topic for analysis and research. It is even involved in causing metabolic syndrome and type 2 mellitus diabetes. It is not clear how it influences glucose metabolism but it has a reverse correlation with glycosylated hemoglobin in pregnancy diabetes. Seemingly, it helps prevent gestational diabetes[7].

deficiency of vitamin D is a common complication among people with type 2 diabetes and pregnant women and it may constitute a dangerous factor of metabolic syndrome in these people[8] and replacing vitamin D reduces insulin resistance[9]. As for those mothers suffering from gestational diabetes and particularly those with type 2 diabetes, the concentration of D will remain below the level reported in healthy mothers[10,11]. As deficiency of vitamin D, diabetes and pregnancy diabetes are common phenomena in Iran, studying the correlation of these diseases with one another can help identify its pathogenesis particularly because no clear link has been established yet between deficiency of vitamin D and sugar tolerance and insulin resistance during pregnancy. The majority of the researches have been conducted on animals in laboratories. As one of the main characters of gestational diabetes is

resistance to insulin and people are exposed to type 2 diabetes, studying the patients suffering from diabetes can provide us with a good sample for the comprehensive study of diabetes. Taking these issues into consideration, the present research seeks to study the correlation between the serum level of 25-hydroxivitamin D and glucose metabolism during pregnancy.

MATERIALS AND METHOD

In the present cross-sectional research, pregnant women within their 24 and 28 week who had resorted to midwifery center of Firouzgar and Shahid Akbar Abadi Hospitals (February 2014 to March 2015) and were qualified for the research entered this project. Without any extra costs, urine examination to determine Glucosuria, HbA1C and serum level of 25-hydroxyvitamin D were requested besides GCT. In the case of disrupted GCT (blood glucose equal to or more than 140 mg/dl after receiving 50 gr oral glucose), GTT was conducted with 75 grams of oral glucose. As for those people diagnosed with GDM (fasting blood sugar level $\geq$ 95 or 1 hour blood glucose $\geq$ 180 or 2 hour blood glucose 155) compared to normal people,

Table 1: Average quantitative quantities for participants

		GDM + (48 cases)	GDM – (282 cases)	Total (330 cases)	Level of significant difference
Age	Average	26.64	26.96	26.78	P = 0.55.
	SD	5.54	4.67	4.50	
Gravity	Average	1.85	1.90	1.89	P = 0.573
	SD	0.98	0.90	0.92	
Parity	Average	0.47	0.63	0.61	P = 0.122
	SD	0.74	0.75	0.75	
Abortion	Average	0.37	0.26	0.28	P = 0.250
	SD	0.60	0.51	0.52	
HbA1c	Average	4.93	4.72	4.75	P = 0.001
	SD	0.43	0.36	0.38	
Vit D	Average	15.61	16.39	15.73	P = 0.133
	SD	5.16	4.80	5.11	

Table 2: Frequency of qualitative quantities among participants

		GDM + (48 people)	GDM – (282 people)	Total (330 people)	Level of significant difference
Glucosuria	Positive	10 (20.8%)	14 (5.0%)	24 (7.3%)	P = 0.001
	Negative	38 (79.2%)	268 (95.0%)	306 (92.7%)	
Vitamin D	Deficiency	37 (77.1%)	241 (85.5%)	278 (84.2%)	P = 0.217
	Insufficiency	10 (20.8%)	33 (11.7%)	43 (13.0%)	
	Sufficiency	1 (2.1%)	8 (2.8%)	9 (2.7%)	
BMI	Normal	15 (31.2%)	113 (40.1%)	128 (38.8%)	P = 0.406
	Overweight	33 (68.8%)	169 (59.9%)	202 (61.2%)	
Family history	Positive	7 (14.6%)	24 (8.5%)	31 (9.%)	P = 0.000
	Negative	24 (50.0%)	216 (76.6%)	240 (72.7%)	
	No information	17 (35.4%)	42 (14.9%)	59 (17.9%)	

glucosuria, HbA1C, and serum level of hydroxyvitamin D are compared. To reduce statistical error, those patients taking vitamin D supplements were excluded from research. There were other variables measured in this research: age and BMI, number of deliveries, number of abortions and healthy deliveries, family history of affliction with diabetes among first grade relatives and background diseases such as diabetes, high blood pressure, hyperlipidemia, renal failure. The following inclusion criteria were defined: aging older than 18 and younger than 35 years old and being in the 24 to 28 week of pregnancy according to trimester sonography or LMP. These were the exclusion criteria: diseases influencing the serum levels of 25-hydroxyvitamin D like thyroid, parathyroid, renal and liver diseases, taking supplements with vitamin D, smoking cigarettes, overt diabetes or fasting blood sugar 126 or HbA1C 6.5 and obesity (BMI 30).

An author-made checklist corresponding to variables of research was used to register the data. LIAISON kit was used to measure vitamin D and Biosystem kits were utilized to measure blood sugar and HbA1C. Cochran formula was used to calculate the size of the sample. The final sample size was finally set to 330. SPSS v.20 was used to analyze the data and the central statistical indicators such as mean, standard deviation, and frequency percentage were calculated. Then, t-test, k2, and correlation tests were used to study the correlation between variables. A p-value below 0.05 was defined to be statistically significant. All the participants were fully aware of the research and entered it with full consent. None of the information was reported individually.

RESULTS

The present research was conducted to find the correlation between the serum level of 25-hydroxyvitamin D and glucose metabolism in diabetes. As many as 330 pregnant women were studied in this research. First, CGT was carried out for everyone. 76 people (23%) had disrupted GCT and 254 (77%) had normal GCT. GTT was conducted on those 76 people and it turned out that 48 of them (63.2%) were suffering from GDM while 28 were diagnosed to be negative (36.8%). Of 330 women studied in this research, 48 (14.5%) were suffering from GDM and 282 (85.5%) were normal. The average age of the participants was 26.78±4.50 (18 to 35 years old). The average number of gravities in these people was 1.89 ± 0.92 (ranging 1 to 5). The average number of parity in these people was 0.61 ± 0.75 (ranging 0 to 3). The average number of abortions in these people was 0.28 ± 0.52 (ranging 0 to 3 times). 138 cases (41.8%) were in their first gravidity and 154 cases (46.6%) had at least one experience of child delivery and 13 of them had a past history of gestational diabetes. Table 1 represents the quantitative values in terms of diabetic and non-diabetic groups.

Levels of vitamin D were divided into 3 groups: deficiency (less than 20 ng/dl), insufficiency (20-30 ng/dl) and sufficiency (more than 30 ng/dl). 278 cases were reported with deficiency (84.2%), 43 were diagnosed with insufficient levels of vitamin D (13.03%) and 9 cases (2.72%) had sufficient levels of vitamin D.

Family history of affliction with overt diabetes among the close relatives of patients was questioned. Access to such information was denied in 59 patients. In the remaining 271 cases, positive histories were reported in 14.6% of diabetic and 8.5% of non-diabetic cases. The information is presented in table 2.

Table 3: Average levels of HbA1c among the participants in terms of Vitamin D

		Deficiency (43 people)	Insufficiency (43 people)	Sufficiency (9 people)	Level of significant difference
HbA1c	Average	4.86	4.87	4.72	P = 0.039
	SD	0.42	0.34	0.38	

The correlation between the levels of HbA1c among the participants and levels of vitamin D are presented in table 3. As for the correlation between the average level of HbA1c and average levels of vitamin D among participants, a value of 0.006 was calculated for P and r = -0.15. No significant correlation was observed between average levels of vitamin D and gestational diabetes and glucosuria in this research.

DISCUSSION

Vitamin D and its metabolites play a major role in calcium Homeostasis and bone metabolism. Various researches have pointed to the major role if the active form of this vitamin (1- and 25- Di-hydroxy-cholecalciferol) in regulating biological processes by activating gene expression through intercellular receptors - like cellular development, differentiation and metabolism[1,10].

The role of vitamin D in non-skeletal structures has been studied in various researches. This vitamin seems to be useful in cardiovascular, digestive, and muscular systems. The exclusive receptor of this vitamin has been found on Pancreatic beta cells and it seems to have some influence over the glucose metabolism. This correlation, however, is not completely clear[12].

No definition concerning the favorable levels of vitamin D has been proposed so far and its serum level differs based upon race, place of residence, nutrition status, and socio-economic status of people. This vitamin passes through the Placenta and is involved in bone metabolism of fetus and causes unfavorable obstetrical complications such as early delivery, premature rupture of membrane, abortion, limited growth of fetus, preeclampsia, and gestational diabetes.

Various studies have studied the correlation between deficiency of vitamin D and glucose metabolism during pregnancy. Indicators such as frequency of affliction with gestational diabetes, serum level of HbA1C and insulin challenge tests (Quicki test) were used and the results were conflicting in some cases.

The review study conducted by Fariba Agha Jafari et al (2013) confirms higher risks of pregnancy diabetes and preeclampsia an low delivery weight as a result of vitamin D deficiency. Parlea et al have also highlighted the fact that hypo-vitamin D during pregnancy is associated with higher risks of affliction with GDM[13,14]. The average levels of vitamin D among the nondiabetic and diabetic people were 16.39 and 15.61 respectively. This difference was not significant (P-value = 0.133).

It should be noted that no significant correlation has been described between hypo-vitamin D and affliction with GDM by Yap and Farrant[15,16]. As for the correlation between mother's level of vitamin D and sensitivity to insulin and serum levels of HbA1C, some researches have been conducted by Magbouli et al. and Ahmed Ellithy. These studies have pointed to the reverse correlation between levels of this vitamin and levels of HbA1C and insulin sensitivity. They have claimed that this sensitivity may be due to the role vitamin D plays in production and secretion of insulin[17,18]. The average level of HbA1C in the diabetic and nondiabetic groups in our research was 4.93 and 4.72 rendering the difference statistically significant (P = 0.001).

A reverse significant correlation was also observed between average level of HbA1C and levels of vitamin D (R = -0.15, P = 0.006). Some researches have defined multi-parity as a risk factor which causes deficiency of vitamin D serum level[19]. In this research, no significant correlation was found between the number of pregnancy among the diabetic and nondiabetic mothers and vitamin D level (P = 0.141).

Glucosuria is one of the symptoms which makes conducting Oral Glucose Tolerance Test mandatory in the first visit (20) and it can help the early diagnosis of gestational or overt diabetes. Glucosuria was observed among 20.8% and 5% of the diabetic and non-diabetic patients respectively which made this difference significant (P = 0.001). However, it had no significant difference with average levels of vitamin D in both groups.

Various researches have pointed to obesity as the risk factor that increases the possibility

of affliction with gestational diabetes and deficiency of vitamin D (21,22). No significant difference was observed among the diabetic and non-diabetic people in terms of BMI. The difference between the average BMI of the participants and serum level of vitamin D was not significant.

CONCLUSION

The deficiency of vitamin D was quite common and frequent in this research. This study never sought to study prescription of supplements and their effects on OGTT. Those cases taking supplements were excluded from the research. Sampling was conducted over a period of one year and exposure to sunlight might have affected the level of vitamin. As the social and economic status can directly influence nutrition, it may also have a direct effect on the serum level of vitamin D. No correlation was observed between the level of vitamin D and affliction with gestational diabetes although it had a reverse significant correlation with HbA1C. Further research can help confirm this correlation and determine the necessity of routine assessment of this vitamin and correcting its deficiency before pregnancy.

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