Low-dose versus high-dose vitamin D supplementation and pregnancy outcome in gestational diabetes

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Abstract

Objective: To compare pregnancy outcome among pregnant women with gestational diabetes mellitus (GDM) who received low-dose supplementary vitamin D, high-dose vitamin D, or placebo.

Methods: In this parallel double-blinded randomized clinical trial, 128 pregnant women with GDM and low serum 25-[OH] D (< 30 ng/mL) were included. They were randomly divided to receive low-dose vitamin D (400 IU tablet once daily, 64 subjects) or high-dose (50,000 IU twice; first at the start of the study and then 21 days later, 64 subjects). In the control group, 64 subjects with GDM but normal serum 25-[OH] D were included. Pregnancy outcome including neonatal anthropometric indices (birth weight, height, and head circumference), hypoglycemia, Apgar scores at minutes 1 and 5, and admission due to pathologic jaundice were recorded.

Results: Mean (±SD) newborn birth height was 50.13 (±1.85) cm which was significantly higher compared to the low-dose group (49.38± 2.18 cm); P= 0.02. It was also higher when compared to the control group (49.02± 2.02); P= 0.002. No significant difference existed among the groups regarding birth weight and head circumference. Pathologic jaundice, hypoglycemia and Apgar score at minutes 1 and 5 were recorded.

Conclusion: Vitamin D supplementation either at low doses or high doses did not have considerable effect on pregnancy outcome in pregnant women with GDM. The only variable which was higher in the high-dose group was the newborn birth height.

Key words: 25-hydroxyvitamin D; gestational diabetes; dietary supplements; pregnancy

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Introduction

Vitamin D is an essential nutrient during pregnancy and has a role in fetal skeletal development and growth (1). Excess calcium required for fetal bone growth in pregnancy necessitates sufficient levels of maternal vitamin D (2). Besides, vitamin D contributes to successful implantation via its immunomodulatory effects (3). Hence, maternal serum vitamin D levels increase to the end of the pregnancy to promote maternal and fetal health (4).

Vitamin D insufficiency/deficiency during pregnancy is a common clinical condition in many countries (5). Several studies have found associations between vitamin D deficiency and maternal and fetal adverse outcomes including pre-eclampsia(6), increased risk of infection, newborn birth size, and mental outcome (7, 8). But, such consequences have not been reported consistently in all studies (9).

One of the vitamin D deficiency complications observed in some studies is maternal higher susceptibility to develop gestational diabetes mellitus (GDM) (10, 11). GDM is manifested by insulin resistance and glucose intolerance and is believed to affect about 6 to 7% of pregnancies in the US (12). In addition to higher risk of developing type II DM later in life in mothers with GDM, short-term complications include polyhydramnios, stillbirth, and macrosomia among others (13).

Low vitamin D levels have been suggested as an independent factor for impaired glucose control and development of GDM and lower levels of vitamin D had an inverse correlation with serum glucose (4, 14, 15). Mothers who were diagnosed with GDM on glucose screening tests at 24-28 weeks of gestation had significantly lower 25-hydroxyvitamin D (25-[OH] D) levels (16). This is probably due to the relation between calcitriol level and beta cell function of the pancreas (17). However, there is controversy in the literature regarding vitamin D level and GDM (18). Some studies reported that vitamin D hypovitaminosis does not relate with either GDM development or pregnancy outcomes (19).

These observations have resulted in studies to investigate the supplemental vitamin D in mothers with normal glucose tolerance (20-23) and GDM (24, 25) to find any beneficial effect of such intervention on glucose level as well as lipid profile, inflammation, and neonatal anthropometric indices. However, studies on mothers with GDM are scarce and not sufficient trials have been conducted to elucidate the exact role of vitamin D supplementation on pregnancy outcome. In addition, the appropriate vitamin D dose is not clear yet (23). Therefore, it seems that further studies are required to answer these ambiguities regarding vitamin D, GDM, and neonatal outcome. This study was done with the objective of determining the effect of two vitamin doses (low-dose vs. high-dose) on pregnancy outcome in mothers with GDM.

Materials and Methods

Study Design and Setting

This was a parallel double-blinded randomized clinical trial comparing low-dose, high-dose, and no vitamin D supplementation on pregnancy outcomes among a sample of mothers with GDM. The patients with low serum 25-[OH] D were randomly (using simple randomization method by random table) were assigned to receive low-dose or high-dose vitamin D supplementation. The control group consisted of mothers who had GDM, but their vitamin D level was normal. This study was carried out from 2015 to 2016 at the Diabetes Research Center, Kermanshah.

Study population

Mothers diagnosed with GDM at gestational weeks 24 to 28 comprised the study population. GDM diagnosis was made considering presence of two of the three criteria: fasting blood glucose > 93 mg/dL, 1-hour oral glucose tolerance test (OGTT)> 180 mg/dL, and 2-h OGTT > 153 mg/dL. Low vitamin D level was considered as serum 25-[OH] D levels of < 30 ng/mL.

Eligibility criteria

Inclusion criteria consisted of pregnant mothers with age range of 18 to 35 years, gestational age of 24 to 34 weeks. Exclusion criteria were smoking, using alcohol, taking medications including corticosteroids, lithium, isoniazid, ketoconazole, anti-seizure medications, supplemental vitamin D and calcium in the preceding 6 months, cardiac, renal, hepatic conditions, malabsorption, malignancy, thyroid and parathyroid diseases, and chronic inflammation. Also, those who had not taken prenatal supplements regularly, pre-eclampsia, stillbirth, pre-term labor, placental abruption, need to administer insulin, long immobility were not included.

Sample

Sampling method was consecutive method and considering the neonatal height as the main dependent variable, the sample size was calculated as 64 subjects in each of the three groups.

Intervention

In the low-dose vitamin D group, oral vitamin D3 (400 IU tablet once daily, Zahravi Pharmaceutics Co., Tabriz, Iran), was administered until the 36th week of gestation. In the high-dose group, vitamin D3 pearl (50,000 IU daily, Zahravi Pharmaceutics Co., Tabriz, Iran) was administered twice (first at the start of the study and then 21 days later). The control group which consisted of mothers with GDM and normal 25-[OH] D level (> 30 ng/mL) received a placebo pearl similar to vitamin D pearl twice as in the high-dose group.

Data Collection

At first, serum 25-[OH] D was measured. The patients were followed until the time of delivery. On the 10th day postpartum the subjects were visited to collect the data about pregnancy outcome. The neonatal anthropometric indices including birth weight (macrosomia was defined

as > 4,000 gr), height, and head circumference, glucose level (to check neonatal hypoglycemia) as well as Apgar scores at minutes 1 and 5 using the recorded data, was documented. Also, admission due to pathologic jaundice was recorded.

Statistics

The descriptive indices including frequency, percentage, mean and its standard deviation (SD) were used to express data. Normal distribution of continuous variables was evaluated using the Kolmogorov-Smirnov (KS) test and normality diagrams. The Student's t test was used to assess continuous data with normal distribution. For non-normally distributed variables, the Mann-Whitney test was used. In order to compare nominal variables between the two groups, the Chi-square test or the Fischer's exact test was used. Analysis of variance (ANOVA) was used to compare continuous data with normal distribution (weight) among the three studied groups. To compare non-normally distributed continuous data (birth height and head circumference) among the three groups, Kruskal-Wallis test was used. To determine compliance, number of unused supplements was subdivided from used supplements and then was divided by used supplements. Significance level was set at 0.05. All analyses were performed using SPSS software (ver. 16.0, IBM).

Ethics

The study protocol was fully supported by the Research Council Ethics Committee of our medical university. The study objectives were explained to the patients and they were asked to provide written consent for enrolment. The study was in conformity with the Declaration of Helsinki.

Results

A total of 192 pregnant women were included. Of this, 128 subjects had low serum 25-[OH] D levels. The age range of mothers was 20 to 35 years with a mean (±SD) value of 28.64 (±4.02) years. No statistically significant difference was observed regarding age among the studied groups (Table 1). Mean (SD) pre-pregnancy weight was 70.53 (8.01) Kg (range, 55 to 98). Likewise, no difference existed among the groups regarding this variable. Mean (±SD) gestational age at the time of study recruitment was 26.96 (±0.87) weeks (range, 26 to 28 weeks). The three groups were comparable regarding this variable. The baseline maternal serum 25-[OH] D level was comparable between low-dose and high-dose vitamin D supplement groups.

Table 1. Comparison of maternal features (average values) among the three studied groups

	Low-dose vitamin D (N= 64)	High-dose vitamin D (N= 64)	Control (N= 64)	P value
Age	27.88	29.22	28.83	0.16
Pre-pregnancy weight	72	70	68.64	0.08
Gestational age at entry	27.02	27.11	26.77	0.08
Maternal serum 25-[OH] D	20.3	18.22	33.58	< 0.05[a] > 0.05[b]

[a] = difference among the three groups; b= difference between low-dose and high-dose vitamin D supplement groups

Table 1 presents comparison of maternal factors among the three studied groups.

Gestational age at the time of delivery did not show significant difference among the groups.

Mean gestational age in control, low-risk, and high-risk groups was respectively 37.88, 37.98, and 37.18 weeks and no significant difference existed between the groups (P> 0.05).

Cesarean section (CS) was required in 110 patients (57.3%) and normal delivery in 82 subjects (42.7%). CS was required in 35 (31.8%), 38 (34.5%), and 37 (33.6%) patients respectively in low-dose, high-dose, and control groups (P= 0.95).

Regarding neonatal anthropometric indices, no significant difference existed in terms of birth weight between the three groups (Table 2). However, mean value of birth height was higher in the high-dose vitamin D group compared to other groups (Table 2). Between group comparisons showed that mean (SD) height was significantly higher in the high-dose group than in the low-dose group (P= 0.02) and in the control group (P= 0.002). No statistically significant difference existed regarding mean height between the low-dose group and control groups (P= 0.29). Similar to birth weight, no difference existed regarding head circumference among the three groups (Table 2).

Table 3 shows distribution of Apgar scores at minutes 1 and 5 in the three groups. Table 4 shows distribution of macrosomia, hypoglycemia, and pathologic jaundice among the three groups. As observed, no significant difference existed among the three groups regarding the mentioned variables.

Table 2. Comparison of neonatal birth weight, height, and head circumference among the three studied groups

	Low-dose vitamin D (N= 64)	High-dose vitamin D (N= 64)	Control (N= 64)	P value
Weight, Kg	3123.44 (±519.07)	3221.09 (±484.91)	3124.41 (±504.5)	0.73[a]
Height, cm	49.38 (±2.18)	50.13 (±1.85)	49.02 (±2.02)	0.04[b]
Head circumference, cm	34.60 (±1.85)	35.1 (±1.98)	34.77 (±1.63)	0.11[b]

[a]ANOVA; bKruskal-Wallis; Data are presented as mean (±SD)

Table 3: Apgar scores at minutes 1 and 5 in the three studied groups

	1-minute Apgar score				5-minute Apgar score			
	5	7	8	9	7	8	9	10
Group 1	1 (1.6%)	2 (3.1%)	4 (6.2%)	57 (89.1%)	0	2 (3.1%)	4 (6.2%)	58 (90.6%)
Group 2	0	3 (4.7%)	5 (7.8%)	56 (87.5%)	0	3 (4.7%)	3 (4.7%)	58 (90.6%)
Group 3	0	1 (1.6%)	6 (9.4%)	57 (89.1%)	0	0	4 (6.2%)	60 (93.8%)

Group 1= Low-dose vitamin D supplement, Group 2= High-dose vitamin D supplement , Group 3= Control

Table 4. Frequency distribution of macrosomia, hypoglycemia, and pathologic jaundice among the three groups

	Low-dose vitamin D (N= 64)	High-dose vitamin D (N= 64)	Control (N= 64)	P value
Macrosomia	2 (3.1%)	2 (3.1%)	2 (3.1%)	> 0.05
Hypoglycemia	13 (20.3%)	8 (12.5%)	5 (7.8%)	0.11
Pathologic jaundice	13 (20.3%)	8 (12.5%)	5 (7.8%)	0.11

Discussion

Vitamin D deficiency during pregnancy is still a public health issue which needs more attention. This state can be associated with unfavorable pregnancy outcomes. GDM and impaired glucose intolerance also can be associated with some unwanted maternal, fetal, and neonatal outcomes. Efforts have been made to study the effect of vitamin D supplements on pregnancy outcomes in pregnant mothers with vitamin D deficiency. The results of such studies can help health care professionals to decide whether vitamin D supplements have any beneficial effect of pregnancy outcomes or not. Based on our findings, vitamin D supplementation did not have any significant effect on pregnancy outcomes regarding newborn birth size, Apgar scores, and the frequency of hypoglycemia, pathologic jaundice, and macrosomia. The only variable which showed a significant difference between the study groups was neonatal height which was higher in the high-dose vitamin D group.

The usefulness of vitamin D supplements in GDM is stemmed from observations that vitamin D is related to glucose metabolism and insulin resistance. However, there is inconsistency among the reports as some believe that factors such as obesity and genetic polymorphisms can act as confounding variables in this relationship (7). It has been shown that administration of vitamin D for 6 weeks in GDM resulted in decreased fasting plasma glucose and serum insulin (24). Such observations in pregnant women are scarce. More studies have been done on non-pregnant women. For instance, vitamin D supplements in women with low serum vitamin D levels resulted in considerable improvement in insulin sensitivity and insulin resistance, in particular when serum 25(OH) D rose to 80 ng/mL(26). 1,25-dihydroxyvitamin D3 has been shown to activate the human insulin receptor (27).

The obtained results are somehow compatible with a previous study on 45 pregnant women with GDM who received high-dose vitamin D (50,000) two times and placebo group (25). The authors reported that vitamin D supplementation resulted in no significant difference in newborn birth size or 1- and 5-minute Apgar scores. However, in contrast to our results, hyperbilirubinemia and hospital admission were significantly lower in the intervention group. The only variable that showed difference between low-dose and high-dose groups was newborn birth height. In the previous similar study, birth height, weight, and head circumference did not show difference between high-dose and control groups (25). There are conflicting results in the literature regarding the effect of treating low vitamin D level on fetal growth in pregnant mothers without GDM. For example, in a study recruiting pregnant patients with vitamin D levels < 30 ng/mL, administration of vitamin D 50,000 IU weekly for 8 weeks resulted in higher newborn birth weight, height, and head circumference in the intervention group (28). In another meta-analysis, it was revealed that vitamin D supplementation resulted in improvement in offspring birth weight and length (29). However, there are studies that, similar to our study, did not find any beneficial effect of vitamin D supplementation regarding newborn anthropometric features (1).

GDM is one of the variables that can lead to increased CS rate, macrosomia, hypoglycemia, and hyperbilirubinemia(15). According to the presented findings, vitamin D administration in two different doses did not affect these outcomes.

Limitations and Strengths

We faced some limitations in this study. We measured serum 25-[OH] D at the time when GDM was diagnosed (i.e., the third trimester). We did not have any information about the first-trimester serum 25-[OH] D level. Some studies have emphasized on serum 25-[OH] D levels at the first trimester as a potential factor in pregnancy outcome. Also, we were not able to follow the mothers to find out what percentage develop type 2 DM. In addition, physical activity and dietary factors were not studied. On the other hand, baseline maternal weight, age, and gestational age were comparable among the groups and these factors cannot have significant effect on the observed findings.

Conclusion

Vitamin D supplementation either at low doses or high doses did not have considerable effect on pregnancy outcome in pregnant women with GDM. The only variable which was higher in the high-dose group was the newborn birth height.

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