Iran J Public Health, Vol. 50, No.1, Jan 2021, pp.139-145

Original Article

Differences of Serum 25- (OH) D3 Level and Adverse Pregnancy Outcomes between Women with Gestational Diabetes and Healthy Pregnant Women

Yingfeng JIANG, Jing ZHANG, Yuan LIU, Ting HUANG, Zheng CAO, *Xiangkui SHI

Department of Pharmacy, Xuzhou Maternity and Child Health Care Hospital, Xuzhou 221009, P.R. China

***Corresponding Author:** Email: xm5fwi@163.com

(Received 14 May 2020; accepted 10 Jul 2020)

Abstract

Background: The difference in serum 25-hydroxyvitamin D_3 (25-(OH) D_3) level between the gestational diabetes mellitus (GDM) and healthy pregnant women was analyzed, to provide the experimental evidence for the vitamin supplement in pregnant women, especially those with GDM.

Methods: Pregnant women (n=50) who received prenatal care in the Obstetrical Clinic of Xuzhou Maternity and Child Health Care Hospital in summer and winter of 2016 were enrolled. They were assigned to the summer GDM group, winter GDM group, summer control group and winter control group. The level of serum 25-(OH)D_3 was determined using immunochromatography.

Results: The mean level of serum 25-(OH)D_3 in pregnant women of four groups was lower than normal level. Compared with control group in corresponding season, the winter and summer GDM groups had significantly lower level of 25-(OH)D_3 than the winter and summer control groups (P<0.05). The winter GDM group had significantly lower level of 25-(OH)D_3 than the summer GDM group (P<0.05). The winter control group had significantly lower level of 25-(OH)D_3 than the summer control group (P<0.05). The percentage of deficient 25-(OH)D_3 level was the highest in winter GDM group. Vitamin D deficiency was severer in pregnant women with GDM than healthy pregnant women. In winter, vitamin D deficiency was severer than that in summer.

Conclusion: Pregnant women, especially those with GDM, should pay more attention to vitamin D supplementation.

Keywords: 25-hydroxyvitamin D_3; Vitamin D drops; Gestational diabetes mellitus; Pregnant women; China

Introduction

At present, with the widespread attention of screening diagnosis of obstetric gestational diabetes mellitus (GDM), the number of patients with gestational diabetes mellitus continues to increase (1). Gestational diabetes has become one of the most common medical complications during pregnancy. Pregnant women with gestational diabetes have significantly higher rates of miscarriages, premature delivery, hypertension during pregnancy, polyhydramnios, intrauterine fetal developmental abnormalities, and gigantic babies (2).

The general low level of vitamin D may be related to the high incidence of gestational diabetes (3, 4), because vitamin D can increase insulin sensitivity and improve insulin resistance. Not only vitamin D deficiency is seen during pregnancy common in China (5), but also in the Unit-

ed States, pregnant women with low vitamin D levels account for two thirds of all pregnant women (6). Serum 25-hydroxyvitamin D3 is the highest and most stable of several major metabolic derivatives of vitamin D in the blood. Serum 25 (OH) VD3 level is the best indicator of vitamin D deficiency in the body (7).

The purpose of this study was to determine the levels of serum 25-hydroxy vitamin D3 (25-(OH) D3) in pregnant women with diabetes mellitus and healthy pregnant women during the second trimester (24-28 weeks) of Xuzhou City, China in winter and summer. It provides reference for clinicians in Xuzhou City to guide pregnant women in different conditions to supplement vitamin D drops in different seasons, and provides basis for the study of the correlation between vitamin D deficiency and gestational diabetes.

Materials and Methods

Clinical data

Pregnant women who received antenatal care in Xuzhou Maternity and Child Health Care Hospital, Xuzhou, China from June to Aug 2016 (summer) and from Dec 2016 to Feb 2017 (winter) were enrolled. Pregnant women underwent the oral glucosetolerance test (OGTT) in our hospital from 24 to 28 weeks of pregnancy, those who failed the OGTT test were included in the GDM group, and those who passed the OGTT test in the control group.

All participants gave informed consent and the study was approve by Ethics Committee of the hospital.

From Jun to Aug 2016 (summer), 50 GDM pregnant women (summer GDM group) and 50 healthy pregnant women (summer control group) were randomly selected. Subjects in the GDM group did not have other metabolic diseases and other complications during pregnancy. The pregnant women in the control group did not have other complications, such as hypertension, liver and kidney dysfunction, autoimmune, and other chronic diseases. From Dec 2016 to Feb 2017 (winter), 50 random GDM pregnant women (winter GDM group) and 50 healthy pregnant women (winter control group) were enrolled according to the same criteria of summer.

ANOVA was used to compare the ages of pregnant women, the body mass index and the gestational week at the time of blood collection between different groups, and the differences were not statistically significant, suggesting the subjects in different groups were comparable. The pregnant women in the four groups were followed up by telephone to record the pregnancy outcomes (Table 1).

Table 1: Comparison of general data of 4 groups of pregnant women

Group	*Case*	*Age(yr)*	*Body mass index*	*Gestational week*
Summer GDM group	50	26.60±2.97	22.05±1.96	25.64±1.40
Winter GDM group	50	26.38±3.78	21.47±2.64	25.88±2.04
Summer control group	50	26.84±3.53	22.60±2.56	26.10±1.46
Winter control group	50	27.84±3.57	21.52±2.57	26.12±1.60
F		1.719	2.339	0.989
P		0.164	0.075	0.399

Procedures

GDM diagnostic criteria (8)

During the period of 24 to 28 weeks of pregnancy, 75 g of glucose was orally administered for

OGTT experiment. Before administration and 1 h and 2 h after administration, the blood glucose levels were lower than 5.1, 10.0, and 8.5 mmol/L respectively. GDM was diagnosed when any one of the blood glucose levels met or exceeded the above criteria.

Experimental method

Five ml of cubital venous blood of pregnant women was taken. After centrifugation at 3500 rpm for 5 min to collect serum, serum 25 (OH) VD3 level was detected by immunochromatographic assay. The kit was provided by Guangzhou Phicon Biotechnology Co., Ltd. Pregnant women underwent oral glucose tolerance test when the serum 25 (OH) VD3 level was detected.

Criteria for test result

At present, there is no standard for ideal serum 25 (OH) VD3 level, but experts define vitamin D deficiency as serum 25 (OH) VD3 level <50 nmol/L, vitamin D inadequacy as 50-75 nmol/L, healthy Vitamin D as 75- 375 nmol/L, and harmful vitamin D as > 375 nmol/L (9-10).

Adverse pregnancy outcomes (11)

Included premature delivery, polyhydramnios, oligohydramnios, premature rupture of membranes, preeclampsia, intrahepatic cholestasis during pregnancy, postpartum hemorrhage, etc.

Statistical analysis

SPSS 20.0 (Chicago, IL, USA) statistical software was used. The measurement data were expressed as mean ± standard deviation. Comparisons among multiple groups were analyzed by ANOVA. Pairwise comparisons between groups were performed by *t* test.

Results

Comparison of serum 25- (OH) D3 level of pregnant women in each group

The mean values of serum 25- (OH) D3 levels in the four groups of pregnant women were lower than the healthy level (75-375 nmol/L). In the analysis of variance of 25- (OH) D3 levels in the four groups, the differences of the 25- (OH) D3 levels were statistically significant (P <0.05). Compared with the control group in the corresponding season, the 25- (OH) D3 levels in the winter GDM group and summer GDM group were significantly lower than those in the winter and summer control groups, respectively (P <0.05). The level of 25- (OH) D3 in the winter GDM group was significantly lower than that in the summer GDM group (P <0.05), and the level of 25- (OH) D3 in the winter control group was significantly lower than that in the summer control group (P <0.05) (Table 2).

Table 2: Comparison of serum 25- (OH) D3 level of pregnant women in each group ($\bar{x}\pm s$, nmol / L)

Group	*Case*	*25- (OH) D3 level*	F	P
Summer GDM group	50	49.94±7.94*	12.865	0.000
Winter GDM group	50	40.41±13.46*#		
Summer control group	50	55.23±12.06		
Winter control group	50	46.17±14.72▲		

Note: * indicates compared with the control group in the corresponding season, P <0.05; # indicates compared with the summer GDM group, P <0.05; ▲ indicates compared with the summer control group, P <0.05

Comparison of the different levels of serum 25- (OH) D3 in pregnant women in each group

The proportion of 25- (OH) D3 inadequacy and deficiency in pregnant women in each group was as high as 82% to 92%, and the inadequacy and deficiency in winter were higher. The proportion of 25- (OH) D3 deficiency in pregnant women with gestational diabetes was higher, but the difference was not statistically different (Table 3).

Table 3: Composition ratio of vitamin D levels in each group (n, %)

Group	*Case*	*Healthy (75-375 nmol/L)*	*Inadequacy (50-75 nmol/L)*	*Deficiency (<50nmol/L)*
Summer GDM group	50	6(12)	22(44)	22(44)
Winter GDM group	50	4(8)	17(34)	29(58)
Summer control group	50	9(18)	22(44)	19(38)
Winter control group	50	7(14)	25(50)	18(36)

Comparison of adverse pregnancy outcomes of pregnant women in each group

The adverse pregnancy outcomes of each group of pregnant women were followed. There were two cases of premature delivery in the summer GDM group, 1 case of premature delivery and 2 cases of polyhydramnios in the winter GDM group, 1 case of premature rupture of the membrane in the summer control group, and 1 case of premature rupture of the membrane in the winter control group. The vitamin D levels of pregnant women with adverse pregnancy outcomes in each group were insufficient. The incidence of adverse pregnancy outcomes was higher in the summer GDM group and the winter GDM group, but there was no statistical difference compared with the corresponding control groups. The differences are shown in Table 4.

Table 4: Pregnancy outcomes (n, %)

Group	*Case*	*Adverse outcomes*	*Term delivery*
Summer GDM group	50	2(4)	49(96)
Winter GDM group	50	3(6)	47(94)
Summer control group	50	1(2)	49(98)
Winter control group	50	1(2)	49(98)

Discussion

The important role of vitamin D in regulating calcium balance and maintaining bone health has been recognized. Due to the increasing awareness of vitamin D receptor (VDR) in the medical community and the widespread distribution of vitamin D, the non-classical effects of vitamin D have attracted more and more attention. Maternal vitamin D deficiency or inadequacy during pregnancy is closely related to a series of adverse pregnancy outcomes including premature delivery, overdue delivery, preeclampsia, and gestational diabetes (12, 13). The occurrence of adverse pregnancy outcomes in pregnant women with gestational diabetes is related to blood glu-

cose control during pregnancy (14, 15). The well-controlled blood glucose level during pregnancy significantly reduce the incidence of adverse pregnancy outcomes and improve mother and infant health. Vitamin D levels in pregnant women with adverse pregnancy outcomes in each group were insufficient. The incidence of adverse pregnancy outcomes was higher in the summer GDM group and the winter GDM group, but there was no statistical difference compared with the corresponding control groups. That may be related to the insufficient sample size of this study. Multi-center, large-sample follow-up studies are recommended in the future, aiming at the association between vitamin D level in pregnant women and the adverse pregnancy outcomes, to draw more conclusions.

The deficiency or inadequacy of 25- (OH) D3 in the serum of pregnant women has certain association with gestational diabetes (16,17). In this study, 25- (OH) D3 levels in the winter and summer GDM groups were significantly lower than those in the winter and summer control groups (P <0.05), suggesting that the pregnant women with diabetes mellitus in Xuzhou City have more sever vitamin D deficiency and deficiency than healthy pregnant women. The phenomenon has been reasonably explained in the previous research as vitamin D reduces insulin resistance and increases insulin secretion from beta cells (18-21). In response to the above explanation, a confirmatory study has been recently conducted, suggesting that deficiency or inadequacy of vitamin D during pregnancy may cause abnormal glucose tolerance in pregnant women, and that oral administration of certain doses of vitamin D can effectively interfere with the development of gestational diabetes (22). However, the above research is still in the observation and research stage in China. Whether oral administration of vitamin D can prevent gestational diabetes still need to be verified by a multi-center study with a large sample size. It is hoped that the future research may play a role in alleviating the increasing incidence of gestational diabetes in recent years.

The 25- (OH) D3 levels of diabetic pregnant women and healthy pregnant women in winter were significantly lower than those in summer respectively (P <0.05). This is because most of the vitamin D in the body is synthesized by the skin's absorption of ultraviolet rays from the sun. It has been reported that the sun exposure time and UV intensity are different in different latitudes, and the sun exposure time and UV intensity are different in different seasons at the same latitude (23). Xuzhou City is located in the southeast of the North China Plain, between 116 ° 22 ' to 118 ° 40 ' east longitude and 33 ° 43 ' to 34 ° 58 ' north latitude. Xuzhou enjoys a temperate monsoon climate, with four distinct seasons. Compared with summer, winter is colder and the light is reduced. People wear thicker clothes, and only the face is exposed. People in winter has less outside activities, especially pregnant women who prefer driving or taxi in winter. As a result, there is very little chance of exposure to sunlight, and the synthesis of vitamin D is relatively reduced. On the contrary, the production of vitamin D in summer is significantly increased. Therefore, vitamin D deficiency can be effectively corrected by more exposure to sunlight. Those with lower vitamin D levels in the body, especially in winter, can take vitamin D drops, which can also correct the vitamin D deficiency in pregnant women.

Conclusion

Vitamin D deficiency during pregnancy is closely related to gestational diabetes, providing reference for study of the association between vitamin D deficiency and gestational diabetes and whether gestational diabetes could be prevented through oral vitamin D drops. It is hoped that this research might attract attention to the vitamin D level of pregnant women. It is recommended that pregnant women, especially pregnant women with gestational diabetes, should be tested for the serum 25- (OH) VD3 level and learn the vitamin D level in the body. The clinicians could instruct pregnant women to supplement vitamin D drops, and encourage pregnant women to take appropriate outdoor activities.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Acknowledgements

No funding was received.

Conflict of interest

The authors declare that there is no conflict of interest.

References

1. Leng J, Shao P, Zhang C, et al (2015). Prevalence of gestational diabetes mellitus and its risk factors in Chinese pregnant women: a prospective population-based study in Tianjin, China. *PLoS One,* 10(3): e0121029 .
2. Garcia-Vargas L, Addision SS, Nistala R, et al (2012). Gestational diabetes and the offspring:implications in the development of the cardiorenal metabolic syndrome in offspring. *Cardiorenal Med,* 2(2): 134-142.
3. Lacroix M , Battista MC , Doyon M , et al (2014). Lower vitamin D levels at first trimester are associated with higher risk of developing gestational diabetes mellitus. *Acta Diabetol,* 51(4): 609-616.
4. Li SY, Lv XF, Tian HM (2011). Vitamin D metabolism and gestational diabetes. *Chinese J Diabetes Mellitus,* 3: 441-443 .
5. Zhang MX, Li L (2015). Situation of 25-hydroxy Vitamin D deficiency in the first and second trimester of pregnant women. *Chinese J Clin Res,* 28: 1637-1639 .
6. Lerchbaum E, Obermayer-Pietsch B (2012). Vitamin D and fertility: a systematic review. *Eur J Endocrinol,* 166(5): 765-778.
7. De Paula FJ, Rosen CJ (2012). Vitamin D safety and requirements. *Arch Biochem Biophys,* 523(1): 64-72.
8. Obstetrics Section of the Obstetrics and Gynecology Branch of the Chinese Medical Association (2014). Guidelines for the diagnosis and treatment of pregnancy with diabetes. *Chinese J Obstet Gynecol,* 49: 561-569.
9. Yang Y, Tian HM, Li PQ, et al (2011). Association of serum 25-hydroxyvitamin D3 with islet β cell function and insulin resistance in new onset type 2 diabetics. *Chinese J Diabetes Mellitus,* 3: 314-318.
10. Holick MF, Binkly NC, Bischoff-Ferrari HA, et al (2011). Evaluation, treatment, and prevention of Vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab,* 96(7): 1911-1930.
11. Li YY, Zhang HK, Li ZL, Zhang CY (2014). Current status of adverse pregnancy outcomes and their influencing factors. *Chinese J Woman and Child Health Res,* 25: 577-580.
12. Lapillonne A (2010). Vitamin D deficiency during pregnancy may impair maternal and fetal outcomes. *Med Hypotheses,* 74(1): 71-75 .
13. Nassar N, Halligan GH, Roberts CL, et al (2011). Systematic review of first trimester vitamin D normative levels and outcomes of pregnancy. *Am J Obstet Gynecol,* 205(3): 208.e1-7 .
14. Sun Y, Yang H, Sun W J (2008). Risk factors for pre-eclampsia in pregnant Chinese women with abnormal glucose metabolism. *Int J Gynaecol Obstet,* 101(1): 74-76.
15. Fan Z, Yang H, Gao X, et al (2006). Pregnancy outcome in gestational diabetes. *Int J Gynecol Obstet,* 94(1): 12-16.
16. Bentley-Lewis R, Huynh J, Xiong G, et al (2015). Metabolomic profiling in the prediction of gestational diabetes mellitus. *Diabetologia,* 58(6): 1329-1332.
17. Shand AW, Nassar N, Von Dadeiszen P, et al (2010). Maternal vitamin D status in pregnancy and adverse pregnancy outcomes in a group at high risk for pre-eclampsia. *BJOG,* 117(13): 1593-1598 .
18. Mozaffari-Khosravi H , Hosseinzadeh-Shamsi-Anar M , Salami MA , et al (2012). Effects of a single post-partum injection of a high

dose of vitamin D on glucose tolerance and insulin resistance in mothers with first-time gestational diabetes mellitus. *Diabet Med,* 29(1): 36-42 .

19. Kayaniyil S, Retnakaran R, Harris SB, et al (2011). Prospective associations of vitamin D with β-cell function and glycemia the PROspective Metabolism and ISlet cell Evaluation (PROMISE) cohort study. *Diabetes,* 60(11): 2947-2953 .
20. Guo J, Xiao Z, Xue X, et al (2013). 25-Hydroxyvitamin D is closely related with the function of the pancreatic islet β cells. *Pak J Med Sci,* 29(3): 809- 813 .
21. Jeddi S, Syedmoradi L, Bagheripour F et al (2015). The effects of vitamin D on insulin release from isolated islets of rats. *Int J Endocrinol Metab,* 13(1): e20620 .
22. Parlea L, Bromberg IL, Feig DS, et al (2012). Association between serum 25-hydroxyvitamin D in early pregnancy and risk of gestation diabetes mellitus. *Diabet Med,* 29(7): e25-32 .
23. Mao X, Zheng H, Liu Z, et al (2014). Analysis of 25(OH)D serum concentrations of hospitalized elderly patients in the Shanghai area. *PLoS One,* 9(3): e90729.