The Efficacy and Safety of a High Dose of Vitamin D in Mothers with Gestational Diabetes Mellitus: A Randomized Controlled Clinical Trial

Mahdieh Hosseinzadeh-Shamsi-Anar1, Hassan Mozaffari-Khosravi1, Maryam-Alsadat Salami2, Hossein Hadinedoushan3, Mohammad Reza Mozayan4

Abstract

**Background:** During pregnancy and lactation outstanding changes occur in mother’s vitamin D metabolism. This study was carried out to evaluate the efficacy of 300,000 IU vitamin D given intramuscularly on body status in new cases of gestational diabetes mellitus (GDM).

**Methods:** This is a randomized clinical trial with the follow-up period of 3 months. Totally 45 participants were randomly divided into intervention group (IG) and control group (CG). The IG received an IM injection of 300,000 IU of vitamin D, whereas CG did not. The glycosylated hemoglobin A1C (HBA1C), serum 25-OH-D, parathyroid hormone (PTH), serum calcium and phosphorus were measured.

**Results:** Forty five patients including 24 with the mean age of 30.7±6.2 years in the IG and 21 with the mean age of 29.5±4.0 years in the CG participated in the study. The median concentration of serum 25(OH)D3 in the IG was to 62.10 nmol/l after the intervention, showing an increase of around 158%, compared to before intervention (24.25 nmol/l) whereas the CG showed a decrease of around 4.5%. Of the patients, 79.2% of IG and 81.9% of CG suffered to some degree from vitamin D deficiency. These figures were 4.2% and 71.4% for the IG and CG, respectively after the intervention.

For the IG, the PTH was significantly lower and Ca was significantly higher after the intervention. The serum Phosphorus before and after the intervention in each group or between the two groups was not significant.

**Conclusions:** The single 300,000 IM dose of vitamin D is regarded as an effective and safe to promptly improve vitamin D status in GDM.

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**Keywords** ● Cholecalciferol ● gestational diabetes mellitus ● vitamin D

Introduction

Vitamin D is a secosteroid, which is metabolized in liver and kidney. During pregnancy and lactation outstanding changes occur in mother’s vitamin D metabolism. These changes occur according to the needs...
for the mineralization of the fetus bones as well as adequate secretion of vitamin D in mother’s milk.1

Due to rapid fetal development, particularly bone calcification at the terminal stages of pregnancy, there is a possibility of vitamin D deficiency to occur in mothers. Since, fetus and baby are both dependent upon mother for blood and milk respectively, mother’s vitamin D supplementation is highly vital. Studies have indicated that during pregnancy vitamin D deficiency varies from 18% to 84%, which varies with the region under the study type of clothing.2–4 Vitamin D deficiency among breast-fed children in the regions with heavy sunshine such as the Middle East is high.3,5 This hypovitaminosis which is due to limited exposure to sun of mothers’ and their babies as well as low vitamin D intake by mothers. These can cause vitamin D deficiency in mothers’ milk as the only source of vitamin D for babies.6

There are evidences showing the role of vitamin D in keeping normal glucose homeostasis.7–10 Resistance to insulin and destruction of insulin secretion in human and animal models has considerably been related to vitamin D deficiency. Such a relation has been attributed to special receptors for vitamin D in pancreatic betacells.9 Moreover, vitamin D was shown to have positive effects on insulin sensitivity, and its deficiency to have negative effects on the function of betacells.11 In agreement with this, cohort studies revealed that vitamin D had a protective effect against diabetes type II.5,11 Also, serum concentration of vitamin D during 24-29th week of pregnancy in women suffering from gestational diabetes mellitus (GDM) was lower than that in women without the disease.12

The study of vitamin D status and improving it in the lactating mothers with previous GDM is of conspicuous value.4,13 Due to the limited exposure to sunshine and inadequate intake, the level of vitamin D is reduced in the milk of lactating mothers. Therefore, vitamin D supplementation in high doses has been recommended, and oral doses of 20000 or 40000 IU were associated with positive outcomes.5,14 Moreover, higher oral dose of (6400 IU per day) to lactating mothers significantly increased vitamin D status in mothers as well as the vitamin D content and antirachitic activity of their milk.14 Therefore, high doses of vitamin D, either orally or through injection, has recently been recommended.15–24

A single dose of vitamin D, administered parenterally, would be more effective, because it is not associated with the noncompliance associated with an oral dose. A dose of 600,000 IU vitamin D resulted in hypercalcemia, therefore, it can not be regarded a safe dose.17 There is no study to evaluate vitamin D status in mothers with previous GDM, and present oral vitamin D products are not fully effective,16 therefore, this study was designed to evaluate the effect of intramuscular injection of 300,000 IU during a three-month period.

**Materials and Methods**

*Ethical Considerations*

The study was explained to all participants, and they could withdraw from the study as they wished. The study was approved by Ethics Committee, Shahid Sadoughi University of Medical Sciences.

*Design and Population*

Design and protocol of the study is shown in figure 1. The study is a randomized controlled clinical trial with the follow-up period of three months after delivery in 48 women with GDM. Gestational diabetes mellitus was diagnosed by performing oral glucose (50 g and 100 g) tolerance test (GTT) at 24-28th week of gestation. The patients had GDM if 50 g resulted in a glucose serum concentration of 7.2 mmol/lit, and if 100 g GTT test was disturbed on the basis of Carpenter and Coustan criteria.25 The study inclusion criteria were the absence of thyroid, kidney and liver diseases as well as malabsorption. The exclusion criteria included changing the routine treatment as well as taking vitamin D, Ca, and multivitamin supplements.

The patients were randomly assigned into intervention group (IG) and control group (CG). This was done using a sequential list prepared based on tables of random numbers. The IG was given intramuscular 300,000 IU of vitamin D, while the CG was not.

The patients were asked to refer to Yazd Diabetes Research Center 3-10 days after delivery, so that some variables are recorded, and their anthropometric parameters such as heights and weights are measured. The patients’ weights were measured by Seca scale with 0.1 kg accuracy. Also, using a questionnaire, data were collected on age, literacy level, occupation, type of therapy for diabetes, and type of delivery using medical history and interview with the patients.

*Laboratory Measurements*

After an overnight fasting, samples of 6 ml peripheral blood were taken from all of the patients at most 10 days after the delivery, and were used to determine plasma glycosylated hemoglobin A1C (HBA1C) test by immunoassay method. Also, blood samples were used to prepare serum, which were kept frozen at -80 °C until analysis. Fasting blood samples were also obtained on follow ups and were used to prepare serum, which were kept similarly. The
Efficacy and safety of single megadose of vitamin D

Serum samples were used to measure 25(OH) vitamin D3, paratormone (PTH), calcium and phosphorus. The serum 25(OH) vitamin D3 was measured by ELISA and kit of immunodiagnostic systems Ltd (Nyco card equipment, Nyco corporation, Norway). The sensitivity of the test was 2 nmol/ml. Serum paratormone was also measured by ELISA and immunodiagnostic systems Ltd (IDS Ltd), which had a sensitivity of 0.6 picomol/l. The serum calcium and phosphorus were respectively measured by calorimetric method by AutoAnalyzer (Echoplus Corporation, Italy), Biosystems kit (Spain), and ELISA method.

**Dose and Follow-Up**

The administered vitamin D was vitamin D3, which were kept from light, frozen, and stored at 15 to 30°C during the study.

Patients’ vitamin D status was determined by measuring serum 25(OH) vitamin D3 concentration. Serum concentrations of lower than 12.5 nmol/l was considered severe deficiency, 12.5 to 24.9 nmol/l was taken as moderate deficiency, 25 to 34.9 nmol/l as mild deficiency, and concentrations higher than 35 nmol/l was regarded as optimal.12

**Statistical Analysis**

The data were analyzed by the SPSS package Version 11 (SPSS Inc., Chicago, IL, USA). Kolmogro-Smirnov test was used to determine the distribution of quantitative data. Between-group comparisons were made using t or Wilcoxon tests, and within-group comparisons were made using paired t-test or Mann-Whitney U-tests. Between-group and within-group comparisons of qualitative data were performed Chi-Square or McNemar tests. A P value of ≤0.05 was considered statistically significant.

**Results**

Forty five patients including 24 with the age of 30.7±6.2 years in the IG and 21 with the age of 29.5±4.0 years in the CG completed the study. There was no significant difference between the body mass index (BMI) for the subjects in the IG (28.9±4.8 kg/m²) and CG (27.9±3.6 kg/m²) (table 1). Moreover, there was no significant difference between the two groups in terms of plasma HA1C, literacy level, type of treatment for GDM, or type of delivery.

There was a significant increase in serum concentrations of 25(OH) vitamin D3 in the IG...
Table 1: The baseline characteristics of subjects from the intervention group (IG) and control group (CG)

| Variables                                | IG (N=24)   | CG (N=21)   | P value |
|------------------------------------------|-------------|-------------|---------|
| Age (year)                               | 30.7±6.2    | 29.5±4      | 0.4     |
| Pregnancy month for diagnosing GDM       | 5.1±2.3     | 4.7±2.2     | 0.6     |
| Weight (kg)                              | 70.2±12.5   | 69.9±11     | 0.9     |
| Height (cm)                              | 155.6±5     | 157.9±4.4   | 0.4     |
| BMI (kg/m²)                              | 28.9±4.8    | 27.9±3.6    | 0.4     |
| HA1C (%)                                 | 5.48±0.69   | 5.2±0.73    | 0.1     |
| Literacy Level                           | Number (%)  | Number (%)  |         |
| Illiterate                               | 2(8.3)      | 3(14.4)     |         |
| Guidance school graduate                 | 10(41.7)    | 11(52.4)    | 0.3     |
| High school graduate                     | 7(29.2)     | 3(14.3)     |         |
| University graduate                      | 5(20.8)     | 4(19)       |         |
| Type of treatment                        |             |             | 0.9     |
| Insulin                                  | 11(45.8)    | 9(42.9)     |         |
| Food therapy                             | 10(41.7)    | 10(47.6)    |         |
| Insulin and diet therapy                 | 2(8.5)      | 3(12.5)     |         |
| Type of delivery                         |             |             | 0.2     |
| Natural                                  | 12(50)      | 14(66.7)    |         |
| Cesarean section                         | 12(50)      | 7(33.3)     |         |

Table 2: The serum concentrations of vitamin D (25(OH)D3), parathyroid hormone (PTH), calcium and phosphorus, and body mass index (BMI) of subjects in the intervention group (IG) and control group (CG)

| Variables                                | IG            | CG            | P value |
|------------------------------------------|---------------|---------------|---------|
| 25(OH)D3 (nmol/l)                        | 24.25(13.3-202.4) | 25.30(12.8-137.2) | 0.44 |
| Before                                   | 62.10(31.7-278.9) | 24.10(18.0-191.7) | <0.001 |
| P value                                  | <0.001        | 0.02          |         |
| PTH Pmol/l                               | 3.42±1.08     | 3.6±1.05      | 0.6     |
| Before                                   | 2.88±1.06     | 4.78±2.40     | 0.003   |
| P value                                  | 0.001         | 0.1           |         |
| Serum Calcium (mg/dl)                    | 9.01±0.2      | 8.9±0.10      | 0.1     |
| Before                                   | 9.17±0.35     | 9.12±0.45     | 0.7     |
| P value                                  | 0.07          | 0.013         |         |
| Serum Phosphor (mg/dl)                   | 3.37±0.45     | 3.61±0.39     | 0.07    |
| Before                                   | 3.25±0.3     | 3.41±0.36     | 0.3     |
| P value                                  | 0.5           | 0.5           |         |
| BMI (kg/m²)                              | 29.15±5       | 27.9±3.6      | 0.4     |
| Before                                   | 29.0±5.6      | 27.4±3.7      | 0.1     |
| P value                                  | 0.35          | 0.25          |         |
| HBA1C (%)                                | 5.48±0.6      | 5.2±0.73      | 0.1     |
| Before                                   | 5.58±12       | 5.21±0.52     | 0.2     |
| P value                                  | 0.73          | 0.67          |         |

δ: Median (Min-Max)

Group, but there was no significant change in that of CG during the study (table 2). There was no difference between the serum concentration of PTH of the IG and CG prior to intervention, however, serum concentration of PTH after the intervention was significantly lower in the IG than that of CG. Moreover, there was no difference between the serum concentration of Ca of the IG and CG prior or after the intervention. Serum concentration of Ca in the CG after the intervention was significantly higher than that of the prior treatment, whereas there was no significant difference between serum concentration of Ca before and after the intervention in the IG. Between-group and within-group comparison did not reveal any significant difference for serum levels of phosphorus, BMI or HA1C (table 2). None of the groups had severe vitamin deficiency.
D deficiency before the intervention. Fifteen (62.5%) of the subjects in the IG were suffering from a moderate vitamin D deficiency, which decreased to zero after the intervention (table 3). The frequencies of subjects suffering from moderate vitamin deficiency in the CG group were 42.9% and 47.6% before and after the intervention, respectively. Four (16.7%) of the subjects in the IG were suffering from a mild vitamin D deficiency, which was reduced to one (4.2%) after the intervention. such values for the control group were 33.3% and 14.3%, respectively. If vitamin D deficiency is regarded as 25-OH vitamin D3 lower than 35 nmol/l, 79.2% of patients from IG and 81.9% from CG suffered to some degrees from vitamin D deficiency prior to the intervention. These values were changed by intervention to 4.2% and 71.4%, respectively. There was a significant difference in the frequency of subjects suffering from vitamin deficiency before and after the intervention in the IG, whereas no significant difference was found between these values in the CG.

Discussion

If vitamin D deficiency is defined as serum concentration of 25(OH) vitamin D3 lower than 35 nmol/l, about 80% of the mothers with GDM in the present study were suffering to some degrees from vitamin D deficiency. Twelve weeks after the administration of a single dose of 300,000 IU of vitamin D, this figure was 4.2% and 71.4% for the IG and CG, respectively. This indicates the efficacy of this procedure in dramatic improvement of vitamin D status in the mothers, especially in the region with high vitamin D deficiency. The elimination of the problem at this short period is valuable in the health of mothers’ and their breast-fed children. Considering the range of obtained serum calcium and phosphorus in mothers, no incidence of hypercalcemia, hyperphosphatemia, or hypervitaminosis, this dosage and route of supplementation of vitamin D seems to be safe for mothers and their infants.

In this study, the median concentration of the serum vitamin D in the IG raised from 24.25 to 62.10 nmol/l, which is in line with a recent survey carried out by Restorff et al. on 33 rheumatoid arthritic patients. They showed that supplementation with an oral dose of 300,000 IU of vitamin D and 500-1000 mg daily of calcium led to an increase in the concentration of serum vitamin D from 15 to 81.4 nmol/l. Moreover, similar to that find by Restroff et al. serum PTH of the IG decreased significantly by 22% in our study. The mechanism of PTH reduction is that an increased serum vitamin D leads to a decrease in PTH gene translation, and thus PTH secretion. On the other hand, increased serum calcium causes the intracellular calcium to attach to calcium receptors on the surface of parathyroid cells causing a change in a special form of the receptors. Such a change results in the inhibition of PTH secretion from parathyroid cells.

The increase of serum calcium in the IG in the present study is similar to that reported in the other studies. The mechanism of increasing serum calcium by vitamin D is that vitamin D attaches optionally to receptors X of retinoic acid (RXR), and composes a heteromeric complex with a certain sequence on the DNA, known as reacting elements to vitamin D. This leads to the transcription of a special mRNA, which results in the translation of several proteins such as epithelial calcium channels and the proteins attached to calcium. This results in the increase of calcium absorption from the intestine.

Previous studies, of intramuscular injection of 600,000 unit of vitamin D was associated with significant increases of serum vitamin D at 1.5, 3, and 6 months, but not significant at 9 and 12 months later. In these studies, as well as ours, serum calcium level considerably increased, but contrary to ours, they reported abnormal calcium level in 7% to 12% of the patients during the study. In another study, administration of 600,000 IU of vitamin D was associated with a significant increase in serum vitamin D, a significant decrease in serum PTH, and hypercalcemia occurring in 4% of the subjects during 4 and 12 months of intervention. In our study, no hypocalcaemia was observed indicating the safety and efficiency of this supplementation method.

A recent study has indicated that administrating a high dose of vitamin D every two months was an easy and comfortable treatment. The study was evaluated as more economic and effective in terms of patients’ compliance. Our

| Groups          | Vitamin D status (nmol/l) | Before | After | Before | After |
|-----------------|---------------------------|--------|-------|--------|-------|
|                 | Severe deficient (<12.5)  | 0      | 0     | 0      | 0     |
|                 | Moderate deficient (12.5-24.9) | 15(62.5%) | 0 | 9(42.9%) | 10(47.6%) |
|                 | Mild deficient (25-34.9)   | 4(16.7%) | 1(4.2%) | 7(33.3%) | 3(14.3%) |
|                 | Optimal (≥35)             | 5(20.8%) | 23(95.8%) | 4(19%) | 6(28.6%) |
study revealed that a single high dose injection of vitamin D is more economic and effective particularly in lactating mothers who refrain from consuming oral daily doses due to postpartum care, unwillingness or depression. Witham et al.24 showed that single doses of 100,000 and 200,000 IU of vitamin D in diabetic type II patients increased serum vitamin D from 41 to 63 and from 48 to 79 nmol/l respectively. However, they showed that the decrease of PTH did not reach statistical significance. Moreover, another study,19 showed that a single dose of 200,000 IU of vitamin D in the healthy youths was associated with a peak in vitamin D concentration after two weeks of treatment, but lower than that of our study at three months after treatment. Therefore, a single dose of 300,000 IU dose employed in this study is of higher effectiveness compared with an oral dose, especially in people suffering from vitamin D deficiency. Our study was advantageous for the presence of a control group in which all measurements were made similar to those of the IG. However, our study is limited for not measuring urine calcium and creatinin, since these variables could confirm the presence of hypervitaminosis more exactly and more confidently. Moreover, serum vitamin D was measured by ELISA kit, which is of lower accuracy compared with HPLC and RIA methods. Further studies are needed to evaluate the effect of postpartum supplementation of vitamin D on antirachitic factor of the mother’s milk, and infant’s health indexes. Moreover, additional clinical trial studies will have to be conducted to determine the effect of mega doses of vitamin D on other health-related parameters such as the factors related to metabolic syndrome as well as inflammatory markers.

**Conclusion**

The findings of the study indicate that intramuscular administration of a single dose of 300,000 IU of vitamin D is effective and safe to improve vitamin D status, and to ameliorate the factors related to the health of mothers and infants, particularly in the regions with severe vitamin D deficiency.

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**Conflict of Interest:** None declared.

**References**

1. Zhang C, Qiu C, Hu FB, David RM, van Dam RM, Braley A, et al. Maternal plasma 25-hydroxyvitamin D concentrations and the risk for gestational diabetes mellitus. PLoS One. 2008;3:e3753. doi: 10.1371/journal.pone.0003753. PubMed PMID: 19015731; PubMed Central PMCID: PMC2582131.
2. Dawodu A, Wagner CL. Mother-child vitamin D deficiency: an international perspective. Arch Dis Child. 2007;92:737-40. doi: 10.1136/adc.2007.122689. PubMed PMID: 17715433; PubMed Central PMCID: PMC2084036.
3. Sachan A, Gupta R, Das V, Agarwal A, Awasthi PK, Bhatia V. High prevalence of vitamin D deficiency among pregnant women and their newborns in northern India. Am J Clin Nutr. 2005;81:1060-4. PubMed PMID: 15883429.
4. Bassir M, Laborie S, Lapillonne A, Claris O, Chappuis MC, Salle BL. Vitamin D deficiency in Iranian mothers and their neonates: a pilot study. Acta Paediatr. 2001;90:577-9. doi: 10.1080/08035250119986. PubMed PMID: 11430721.
5. Gannagé-Yared MH, Chemali R, Yaacoub N, Halaby G. Hypovitaminosis D in a sunny country: relation to lifestyle and bone markers. J Bone Miner Res. 2000;15:1856-62. doi: 10.1359/jbmr.2000.15.9.1856. PubMed PMID: 10977006.
6. Hollis BW, Wagner CL. Vitamin D requirements during lactation: high-dose maternal supplementation as therapy to prevent hypovitaminosis D for both the mother and the nursing infant. Am J Clin Nutr. 2004;80:1752S-8S. PubMed PMID: 15585800.
7. Chiu KC, Chuang LM, Yoon C. The vitamin D receptor polymorphism in the translation initiation codon is a risk factor for insulin resistance in glucose tolerant Caucasians. BMC Med Genet. 2001;2:2. PubMed PMID: 1123188; PubMed Central PMCID: PMC29095.
8. Mattila C, Knekt P, Männistö S, Rissanen H, Laaksonen MA, Montonen J, et al. Serum 25-hydroxyvitamin D concentration and subsequent risk of type 2 diabetes. Diabetes Care. 2007;30:2569-70. doi: 10.2337/dc07-0292. PubMed PMID: 1762691.
9. Norman AW, Frankel JB, Heldt AM, Grodsky GM. Vitamin D deficiency inhibits pancreatic secretion of insulin. Science. 1980;209:823-5.
Efficacy and safety of single megadose of vitamin D

doi: 10.1126/science.6250216. PubMed PMID: 6250216.

10 Palomer X, González-Clemente JM, Blanco-Vaca F, Mauricio D. Role of vitamin D in the pathogenesis of type 2 diabetes mellitus. Diabetes Obes Metab. 2008;10:185-97. doi: 10.1111/j.1463-1326.2007.00710.x. PubMed PMID: 18269634.

11 Chiu KC, Chu A, Go VL, Saad MF. Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction. Am J Clin Nutr. 2004;79:820-5. PubMed PMID: 15113720.

12 Maghbooli Z, Hossein-Nezhad A, Karimi F, Shafaei AR, Larijani B. Correlation between vitamin D3 deficiency and insulin resistance in pregnancy. Diabetes Metab Res Rev. 2008;24:27-32. doi: 10.1002/dmrr.737. PubMed PMID: 17607661.

13 Hashemipour S, Larijani B, Adibi H, Javadi E, Sedaghat M, Pajouhi M, et al. Vitamin D deficiency and causative factors in the population of Tehran. BMC Public Health. 2004;4:38. PubMed PMID: 15327695; PubMed Central PMCID: PMC517720.

14 Wagner CL, Taylor SN, Hollis BW. Does vitamin D make the world go 'round'? Breastfeed Med. 2008;3:239-50. doi: 10.1089/bfm.2008.9984. PubMed PMID: 19086827; PubMed Central PMCID: PMC2981372.

15 Diamond TH, Ho KW, Rohl PG, Meerkin M. Annual intramuscular injection of a megadose of cholecalciferol for treatment of vitamin D deficiency: efficacy and safety data. Med J Aust. 2005;183:10-2. PubMed PMID: 15992330.

16 Ebeling PR. Megadose therapy for vitamin D deficiency. Med J Aust. 2005;183:4-5. PubMed PMID: 15992326.

17 Einarsdóttir K, Preen DB, Clay TD, Kiely L, Holman CD, Cohen LD. Effect of a single 'megadose' intramuscular vitamin D (600,000 IU) injection on vitamin D concentrations and bone mineral density following biliopancreatic diversion surgery. Obes Surg. 2010;20:732-7. doi: 10.1007/s11695-009-0024-3. PubMed PMID: 19949888.

18 Mallet E, Philippe F, Castanet M, Basuyau JP. [Administration of a single Winter oral dose of 200,000 IU of vitamin D3 in adolescents in Normandy: evaluation of the safety and vitamin D status obtained]. Arch Pediatr. 2010;17:1042-6. PubMed PMID: 20542672.

19 Markesat T, Hesse V, Siebenhuner M, Jahreis G, Aksnes L, Plent W, et al. Intermittent high-dose vitamin D prophylaxis during infancy: effect on vitamin D metabolites, calcium, and phosphorus. Am J Clin Nutr. 1987;46:652-8. PubMed PMID: 3499065.

20 Sanders KM, Stuart AL, Williamson EJ, Simpson JA, Kotowicz MA, Young D, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. JAMA. 2010;303:1815-22. doi: 10.1001/jama.2010.594. PubMed PMID: 20460620.

21 Shakiba M, Sadr S, Nefei Z, Mozaffari-Khosravi H, Lofifi MH, Bemanian MH. Combination of bolus dose vitamin D with routine vaccination in infants: a randomised trial. Singapore Med J. 2010;51:440-5. PubMed PMID: 20593151.

22 Soliman AT, Adel A, Wagdy M, Alali M, Aziz Bedair EM. Manifestations of severe vitamin D deficiency in adolescents: effects of intramuscular injection of a megadose of cholecalciferol. J Trop Pediatr. 2011;57:303-6. doi: 10.1093/tropej/fmq028. PubMed PMID: 20427425.

23 von Restorff C, Bischoff-Ferrari HA, Theiler R. High-dose oral vitamin D3 supplementation in rheumatology patients with severe vitamin D3 deficiency. Bone. 2009;45:747-9. doi: 10.1016/j.bone.2009.06.012. PubMed PMID: 19539796.

24 Witham MD, Dove FJ, Dryburgh M, Sugden JA, Morris AD, Struthers AD. The effect of different doses of vitamin D(3) on markers of vascular health in patients with type 2 diabetes: a randomised controlled trial. Diabetologia. 2010;53:2112-9. PubMed PMID: 20596692.

25 Ferrara A, Hedderon MM, Quesenberry CP, Selby JV. Prevalence of gestational diabetes mellitus detected by the national diabetes data group or the carpenter and coustan plasma glucose thresholds. Diabetes Care. 2002;25:1625-30. doi: 10.2337/diacare.25.9.1625. PubMed PMID: 12196438.

26 Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. Am J Obstet Gynecol. 1982;144:768-73. PubMed PMID: 7148898.

27 O'Sullivan JB, Mahan CM, Charles D, Dandrow RV. Screening criteria for high-risk gestational diabetic patients. Am J Obstet Gynecol. 1973;116:895-900. PubMed PMID: 4718216.