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A COMPARISON OF SERUM LEVELS OF 25-HYDROXY VITAMIN D IN PREGNANT WOMEN AT RISK FOR GESTATIONAL DIABETES MELLITUS AND WOMEN WITHOUT RISK FACTORS

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ABSTRACT

Background: During pregnancy, Low serum 25-hydroxyvitamin-D [25(OH)D] concentration is even more critical. This deficiency leads to higher incidences of preeclampsia, gestational diabetes,preterm birth, bacterial vaginosis, and also affects the health of the infants. The aim of this study was to evaluate the relationships between serum levels of 25-hydroxyvitamin D (25[OH]D) and gestational diabetes mellitus (GDM) and differences in high-risk pregnant women and women without risk factors for GDM. **Methods:** This cross sectional study including 155 pregnant women, who are still in the first trimester of pregnancy (less than 12 weeks gestation), were randomized to two groups of high and low risk for GDM. For these people, once at the gestational age less than 12 times a week and once at for 24 to 28 weeks of pregnancy, tests of FBS / BS / HbA1C / 25OHD / insulin / Ca / Albumin was requested. Besides, the OGTT test was performed with 75 g glucose at 24 and 28 weeks of pregnancy to diagnose GDM. **Results:** Serum levels of 25(OH)D in the second trimester of pregnancy ng / ml (24.1 ± 39.5) was significantly lower than that of the first trimester ng / ml (25.9 ± 45.6) ($p < 0.001$).But serum 25(OH)D levels in the first and second trimester of pregnancy was significantly different in women at high risk for GDM than women who had no risk factors ($p = 0.584$ and $p = 0.99$). Serum levels of 25(OH)D has an inverse and significant relationship with HbA1C at the beginning of pregnancy ($p = 0.007$). In addition, a significant and inverse relationship was shown between serum levels of 25(OH)D in the second trimester with insulin ($p = 0.047$) and blood sugar 2 hours after ingestion of 75 g glucose ($p = 0.045$) at 24-28 weeks of gestation. **Conclusion:** Regarding to the relationship between serum levels of 25(OH)D and blood sugar and insulin at the second trimester of pregnancy, it is recommended for pregnant women to take vitamin D supplementation.

Key words: gestational diabetes mellitus(GDM), 25-hydroxyvitamin D, vitamin D, pregnancy.

1. INTRODUCTION

Gestational diabetes mellitus (GDM) is considered as glucose intolerance with onset or first recognition during pregnancy (1). Prevalence of GDM during pregnancy ranges from 1 to 14 % of all pregnancies depending on the population under study and the diagnostic tests applied (2-4). The prevalence of this type of deficiency is 4.7 % among Iranian pregnant women (5). GDM is associated with increase in risks of maternal and neonatal gestational complicacy and delivery problems, including pre-eclampsia, preterm labor, cesarean delivery, fetal macrosomia and neonatal hypoglycaemia (6, 7). Those issues trigger GDM become an essential topic for investigation (1) that increases concern in vitamin deficiency as a potential cause (8). Although epidemiologic studies have shown a relatively consistent connection between vitamin D deficiency and a higher risk of type 2 diabetes mellitus (9, 10) and although obesity is associated mainly with both GDM (11,12)and vitamin D deficiency(13-15), it remains dubious whether vitamin D level risks a mother to experience GDM or not. Vitamin D is a prohormone that can be gained from both dietary factors and sunlight exposure (16). The prevalence of 25(OH)-vitamin D deficiency and insufficiency is increasing in Western societies and is particularly common in women of reproductive age and during and after pregnancy (17, 18). Vitamin D deficiency during pregnancy has

been connected to maternal osteomalacia, GDM, preeclampsia, small birth size, respiratory diseases, impaired fetal growth and bone development later in childhood (19-21), and more recently adequate vitamin D level has been linked to embryonic neurodevelopment (22,23). Epidemiological data have shown that pregnant women with GDM were probably being vitamin D deficient (24). A few studies support relationship between low 25-hydroxyvitamin D (25[OH]D) levels and an increased risk of GDM (25-28), but a recent prospective study did not find any evidence of an association between first-trimester 25(OH) D levels and the further development of GDM (29). Due to previously found differences in vitamin D status in pregnant women, and because pregnancy is a vulnerable period for both the woman and the growing fetus, the aim of this study was to compare of serum levels of 25-hydroxyvitamin D in pregnant women at risk for GDM and women without risk factors.

2. PATIENTS AND METHODS

This cross-sectional study was carried out on 155 pregnant women, who do not yet finished the first trimester of pregnancy (less than 12 weeks gestation). They were selected among 400 pregnant women with gestational age less than 12 weeks during the 5 month, who referred to Shahrekord prenatal care clinics affiliated to Shahrekord University of Medical Sciences,Iran. The design of study was approved by the Ethics Committee of Shahrekord University of Medical Science,Iran. Consent forms were filled in by participants of this study .All the participants have the inclusion criteria in this study. All of them were clinically and thoroughly examined and their medical and health history were completely collected and recorded. The inclusion criteria in this study were: complete and full consent, no intake of calcium supplementation and vitamin D during the past 6 month, the absence of any history of chronic liver disease, renal, endocrine, heart and respiratory disease based on examination and record history, no diagnosed diabetes type 1 and 2, no medication intake medication influence on metabolism, vitamin D homeostasis during the past 6 months and not having previous history of GDM. Exclusion criteria included: lack of consent to continue the follow-up, lack of referring for the next follow-ups, lack of consent to OGTT in the first trimester, emergence of any chronic liver, renal, endocrine, cardiovascular and respiratory disease during pregnancy, emergence of any adverse obstetrical events during pregnancy, forced consumption of drugs influencing metabolism and hemostasis calcium and vitamin D during pregnancy and, definitive diagnosis of diabetes at the beginning of the study based on the experiments done. Method of Sampling was simple sampling. Pregnant women were randomized to two groups of high and low risk for GDM. They were referred to the laboratory for testing in the first trimester of pregnancy. A mount of their serum levels of 25(OH)D, blood sugar level, blood insulin level, levels of HbA1C, GDM, Ca (calcium), FBS (FBS) and albumin were measured. Then, they were again examined between weeks of 24 to 28 based on the standard method using 75 gr of glucose powder (30) and other OGTT were measured based on the examination which were done for them during the first trimester of pregnancy. In the case that any of the pregnant women suffer from severe Vitamin D deficiency, they were excluded from the study and were treated. Experiments were performed in a single laboratory using Electrochemiluminiscence method by means of Cobas E411 device manufactured by Roche-Hitachi-Cobas Company (2010).

2.1. Statistical analysis

All data were entered and analyzed by using SPSS software version 17. Statistical analysis of the data was performed using the T test, ANOVA and Pearson correlation coefficient.

3. RESULTS

In the first phase of this study, the data related to a total of 155 pregnant women were collected and in the second phase, 64 of these women attended for complementary examinations. They aged from 18 to 43 years with an average of 5.3 ± 27.4 years. Their weight range from 42 to 111 kg with an average of 11.7 ± 64.6 kg. BMI (body mass index) of these people ranges from 16.5 to 45 with an average of 4.8 ± 25.3 kg/m2. Systolic and diastolic blood pressure were in the range of 70 to 150 mm Hg, with an average of 12.1 ± 106 mm Hg and 50 to 80 with an average of 10.4 ± 62.6 mm Hg respectively. 116 (74.8%) of them live in urban areas and others reside in rural areas. 16 (10.3%) of them were employed and the rest were housewives. ANOVA showed no association between serum levels of 25(OH)D and the number of pregnancies (p =0.88). T-test showed no association between serum levels of 25(OH)D (p =0.21) with the place of residence. The t-test showed no significant association between serum levels of 25(OH)D and the number of pregnancy (p =0.49). As shown in Table 1., there were a significant relationship between serum levels of 25(OH)D in pregnant women in their first trimester of pregnancy and physiological characteristics including age (p=0.95), weight (p =0.19), BMI (p =0.09), systolic blood pressure (p =0.23) and diastolic blood pressure (p =0.63).

Factor	Correlation coefficient	p value
Age	0.005	0.949
Weight	0.104-	0.196
Body mass index(BMI)	0.133-	0.09
Systolic blood pressure	0.960-	0.235
Diastolic blood pressure	0.039-	0.629

Table 1. Association between serum vitamin D levels in pregnant women in the first trimester of pregnancy with their physiological characteristics

The results of metabolic parameters in the first and second trimester of pregnancy in patients are summarized in Table 2. Defining the risk factors for GDM (based on the Standard of Medical Care in Diabetes-2012, American Diabetes Association (31), 27 of 155 patients (17.4 %) were diagnosed with high risk based on the existence of at least one of the following criteria "BMI≥35, history of GDM, birth weight of more 4 kg, and positive family history for type 2 diabetes. Average level of serum of 25(OH)D for 64 of the cases who were referred in the

variable	first trimester (No.155)			second trimester(No.64)		
	mean±SD	Max.	Min.	mean±SD	Max.	Min.
Fasting blood sugar	8.10±7.89	163	71	21.2±88.8	184	65
Random blood sugar (BS) (mg/dl)	1.18±3.93	197	50	27.5±112.1	165	68
Calcium(mg/dl)	0.5±8.9	14	7.5	0.4±9.2	10.2	8.2
Albumin(gr)	0.4±4	7.1	2	0.1±3.5	3.9	3
Vitamin D	25.9±45.6	159.2	13.46	24.1±39.5	142.3	9.3
Hb A1C (%)	0.7±5.8	7.2	4	0.8±5.8	7.9	4.1
insulin	14.3 ±6.3	175	0.2	13.5±11.1	84.9	0.6

Table 2. Results of metabolic parameters in patients during the first and second trimester of pregnancy

second trimester was 32.11 ± 53.9 (ng / ml) at the beginning of the study and was 24.1 ± 39.5 (ng / ml) in the second trimester. Paired t-test showed a significant decrease in the levels of serum of 25(OH)D in the second trimester compared to the first trimester (p <0.001). There was no significant difference for levels of serum of 25(OH)D at the beginning and end of the study in the high risk group comparing the low-risk group (Table 3).

Group	Low risk	High risk	p value
	mean±SD	mean±SD	
Measurement stage			
First trimester(n=155)	26.9± 46.2	21.1± 43.1	0.58
Second trimester(n=64)	25.5±39.5	3.17±39.6	0.99

Table 3. Levels of Vitamin D in pregnant women the first and second trimester in low-risk and high-risk groups

The relationship between serum levels of 25(OH)D and metabolic factors in the first and the second trimester based on the Pearson correlation coefficient is shown in Table 4. There was a direct and significant correlation between serum levels of 25(OH)D in early pregnancy and fasting blood sugar. In other words, in the case of decrease in the level of serum of 25(OH)D in early pregnancy , fasting blood sugar may also be decreased and vice versa. It was also found that a serum levels of 25(OH)D in early pregnancy in the first trimester of pregnancy associated with HbA1C. There was a direct and significant correlation in the second trimester of pregnancy. Based our findings, there was a significant and inverse correlation between serum levels of 25(OH)D in early pregnancy and HbA1C level in the first trimester of pregnancy and there is a direct and significant correlation between serum levels of 25(OH)D in early pregnancy and HbA1C level in the second trimester of pregnancy. It means that in the first trimester of pregnancy, serum levels of 25(OH)D reduced with the increase of HbA1C levels .While in the second trimester of pregnancy, the level of serum of 25(OH)D reduced with the decrease of HbA1C levels. There was a significant correlation between serum levels of 25(OH)D and postprandial glucose levels in the second trimester of pregnancy. In fact, at the end of pregnancy, the amount of resistance to insulin reaches to the highest level and in the case, vitamin D have impact on the insulin secretion, probably with the decrease of vitamin D level, the level of insulin secretion will be reduced as well and this cause increase in the blood sugar. It was shown that there was significant and inverse correlation between serum levels of 25(OH)D in the first and second trimester of pregnancy and serum insulin levels at the end of pregnancy. In other words, the reduction of serum levels of 25(OH)D both at the beginning and at the end of pregnancy increase blood insulin levels in the pregnant women at the end of pregnancy. While serum levels of 25(OH)D in early pregnancy did not change serum insulin levels significantly. In this study, there was not a significant association between serum levels of25(OH)D in the first trimester of pregnancy and incidence of GDM in the second trimester. Although there was a significant association between decrease of serum levels of 25(OH)D in the second trimester of pregnancy and increase in postprandial blood sugar / glucose, the increase is not enough to make the test of diagnosis of GDM positive. In this study, there was no significant relationship between serum levels of 25(OH)D in the first and second trimester of pregnancy and calcium and serum albumin level (Tables 5, 6).

	First trimester (no=155)		Second trimester (no=64)	
	Correlation coefficient	P value	Correlation coefficient	p value
Fasting blood sugar(FBS)	0.238	*0.003	-0.196	0.123
Postprandial blood sugar(BS)	-0.085	0.291	-0.146	0.249
calcium	-0.077	0.344	0.224	0.077
albumin	0.038	0.635	0.117	0.360
HbA1C	-0.217	*0.007	0.249	*0.047
insulin	0.034	0.671	-0.311	*0.012

Table 4. Relationship between vitamin D and metabolic factors in the first trimester of pregnancy *p<0.05

Factor	Correlation coefficient	(p value)
Fasting blood sugar (FBS)	0.201-	0.115
OGTT	0.252-	0.047*
Calcium	0.192	0.132
Albumin	0.098	0.447
Hb A1C	0.005-	0.968
Insulin	0.246-	0.047*

Table 5. Relationship between vitamin D levels and metabolic factors in the second trimester of pregnancy *p<0.05

Type of test	mean±SD	p value
OGTT*(+)	7.7 ± 3.41	0.206
OGTT(-)	4.46±56	

Table 6. Vitamin D levels in the first trimester of pregnancy based on the incidence of pregnancy diabetes in the second trimester * (Blood sugar two hours after 75 g glucose intake≥155)

4. DISCUSSION

Vitamin D deficiency during pregnancy is associated with adverse outcomes. This is essentially an issue of health worldwide (32).The main sources of vitamin D in the body is diet and supplementations containing vitamin D and the production of this vitamin in the skin exposed to sunlight. Biologically active form of vitamin D is 1, 25- [OH] 2 D, while the 25- [OH] 2 D is a better indication of vitamin D status in the body as the main mechanism for the renal and non-renal production is 1,25- [OH] 2 D and have a higher half-life and higher blood concentrations than 1,25- [OH] 2 D (27). It is expected that normal level of vitamin D in pregnant women be 18-27 ng in the first trimester and 10-22 ng / ml in the second trimester (30). Accordingly, in the present study, of 155 pregnant women in the first trimester, 96.1 % have an optimal serum levels of 25(OH)D and 3.9% below the optimal level (ng / ml <18), respectively. In the second trimester ,of 64 pregnant women 90.6% have Optimal levels of serum levels of 25(OH)D and 9.4% lower than optimal levels (ng / ml <10), respectively. As it is described in the result of this study, decrease of levels of serum levels of 25(OH)D in the second trimester has been very significant comparing to the first trimester of pregnancy. This represents a severe reduction of serum levels of 25(OH)D in the second trimester compared to the first trimester of pregnancy in our study population. It seems that significant reduction of serum levels of 25(OH)D is much higher that can be justified by dilution of blood during pregnancy and following that, decrease of vitamin D concentration. In this study, no significant correlation was observed between serum levels of 25(OH)D and GDM among pregnant women at high and low risk. Unlike previous studies, this study

has been investigated pregnant women in different gestational age (first trimester and second trimester). Considering to this fact that the physiological condition of the pregnant person (such as blood volume in circulation, blood levels of HCG hormone, the expected levels of vitamin D, etc.) is different in each of this time period, result of this study is likely to be more precise than the similar studies in the past in the indication of the relationship between serum levels of 25(OH)D and blood sugar level of pregnant women. The climate, geography and culture of research community were in a way that reduces the amount of cooperation and participation of pregnant women. In this study, the relationship between serum levels of 25(OH) D and GDM was examined with the aim of effectiveness of vitamin D level on the incidence of this disease. Contrary to what some previous literatures were said on the prevalence of vitamin D deficiency in women with GDM than in normal pregnant women (32-34, 28), this study did not confirm such an outcome. In fact, no significant difference is observed a in serum levels of 25(OH)D in the pregnant women at risk of incidence of GDM in both the first and the second trimester of pregnancy comparing to the pregnant women lack of risk factor. In previous studies, it was only examined the relationship between the vitamin D level and the incidence of GDM and type 2 diabetes and it was not clearly examined the relationship between the level of this vitamin and risk factors of incidence of gestational diabetes. It was found that those pregnant women, who in the second trimester of pregnancy have higher blood sugar level after taking 75 g glucose, have lower serum levels of 25(OH)D.

It should also be noted that recent studies provide no evidence of association between serum 25OHD levels in the first trimester of pregnancy and gestational diabetes (35). In addition, in the second trimester of pregnancy, insulin levels were higher in women who had lower vitamin D levels. Rudnicki and Pedersen described previously considering to this fact that the prescription of vitamin D in pregnant women with gestational diabetes affect glucose and insulin levels and decreases blood sugar and blood insulin level expressed the mechanism of increase in sensitivity to insulin by vitamin D (33). Besides, the effect of vitamin D deficiency on the decrease of insulin secretion in mice and humans as well as the mechanisms of decrease function of cells of pancreatic beta and reduction in glucose tolerance had already been investigated (26). In this study, the incidence of GDM was measured through OGTT test by 75 g of glucose and measurement of blood sugar 2 hours after its intake and that was 14.1 %, which was higher than the prevalence reported in the medical texts (3% to 10%). In this study, there was a significant and inverse relationship between serum levels of 25(OH)D in early pregnancy (first trimester) and HbA1C levels at the same age of pregnancy (first trimester), whereas there is a significant and direct relationship between fasting plasma glucose (unlike some of the previous literature (36)). In other words, those who have lower levels of vitamin D at the time of pregnancy had higher levels of HbA1C, but lower level of fasting blood glucose levels in the first trimester of pregnancy, and vice versa. This is perhaps because at the beginning of pregnancy, secretion of hormones such as GH, ACTH, and cortisol influence blood sugar and interfere in the assessment of the relationship between vitamin D and blood sugar levels. Previously, several studies have investigated the relationship between vitamin D and HbA1C (37, 28). For example in 2009, a case-control study has carried out by Alamolhoda and colleagues on 60 pregnant women in the case group and 61 women with no history of disease as the control group (38). However, it was found that there is a inverse relationship between vitamin D levels in the first trimester and HbA1C level in the second trimester of pregnancy. Since HbA1C blood sugar is the best predictive factor of blood sugar, probably the measured HbA1C in the first trimester of pregnancy has been associated with blood sugar level pre-pregnancy and as far as these women has been referred to many gynecologists for their prenatal care, probably vitamins supplementation intake before doing experiments associated with the second trimester of pregnancy. Although in this study no clearly significant association between serum levels of 25(OH)D and risk of GDM was found, according to what was explained in this study, we can probably confirm partly what come in earlier literature in connection with significant relationship between low serum levels of 25(OH)D and increase in blood sugar level and insulin resistance in pregnancy.

5. CONCLUSION

Evidence suggests a possible role of vitamin D deficiency in the pathogenesis of type 2 diabetes. Changes in serum levels of 25(OH)D or function of this vitamin in the body maybe influence insulin allergy (allergic reaction to insulin), pancreatic beta cell function or both of them. In addition, it has been found that several genes are associated with vitamin D in the pathogenesis of this disease. Therefore, vitamin D and its related immune and metabolic pathways may be involved to the pathogenicity of type 2 diabetes through heredity and environment (39). The possible role of vitamin D in the type 2 diabetic is not completely clear. In addition, more information about this topic may identify new targets for treatment and prevention of this disease. Therefore requires further investigation about this case. Given that the percentage of incidence of pregnant women to vitamin D deficiency in this study was 14.1 % and it is higher than stated in previous studies, it seems that this issue requires special attention to the health of pregnant women in ChaharMahal and Bakhtiari province considering to the prevention of this disease. Regarding to what is said about the relationship between vitamin D, blood sugar and blood insulin levels in the second trimester of pregnancy and also due to the influence of the human placental lactogen (hpl) in competition with insulin in the second trimester, it seems that intake of vitamin D supplements can be very useful for pregnant women not to suffer from GDM.

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CONFLICT OF INTEREST: NONE DECLARED

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