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Role of vitamin D on gestational hypertension, diabetes mellitus, timing and mode of delivery

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Abstract. – OBJECTIVE: To determine the efficacy of vitamin D (VD) in preventing the development of gestational diabetes mellitus (GDM) and pregnancy-induced hypertension (PIH). The secondary purpose is to investigate the effect of VD on the mode and time of delivery.

PATIENTS AND METHODS: A vitamin D value of <20 ng/mL during pregnancy is considered a deficiency according to the Endocrine Society, and 400-600 IU/day VD replacement is recommended. Forty patients whose serum VD levels were below 20 ng/mL during routine pregnancy follow-up and who were planned for VD replacement therapy were included in the study. They were divided into two equal groups with 20 patients in each group. Twenty pregnant women with serum VD levels greater than 20 ng/mL were considered as the control group. While 400 IU/day VD replacement was applied to the patients in Group 1, 600 IU/day VD was given to Group 2. Group 3 consisted of control patients who did not undergo VD replacement. VD replacement was continued from the 14th week of pregnancy until delivery. Each group of participants was screened with a 50-g GCT at 24-28 weeks of gestation. Following 50-g GCT if serum glucose level was found >140 mg/dL, patients underwent 100-g OGTT. GDM was diagnosed in the presence of at least two of the following results: fasting serum glucose ≥92 mg/dL and/or 1-hour glycemia ≥180 mg/dL, and/or 2-hour glycemia ≥153 mg/dL. PIH was defined as systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg. Patients in each group delivered by cesarean section or normal vaginal route. In addition to the incidence of PIH and GDM, the time and mode of delivery were recorded.

RESULTS: PIH was detected in two patients in each of the 400 IU/day and 600 IU/day vitamin D replacement groups (10%). In the control group, PIH developed in 3 patients (15%). Although PIH was detected in an extra case in the control group, no significant difference was found between the replacement group and the control group in terms of PIH (p<0.44). While GDM was not detected in the 400 IU/day vitamin D group, GDM was detected in one patient (5%) in the 600 IU/day vitamin D group. No case of GDM was found in the control group either. There was no significant difference between the VD replacement and the control groups in terms of GDM rates. No significant difference was found between the VD replacement and the control groups in terms of mode of delivery. While the C/S ratio was 65% in the 400 IU/day vitamin D group, this ratio was 75% in the 600 IU/day vitamin D group. There was an insignificant trend of increase in C/S ratios in the group given 600 IU/day of vitamin D. The C/S ratio of the control group, which could not be given VD replacement, was found to be 70%.

CONCLUSIONS: VD replacement therapy during pregnancy does not prevent the development of PIH and GDM, and does not significantly contribute to the time and mode of delivery.

Key Words:
Vitamin D, Pregnancy, GDM, PIH, Delivery.

Introduction

Vitamin D (VD) is a basic secosteroid hormone that acts through its specific receptors responsible for calcium and phosphate homeostasis during pregnancy[1]. Changing serum levels of VD lead to many endocrine and vascular pathologies, including hypertension and gestational diabetes during pregnancy. Disturbances in calcium and phosphate metabolism are one of the most important causes of endothelial damage and vascular tone pathologies. Endothelial damage is the initiator of vascular pathologies such as pregnancy-induced hypertension (PIH) and preeclampsia. It has been known for a long time that VD levels decrease during pregnancy compared to non-pregnant women[2]. Impaired immunomodulation and inflammatory pathway activations in VD deficiency may lead to insufficient placentation, endothelial dysfunction as well as hypertensive disease of

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pregnancy. Similarly, insulin resistance and beta cell dysfunction develop in VD deficiency, which increases the tendency to diabetes[3].

The results of studies investigating the relationship between VD deficiency and the development of gestational diabetes mellitus (GDM) during pregnancy are heterogeneous[4]. Since immunomodulatory and inflammatory pathway functions are not fully realized in VD deficiency, glucose tolerance and insulin sensitivity are also impaired. Consistent with this, it has been reported that serum VD levels of GDM patients are significantly lower than those of normoglycemic patients[5]. Moreover, it is also known that the risk of GDM is around 50% in patients with VD deficiency[6,7]. Contrary to these findings, some researchers could not find a relationship between VD levels and the development of GDM[3]. A Cochrane meta-analysis and a clinical trial indicated that VD replacement had no preventive effect on the risk of developing GDM[8,9]. Another comprehensive analysis reported that VD replacement reduces the risk of GDM[10].

Since the role of calcium in endothelial function and vascular tone has been known for a long time, it has been thought that VD deficiency also plays a role in the development of gestational hypertension. In particular, the detection of the relationship between the development of preeclampsia and low calcium intake suggests that VD is an important steroid hormone in the regulation of blood pressure in pregnancy[11]. By regulating placental vascular endothelial growth factor (VGEF) synthesis VD replacement in pregnancy prevents hypertension[12]. The immunomodulatory effect of VD prevents feto-placental rejection and enables healthy placentation and blood pressure regulation[4]. Apart from PIH and GDM, VD status can also affect timing and mode of delivery. Supporting this, it has been reported that cesarean section rates increase in VD deficiency[13]. Although high-dose VD replacement has been reported to reduce cesarean delivery rates[14], many studies[8,10] have failed to establish a relationship between VD status and cesarean section rates. If the risk of GDM, HT, and cesarean delivery really increases in VD deficiency, these pathologies are expected to improve with VD replacement. This study was planned to determine the efficacy of VD replacement therapy in preventing the development of GDM and pregnancy-induced hypertension. The secondary aim of the study is to investigate the effect of VD replacement on the mode and time of delivery.

Patients and Methods

A vitamin D value of <20 ng/mL during pregnancy is considered a deficiency according to the Endocrine Society, and 400-600 IU/day VD replacement is recommended. Forty patients whose serum VD levels were below 20 ng/mL during routine pregnancy follow-up and who were planned for VD replacement therapy were included in the study. Participants were selected among pregnant women who applied to the Obstetrics outpatient clinic of Private Gözde Akademi Hospital (Malatya). Participants were divided into two equal groups with 20 patients in each group. Twenty pregnant women with serum VD levels greater than 20 ng/mL were considered as the control group. While 400 IU/day VD replacement was applied to the patients in Group 1,600 IU/day VD was given to Group 2. Group 3 consisted of control patients who did not undergo VD replacement. VD replacement was continued from the 14th week of pregnancy until delivery. Forgotten doses were taken again in the first 5 days. All of the participants completed the study.

Participants were randomly selected among primiparous or multiparous pregnant women. The groups consisted of women older than 20 years of age and younger than 35 years of age with a spontaneous singleton pregnancy. Multiple pregnancies and IVF/ICSI pregnancies were not included in the study. Gestational age and estimated delivery date were calculated according to the last menstrual period or first USG records. Patients who were allergic to VD or who had taken drugs containing VD in the last three months were not included in the study. Those with hypercalcemia and kidney stone risk, those with partroid disease, and those with kidney pathology causing proteinuria were excluded from the study. Those with a history of hypertension or diabetes before pregnancy were excluded from the study. Those with a history of peeclampsia or gestational diabetes in their previous pregnancies were excluded from the study. Patients who were taken to C/S due to maternal request were excluded from the study. The primary outcome of the study was to investigate whether VD replacement has a protective effect on the formation of GDM and gestational hypertension. The secondary outcome was to determine whether the VD replacement affects the timing and mode of delivery. The study was conducted according to the Declaration of Helsinki. Ethical consent was obtained from the Ethics Committee of SBU Gazi Yaşargil Training and Research Hospital (Ethics approval No.: 2022/152).

All patients were followed up with strict antenatal care. Blood pressure was measured and recorded on a monthly basis. Spot urine protein analysis was performed in cases with hypertension. In cases where necessary, 24-hour urine was collected and protein values were checked. Each group of participant were screened with a 50-g GCT at 24-28 weeks of gestation. Following 50-g GCT if serum glucose level was found >140 mg/dL, patients underwent 100-g OGTT. GDM was diagnosed in the presence of at least two of the following results: fasting serum glucose ≥92 mg/dL and/or 1-hour glycemia ≥180 mg/dL, and/or 2-hour glycemia ≥153 mg/dL. Gestational hypertension (PIH) was defined as systolic blood pressure (SBP) >140 mmHg and diastolic blood pressure (DBP) >90 mmHg[15]. Patients in each group delivered by cesarean section or normal vaginal route. In addition to the incidence of PIH and GDM, the time and mode of delivery were recorded.

Statistical Analysis

All analyses were carried out using SPSS for Windows version 21 (IBM Corp., Armonk, NY, USA). Normality of distribution was assessed with the Kolmogorov-Smirnov test. Continuous variables were analyzed using parametric One-Way ANOVA test data are presented as mean ± SD or percentage. A p-value <0.05 was considered statistically significant.

Results

Table I shows demographic, obstetrics, and fetal characteristics of the VD replacement and control group. The age, gravida and parity of the VD replacement and control groups were similar. Serum VD levels of the patients who were planned to be replaced were recorded as 13.9±4.07 ng/mL and 14.5±2.09 ng/mL. VD levels were similar between the replacement groups (p<0.30). These values are considered as VD deficiency according to Endocrine Societey Proposal. The VD level of the patients in the control group was found to be 23.2±4.02. The VD levels of the patients in the control group were found to be significantly higher than in both VD replacement groups (p<0.01). Maternal serum VD levels were not evaluated at the time of delivery. The gestational age at the time of delivery of the patients who underwent VD replacement and the patients in the control group was found to be similar. All of the patients who were given or not given VD replacement gave birth at term. Preterm labor was not seen in neither the replacement group nor the control group. Similarly, fetal birth weight of the replacement and control groups were similar. Although fetal birth weight was slightly higher in patients given 600 IU/day vitamin D replacement compared to the group given 400 IU/day, the difference was not significant.

PIH was detected in two patients in each of the 400 IU/day and 600 IU/day vitamin D replacement groups (10%). In the control group, PIH developed in 3 patients (15%). Although PIH was detected in an extra case in the control group, no significant difference was found between the replacement group and the control group in terms of PIH (p<0.44). While GDM was not detected in the 400IU/day vitamin D group, GDM was detected in one patient (5%) in the 600IU/day vitamin D group. No case of GDM was found in the cont-

Table I. Demographic, obstetrics, and fetal characteristics of vitamin D replacement and control group.

	Group 1 (n=20) 400IU/day Vitamin D	Group 2 (n=20) 600 IU/day Vitamin D	Group 3 (n=20)
Age (years)	27.6±5.03	28.3±3.50	27.1±4.11
VD level (ng/mL)*	13.9±4.07	14.5±2.09	23.2±4.02
Gravidity	2.80±1.02	2.87 ±1.03	2.43±0.20
Parity	1.78 ±0.33	1.67±0.55	1.43±0.21
Gestational age at birth (weeks)	36.5±6.44	37.3±3.04	36.8±5.01
Fetal birth weight (gr)	2840.8±302.6	2887.7±230.5	2790.5±320.4
GDM (n/%)	0	1 (5%)	0
PIH (n/%)	2 (10%)	2 (10%)	3 (15%)
Mode of delivery (n/%)	13 C/S (65%), 7 vaginal birth (35%)	15 C/S (75%), 5 vaginal birth (25%)	14 C/S (70%), 6 vaginal birth (30%)

*: Indicates the existence of statistical significance between groups (One-way ANOVA). Parameters without an asterisk indicate that there is no statistical significance between groups.

rol group either. There was no difference between the replacement groups and the control group in terms of GDM rates. No significant difference was found between the VD replacement and the control groups in terms of mode of delivery. While the C/S ratio was 65% in the 400 IU/day vitamin D group, this ratio was 75% in the 600 IU/day vitamin D group. There was an insignificant trend of increase in C/S ratios in the group given 600 IU/day of vitamin D. The C/S ratio of the control group, which could not be given VD replacement, was found to be 70%.

Discussion

It has long been accepted that vitamin D deficiency during pregnancy increases the occurrence of certain diseases related to calcium and phosphate metabolism. Fetal growth retardation, pregnancy-induced hypertension (PIH), preeclampsia, and gestational diabetes (GDM) are some diseases thought to be associated with VD deficiency[16]. Moreover, it has been stated that VD deficiency affects timing and mode of delivery and increases cesarean delivery rates. However, the results of studies investigating the relationship between VD deficiency and these pathologies are not homogeneous[6,7]. In this study, we investigated how the rates of GDM, PIH, and cesarean section differed in patients who underwent VD replacement compared to patients who did not undergo replacement[4].

It has been claimed that VD has a role in the regulation of vascular tone due to the increased risk of endothelial dysfunction and preeclampsia in calcium deficiency. Consistent with this, VD replacement has been reported to regulate blood pressure by increasing the release of angiogenic factors from the placenta[17]. Similarly, it was emphasized that the risk of preeclampsia increases significantly in VD deficiency[18-20]. However, despite all these positive effects of VD, a recent metaanalysis reported that VD replacement did not have a significant effect on PIH[10]. Our results showed that VD replacement applied during pregnancy did not have a significant effect on the incidence of PIH. The doses we use for VD replacement are the lowest doses considered safe in pregnant women by the Endocrine Society[18]. PIH was detected in only two patients (10%) in both groups who underwent VD replacement. In patients who did not receive VD replacement, PIH was detected in three patients (15%). Despite one excess of PIH in the control group, the incidence of PIH in the replaced and non-replaced groups was similar. Giving 400 IU/day or 600 IU/day VD did not cause a significant change in the incidence of PIH. However, this result does not mean that VD does not have a positive effect on the placental and systemic vascular bed. The doses we use may not be sufficient for the regulation of vascular tone. Studies involving higher replacement doses may reveal a possible relationship between VD dose and vascular tone. The development of PIH in 10% of the replacement patients suggests that the incidence of PIH remains at the normal population level and that VD replacement does not provide any additional benefit[18-21].

Both immunomodulatory and anti-inflammatory effects of VD prevent the development of diabetes by preserving beta cell functions like myo-inositol plus α-lactalbumin[21]. In VD deficiency, the cytotoxic effect of T cells increases, leading to beta cell destruction and an increased tendency to diabetes[3]. Serum VD levels of patients with GDM have been reported to be significantly lower than normoglycemic controls[7]. Similarly, the risk of developing GDM has been noted to be higher in those with VD deficiency. However, many observational studies have failed to establish a link between VD levels and the development of GDM[20,22]. Moreover, it has been reported that VD replacement is not effective in preventing the development of GDM[8]. In the present study, GDM was not detected in any of the patients who received 400 IU/day VD replacement, whereas GDM was detected in only one patient in the 600 IU/day vitamin D group. GDM was not detected in the control group. Consistent with the literature data, VD replacement did not significantly reduce the risk of developing GDM compared to the control group. While GDM was detected in the high-dose VD replacement group, the absence of GDM in low-dose VD replacement patients suggests that VD does not improve pancreatic beta cell dysfunctions. If VD had an immunomodulatory effect on beta cells, GDM would not have been detected in the 600 IU/day replacement group. However, since GDM formation is a pathology with multifactorial etiology, it cannot be expected to improve with VD replacement alone. Comprehensive studies[12-14] that evaluate other risk factors for GDM and compare the effect of different VD doses are essential to make a clearer interpretation.

We believe that delivery mode should be as natural as possible. Although it was not found safe, we are in a period where even water birth is dis-

cussed[23,24]. An attempt has been made to establish a connection between VD satus and mode and timing of delivery. The mechanism behind this idea is the role of the VD in the contraction and autonomic control of the pelvic muscles. It has been suggested that cesarean section rates increase because the decreased pelvic muscle strength due to VD deficiency cannot provide sufficient propulsion for normal delivery[20,25]. Although cesarean rates have been reported to decrease with high-dose VD replacement (4,000 IU/day), a meta-analysis showed that VD replacement had no effect on cesarean delivery rates[8]. We found the incidence of cesarean section to be 65% in the group given 400 IU/day VD, and 75% in the group given 600 IU/day VD. The cesarean rate of the non-replacement group was 70%. There was no difference in cesarean section rates between the replacement and control groups. The increase in cesarean rates due to maternal request in the last two decades prevents us from clearly evaluating the effect of VD on cesarean rates. Even if VD levels reach normal levels after replacement, the patient or physician may determine the delivery method as cesarean section. Therefore, the effect of VD on pelvic muscle strength alone cannot be a determinant of the mode of delivery. Similarly, no significant difference was found between the birth weeks and fetal birth weights of the VD replacement group and the control group. Although some researchers say that low VD levels lead to chronic inflammation and cause preterm delivery, most studies have failed to establish a link between VD and time of delivery[20,21,26]. Although there is a positive link between VD levels and birth weight, birth length and calvarium development, many studies have not been able to confirm this relationship[27]. Although VD replacement increases fetal bone content, its effect on fetal weight is unclear. Because fetal weight is a multicomponent condition, including paternal genetics and environmental factors, it is unusual for VD to determine fetal weight alone[4].

Conclusions

Despite the small number of cases, our study provides important data in terms of examining many obstetrical complications associated with VD deficiency. VD replacement therapy during pregnancy does not prevent the development of PIH and GDM, and does not significantly contribute to the time and mode of delivery. More comprehensive investigation of the relationship between high-dose VD replacement and obstetric complications will provide a clearer answer to the question of whether we should replace in pregnant women with low VD values.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Autors' Contributions

Material preparation was performed by Fatma Cagıran and Zercan Kali. Data were collected by Fatma Cagiran and Zercan Kali. All authors contribited to statistical analysis. The first draft was written by Fatma Cagıran. All authors approved the final version of the manuscript.

Ethics Approval

The study was conducted according to the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of SBU Gazi Yaşargil Training and Research Hospital (No.: 2022/152).

Data Availability

Data can be accessed by the joint consent of all authors.

Informed Consent

Informed consent was obtained from all participants.

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