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Effect of vitamin D3 supplementation during pregnancy on high risk factors — a randomized controlled trial

https://doi.org/10.1515/jpm-2020-0318
Received July 9, 2020; accepted December 3, 2020;
published online December 18, 2020

Abstract

Objectives: Vitamin D plays an important role in the release of the placenta and implantation, and low levels are a risk factor for pre-eclampsia. Studies have also shown that symptomatic treatment of vitamin D3 deficiency can effectively reduce the risk of pre-eclampsia. In this study, vitamin D3 supplementation was performed on the risk of pre-eclampsia to observe its effect.

Methods: From January 2016 to December 2018, 450 women with maternal treatment and delivery in our hospital underwent an open-label randomized study. The pregnant women were divided into low-dose, medium-dose, and high-dose groups. Compare the incidence of pre-eclampsia and the dose effect of vitamin D levels.

Results: In the maternal and perinatal periods of the 450 maternal women, the 25[OH] index of the three groups of pregnant women was significantly increased, while the high-dose increase index was more obvious. The relative risk reduction rate was significantly lower. Compared with the low-dose and middle-dose groups, the high-dose group had a significantly lower incidence of pre-eclampsia, while the IUGR index was lower, and other obstetric indicators were comparable.

Conclusion: Vitamin D supplementation can effectively reduce the incidence of pre-eclampsia, while reducing the IUGR index, which has important value and significance in its clinical application.

Keywords: pregnancy; pre-eclampsia; vitamin D3.

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Introduction

Vitamin D deficiency has a potential negative impact on the health of pregnant women and newborns [1]. Vitamin D can induce immune responses and promote the formation of placenta [2, 3]. Studies have shown that placental biomarkers and vitamin D deficiency increase the risk of pre-eclampsia [4, 5]. There are many predisposing factors for pre-eclampsia, which occur in pregnant women who have 20 weeks of gestational weeks [5]. Globally, pre-eclampsia has a high risk to both mothers and fetuses, and has a high incidence in both developed and developing countries, becoming an important public health problem.

Vitamin D deficiency in pregnant women is closely related to insufficient intake and lack of sunshine time [6]. At the same time, the fetus needs extra vitamin D. Therefore, the lack of vitamin D during pregnancy can cause great adverse effects on the health of pregnant women, and low levels of vitamins D in pregnant women can also have long-term effects on pre-eclampsia, gestational diabetes, and neonatal health [7, 8]. Pregnant women with vitamin deficiency may also increase the risk of serious risks such as premature birth and childhood asthma [9]. At present, the targeted supplementation of vitamin D deficiency during pregnancy has not been fully applied at home and abroad [10, 11]. Many studies have pointed out that vitamin D deficiency is positively correlated with pre-eclampsia [12], but studies have also pointed out that pre-eclampsia is also closely related to other malnourished conditions. Therefore, it is very important for pregnant women to have a balanced nutrition during pregnancy. Based on the current association between vitamin D deficiency and pre-eclampsia, it is not well understood that conventional low-dose vitamin D supplements have not shown significant effects in reducing the risk of pre-eclampsia [13], and randomized to explore the effects of vitamin D supplements on pregnant women, most recently a literature review of people in parts of developed countries showed that vitamin D supplementation is beneficial [14]. With 4000 IU of supplements, the results showed that both pregnant women and newborns were in good condition, but the results were subject to regional

restrictions [15, 16]. Therefore, we hypothesized that the use of high-dose vitamin D supplements in pregnant women with vitamin D deficiency in the region would reduce the incidence of eclampsia first.

Materials and methods

Clinical case inclusion and exclusion

Cases inclusion criteria: pregnant women aged 20–40 years, pregnant women were singleton pregnancies, signed a paper version of informed consent at the first visit, pregnant women Low-risk pregnancy, while the 25 [OH] D indicator is lower than 25 nmol/L, pregnant women agree to participate in all prenatal care and care in our hospital. Exclusion criteria: fetal abnormalities, repeated abortions in pregnant women, history of hypertension, chronic liver and kidney disease, pre-eclampsia, and malignant tumors. Subjects participated in the study at 6–12 weeks of gestation and all pregnant women were followed up to three months after surgery. This study was approved by the Ethics Committee, strictly following the Declaration of Helsinki drafted by the World Medical Congress, and a statement of ethical guidelines for human medical research to guide doctors and other participants in medical research.

Grouping

During the period from January 2016 to December 2018, 450 women with maternal treatment and delivery in our hospital underwent an open-label randomized study. All pregnant women had a clinically definitive diagnosis of vitamin D deficiency. The pregnant women were divided into low-dose vitamin supplement group (400 IU), middle-dose group (1500 IU) and high-dose group (4000 IU), and the dose-effect of pre-eclampsia and vitamin D levels were compared. In this study, the ethics committee reviewed and signed the corresponding informed consent.

First questionnaire

All subjects completed the questionnaire and the basic health status and medical history. At the initial visit, each participant was given a blood sample and a urine sample. All subjects received vitamin D supplementation after the 12th week of pregnancy.

Group intervention

Vitamin D supplement in the low-dose group for daily replenishment, once daily, at a dose of 400 IU. The middle-dose group was given daily daily supplementation of vitamin D supplements once a day at a dose of 1500 IU. The high-dose group was treated with vitamin D supplements for daily use. Supplement, once a day, the dose is 4000 IU. All pregnant women started taking vitamin D supplements from the 13th week of pregnancy.

Test indicators

The incidence of pre-eclampsia events in the three groups of pregnant women was recorded and recorded at 20 weeks of gestation. The criteria for pre-eclampsia are headache, vertigo, nausea, vomiting, epigastric discomfort symptoms, edema, proteinuria, and systolic blood pressure >160 mmHg. At the same time, the vitamin D level was monitored at the 36th week of pregnancy, and the occurrence of intrauterine growth retardation during childbirth was recorded. The medications used by the three groups of pregnant women were all distributed by the pharmacy.

Follow-up and data collection

Each clinical case was followed up to 12 weeks postpartum, and the age, parity and BMI of the case were recorded, and serum vitamin D3 levels before and after supplementation were measured. Adverse reactions and liver and kidney function were monitored throughout the period and regular ultrasound, blood pressure and weight monitoring were performed. The criterion for pre-eclampsia is hypertension and proteinuria after 20 weeks of gestation.

Indicator measurement

25 [OH] D is measured using a kit, and The Roche Diagnostic Vitamin D total assay was used to measure the morning blood collected by pregnant women using the electrochemiluminescence binding assay to quantify the total 25 [OH] D levels in human serum and plasma. This assay uses vitamin D binding protein (VDBP) as a capture protein to capture 25 [OH] D3 and 25 [OH] D2 (Roche Diagnostics, Mannheim, Germany).

Data analysis

The number of cases and clinical data were statistically displayed using the mean ± standard deviation. The categorical data were expressed as a percentage. The incidence of pre-eclampsia was compared by chi-square test and regression analysis was performed. SPSS 23.0 software was used for data analysis. Analytical indicators were compared between pre-eclampsia between 20 weeks of gestation and 12 weeks after delivery.

Results

Comparison of basic data between the two groups of subjects

An open-label randomized study of 450 pregnant women undergoing treatment and delivery in our obstetrics department included data registration, assignment processing, and follow-up of the initial stage of pregnancy. Among the 450 patients who participated in the study, among the 150 patients in the three groups, 135 patients in the low-dose

supplement group completed the trial, 134 patients in the middle-dose group completed the trial, and 138 in the high-dose group completed the trial. The basic statistical data of the two groups of pregnant women were compared. The data showed that there was no data difference between the three groups ($p>0.05$) in Table 1. Each group followed the principle of randomization, and the initial blood pressure is normal, and there is no difference in the basic data between the three groups.

Comparison of the incidence of pre-eclampsia in three groups of subjects

In the three groups of study populations, the incidence of pre-eclampsia was significantly lower in the high-dose group than in the low-dose group ($p=0.032$). In contrast, during the vitamin D supplementation, the number of pre-eclampsia events in the high-dose group was significantly lower than in the low-dose group. Two pregnant women in the high-dose group developed pre-eclampsia and returned to normal levels after delivery. The vitamin D levels of two patients with pre-eclampsia in the high-dose group reached normal levels through childbirth. The detailed data are shown in Table 2, and there was no data difference in the levels of vitamin D levels in the three groups before delivery (Figure 1A, B).

Comparison of 25 [OH] D expression levels in three groups of pregnant women

In the 25 [OH] D comparison of the three groups of pregnant women, the high dose group was significantly higher than the low dose group, and the high dose group had significantly higher vitamin D adequacy than the low dose group (Figure 2). In the high-dose group, the IGUR index was significantly lower compared to low-dose group (Table 2).

Table 1: Comparison of basic data of three groups of pregnant women.

Index	Low dose group	Medium dose group	High dose group
Cases, n	135	134	138
Age, years	28.76±3.16	28.54±3.27	28.94±3.21
Account category, town/country	50/85	52/82	52/86
Pre-pregnancy BMI, kg/m^2	19.83±1.34	19.98±1.23	19.65±1.27

Table 2: Comparison of maternal and neonatal indicators in three groups of pregnant women.

Index	Low dose group	Medium dose group	High dose group
Cases, n	135	134	138
Caesarean section, n (%)	45 (33.33)	48 (35.82)	49 (35.51)
Miscarriage, n (%)	4 (2.96)	5 (3.73)	5 (3.62)
Preterm delivery, n (%)	20 (14.81)	21 (15.67)	22 (15.94)
IUGR, n (%)	33 (24.4)	20 (14.93)[a]	12 (8.70)[ab]
Pre-eclampsia, n (%)	13 (9.63)	9 (6.72)	2 (1.45)[a]
Gestational diabetes, n (%)	16 (11.85)	17 (12.69)	16 (11.59)
Newborn birth weight, kg	2.98±0.43	2.91±0.45	2.95±0.49

[a]$p<0.05$ compared with the low dose group. [b]$p<0.05$ compared to the medium dose group.

Discussion

The results of this study showed that pregnant women with vitamin D deficiency had more obvious pre-eclampsia, and the dose of 4000 IU could achieve a good vitamin D supplementation rate, which was close to 1.0%. In the conventional low-dose supplementation comparison, high doses can effectively reduce the incidence of pre-eclampsia [15, 17], and the results further clarify the incidence of vitamin D and pre-eclampsia. The results reported in this study are somewhat similar to those reported in the earlier reports. In the study, vitamin D supplementation in the low-dose group still has a higher incidence of pre-eclampsia. In the clinical case of the vitamin D-deficient group, the dose gradient can be used. Although different doses of vitamin D supplementation can reach normal doses, supplementation at the beginning of pregnancy confirms the inverse relationship between vitamin D and pre-eclampsia [18–20]. Therefore, supplementation with high-dose vitamin D3 is a safe and reliable method, and studies have shown that vitamin D3 supplementation can reduce the damage of endometrial cells by inhibiting the inflammatory signaling pathway [21]. In addition, studies have shown that the display has a regulatory effect on metabolism and endocrine, thereby changing the placental vasculature.

Studies have shown that vitamin D and pre-eclampsia occur in a positive relationship, and then in the early detection of vitamin D levels found that early pregnancy is accompanied by some indicators of changes [22], such as maternal serum calcitriol, placental vitamin D receptor And CYP27B1 cytochrome in the kidney and placenta, while 25

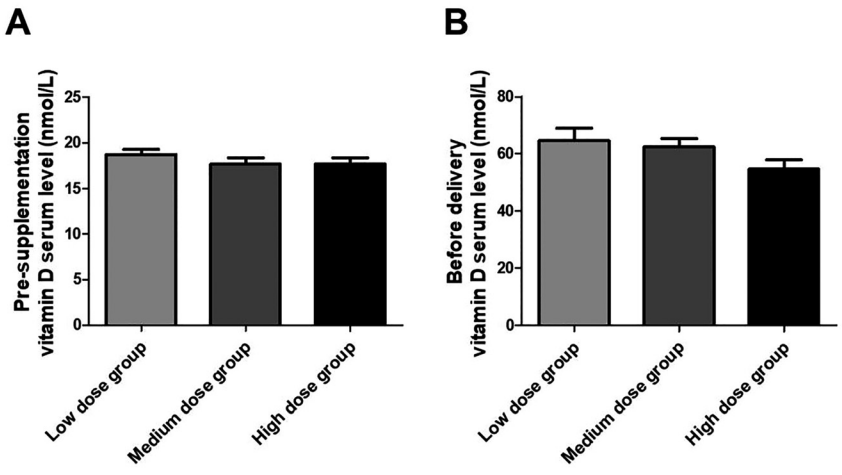

Figure 1: Vitamin D level pre-supplementation and before gestation.

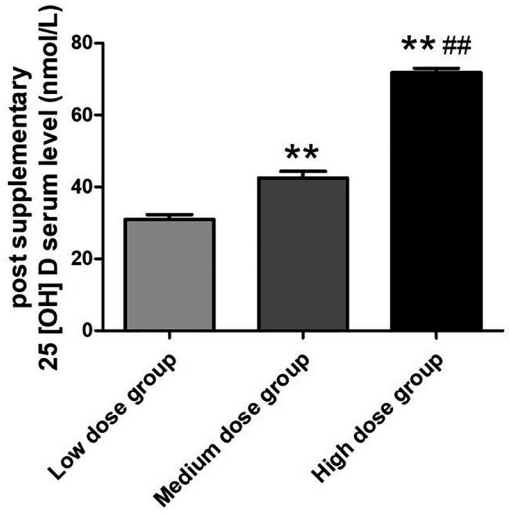

Figure 2: 25 [OH] D serum level post-supplementation. $^{**}p<0.01$ compared with the low dose group. $^{\#\#}p<0.01$ compared to the medium dose group.

[OH] has not changed [23]. Cortisol is inversely related to the level of vitamin D [7, 24]. In recent years, many studies have denied the association between insufficient vitamin D levels and pre-eclampsia, gestational hypertension, and preterm birth [25]. However, baseline levels of vitamin D are affected by race, environment, and topography, but at present, there is no comprehensive clinical trial linking early intervention systems to pre-eclampsia. Previous studies have shown that high doses of supplementation with 2000 IU have yielded good results [26], and increased doses can achieve similar results.

In this study, a comparative study of vitamin D was performed in the advanced dose group, and the supplemental doses were all safe doses. As a fat-soluble reagent, vitamin D requires an alcohol medium for its dilution, and our vitamin tablets have good safety. The 4000 IU dose we used may have high drug dose problems, but no drug intolerance was seen during treatment. Supplementing 4000 IU of vitamin D can reduce the incidence of IUGR and have more effects on improving pregnancy. In this study, the sample of this region was used to exclude the influence of population species, and the results were better consistent. However, this randomized open trial has certain limitations, no blank controls, and no more comprehensive metabolic index records. However, with the increase in related clinical trials, this double-blind study provides more gospel for women's pregnancy health.

Research funding: None declared.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: Authors state no conflict of interest.

Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: This study was approved by the Ethics Committee, strictly following the Declaration of Helsinki drafted by the World Medical Congress, and a statement of ethical guidelines for human medical research to guide doctors and other participants in medical research.

References

1. Kassai MS, Cafeo FR, Affonso-Kaufman FA, Suano-Souza FI, Sarni ROS. Vitamin D plasma concentrations in pregnant women and their preterm newborns. BMC Pregnancy Childbirth 2018; 18:412.
2. Infante M, Ricordi C, Sanchez J, Clare-Salzler MJ, Padilla N, Fuenmayor V, et al. Influence of vitamin D on islet autoimmunity and beta-cell function in type 1 diabetes. Nutrients 2019;11:2185.

3. Liu NQ, Larner DP, Yao Q, Chun RF, Ouyang Y, Zhou R, et al. Vitamin D-deficiency and sex-specific dysregulation of placental inflammation. J Steroid Biochem Mol Biol 2018;177:223–30.
4. Serrano NC, Guio E, Quintero-Lesmes DC, Becerra-Bayona S, Luna-Gonzalez ML, Herrera VM, et al. Vitamin D deficiency and pre-eclampsia in Colombia: PREVitD study. Pregnancy Hypertens 2018;14:240–4.
5. Ullah MI, Koch CA, Tamanna S, Rouf S, Shamsuddin L. Vitamin D deficiency and the risk of preeclampsia and eclampsia in Bangladesh. Horm Metab Res 2013;45:682–7.
6. Aydin CG, Dincel YM, Arikan Y, Tas SK, Deniz S. The effects of indoor and outdoor sports participation and seasonal changes on vitamin D levels in athletes. SAGE Open Med 2019;7:1–6.
7. Accortt EE, Mirocha J, Dunkel Schetter C, Hobel CJ. Adverse perinatal outcomes and postpartum multi-systemic dysregulation: adding vitamin D deficiency to the allostatic load index. Matern Child Health J 2017;21:398–406.
8. Wei SQ, Qi HP, Luo ZC, Fraser WD. Maternal vitamin D status and adverse pregnancy outcomes: a systematic review and meta-analysis. J Matern Fetal Neonatal Med 2013;26:889–99.
9. Hennessy A, Hourihane JO, Malvisi L, Irvine AD, Kenny LC, Murray DM, et al. Antenatal vitamin D exposure and childhood eczema, food allergy, asthma and allergic rhinitis at 2 and 5 years of age in the atopic disease-specific cork baseline birth cohort study. Allergy 2018;73:2182–91.
10. Smith M, O'Brien EC, Alberdi G, Geraghty AA, Kilbane M, McKenna MJ, et al. Association between vitamin D status in early pregnancy and atopy in offspring in a vitamin D deplete cohort. Ir J Med Sci 2019;189:563–70.
11. Zhao Y, Teng Y, Wang J, Yang Z, Dong S, Hu J, et al. Effects of vitamin D supplementation in early pregnancy on high-risk groups of gestational diabetes mellitus. J Hyg Res 2019;48: 226–31.
12. Ma SL, Tian XY, Wang YQ, Zhang HF, Zhang L. Vitamin D supplementation prevents placental ischemia induced endothelial dysfunction by down regulating placental soluble FMS-like tyrosine kinase-1. DNA Cell Biol 2017;36: 1134–41.
13. Karras SN, Anagnostis P, Paschou SA, Kandaraki E, Goulis DG. Vitamin D status during pregnancy: time for a more unified approach beyond borders? Eur J Clin Nutr 2015;69:874–7.
14. Zhang Q, Cheng Y, He M, Li T, Ma Z, Cheng H. Effect of various doses of vitamin D supplementation on pregnant women with gestational diabetes mellitus: a randomized controlled trial. Exp Ther Med 2016;12:1889–95.
15. Ali AM, Alobaid A, Malhis TN, Khattab AF. Effect of vitamin D3 supplementation in pregnancy on risk of pre-eclampsia - randomized controlled trial. Clin Nutr 2019;38:557–63.
16. Hajhashemi M, Khorsandi A, Haghollahi F. Comparison of sun exposure versus vitamin D supplementation for pregnant women with vitamin D deficiency. J Matern Fetal Neonatal Med 2019;32: 1347–52.
17. Roth DE. Vitamin D supplementation during pregnancy: safety considerations in the design and interpretation of clinical trials. J Perinatol 2011;31:449–59.
18. Palacios C, Kostiuk LK, Pena-Rosas JP. Vitamin D supplementation for women during pregnancy. Cochrane Database Syst Rev 2019;7:CD008873.
19. Beentjes CHL, Taylor-King JP, Bayani A, Davis CN, Dunster JL, Jabbari S, et al. Defining vitamin D status using multi-metabolite mathematical modelling: a pregnancy perspective. J Steroid Biochem Mol Biol 2019;190:152–60.
20. Santorelli G, Whitelaw D, Farrar D, West J, Lawlor DA. Associations of maternal vitamin D, PTH and calcium with hypertensive disorders of pregnancy and associated adverse perinatal outcomes: findings from the born in Bradford cohort study. Sci Rep 2019;9:1205.
21. Qian L, Wang H, Wu F, Li M, Chen W, Lv L. Vitamin D3 alters toll-like receptor 4 signaling in monocytes of pregnant women at risk for preeclampsia. Int J Clin Exp Med 2015;8:18041–9.
22. Al-Musharaf S, Fouda MA, Turkestani IZ, Al-Ajlan A, Sabico S, Alnaami AM, et al. Vitamin D deficiency prevalence and predictors in early pregnancy among Arab women. Nutrients 2018;10:489.
23. Cirillo M, Bilancio G, Guarino E, Cavallo P, Lombardi C, Costanzo S, et al. Vitamin D status and indices of mineral homeostasis in the population: differences between 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D. Nutrients 2019;11:1777.
24. Barebring L, O'Connell M, Winkvist A, Johannsson G, Augustin H. Serum cortisol and vitamin D status are independently associated with blood pressure in pregnancy. J Steroid Biochem Mol Biol 2019;189:259–64.
25. Van Winden KR, Bearden A, Kono N, Frederick T, Operskalski E, Stek A, et al. Low bioactive vitamin D is associated with pregnancy-induced hypertension in a cohort of pregnant HIV-infected women sampled over a 23-year period. Am J Perinatol 2019;37:1446–54.
26. Motamed S, Nikooyeh B, Kashanian M, Hollis BW, Neyestani TR. Efficacy of two different doses of oral vitamin D supplementation on inflammatory biomarkers and maternal and neonatal outcomes. Matern Child Nutr 2019;15:e12867.