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Vitamin D supplementation during pregnancy on infant anthropometric measurements and bone mass of mother-infant pairs: A randomized placebo clinical trial

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ABSTRACT

Introduction: Based on the essential role of vitamin D in the regulation of calcium metabolism, we evaluated the effects of 2000 IU vitamin D/day in late pregnancy on infant's anthropometric measurements and bone mass parameters of mother-infant pairs.
Material and methods: In this randomized clinical trial, the main inclusion criteria were: aged 18 or older, no history of internal diseases and pregnancy complications, and a singleton live fetus. The intervention group received two 1000 IU vitamin D_3 pills (2000 IU) daily from weeks 26–28 until childbirth. Maternal serum 25-hydroxyvitamin D, infants' anthropometric measurements (at birth, 4th and 8th weeks postnatal), and maternal and infant bone mass parameters were examined.
Results: The two groups were not statistically different in relation to baseline 25-hydroxyvitamin D concentrations. However, there was a significant difference between the study groups with regard to change in vitamin D status over time ($p < 0.001$). In cross-sectional analysis, the two groups were not different with respect to anthropometric measurements in three time points. Also, in repeated measure analysis, the two groups did not show any statistical differences concerning the infants' anthropometric measurements. The bone mass measurements of all the 28 mothers who belonged to the two study groups were not different. Finally, the bones mass measurements of the infants in the two study groups were not different.
Conclusion: Ingestion of 2000 IU vitamin D_3/day during late pregnancy did not improve anthropometric measurements of infants from birth until the 8th week postnatal, nor improve the maternal and infant bone mass measurements.

1. Introduction

Circulating concentration of vitamin D depends on both endogenous UV-induced synthesis and exogenous sources such as diet and supplements. Regardless of vitamin D sources, the first hydroxylation of vitamin D occurs in the liver and 25-hydroxyvitamin D [25(OH)D] is produced. The production of active form of hormone, 1, 25-dihydroxyvitamin D [1,25(OH)2D], demands a further hydroxylation of 25(OH)D in the kidney, under the control of a 1α-hydroxylase [1,2].

Vitamin D plays a vital role in calcium metabolism and bone mineralization. When plasma calcium levels are low, the active form of vitamin D leads to an increase in calcium absorption from the gut to maintain adequate levels for bone mineralization, bone growth and remodeling, as well as to prevent hypocalcemic tetany. Parathyroid hormone (PTH) is linked to vitamin D through calcium-phosphate homeostatic system. Low levels of calcium and phosphorus in the blood can lead to an increase in PTH. Hence, increases in PTH can stimulate the kidney to produce calcitriol, the active form of vitamin D, 1,25(OH)2D [3–5]. Then again, growing evidence suggests that the role of vitamin D is not limited to the skeletal system. Detection of vitamin D receptors in most tissues and cells in the human body allowed researchers to consider other consequences of the active form of vitamin D beyond the skeletal system. It has been suggested that there is a relationship between vitamin D insufficiency or deficiency and the

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occurrence of chronic illnesses including autoimmune thyroiditis, cardiovascular diseases, rheumatoid arthritis, multiple sclerosis, diabetes, and depression [6,7]. Furthermore, researchers have examined the link between serum vitamin D concentration and pregnancy complications and its outcomes [8–10].

Vitamin D deficiency is a major problem among people around the world [11–14], and Iran is no exception [15,16]. Thus, it is expected that healthcare systems be challenged with this issue during pregnancy and infancy period [17–20]. Women need a high volume of calcium during their pregnancy and lactation. Throughout pregnancy, an average calcium requirement for the growing fetus is about 30 g. High demand for calcium occurs especially in the third trimester of pregnancy when the fetal bone reaches its peak growth. This high demand for calcium is provided through a twofold increase in the mother's intestinal mucosa absorption. This physiologic process in mothers is accompanied with an increase in the synthesis of active metabolite 1,25(OH)2D [21,22]. Based on the role of vitamin D in the regulation of calcium metabolism, several observational studies have examined whether serum vitamin D status is associated with PTH concentration and bone health. The studies in adolescent and pre-pubertal girls have shown that low vitamin D levels were associated with lower bone mineral density (BMD) of the forearm, distal radius, and tibia shaft as well as higher PTH concentration [23–25]. A study by Arya et al. showed that there was a significant connection between serum 25(OH)D level and BMD at the femoral neck and Ward's triangle among adult females [26]. Another subject investigated in several studies was the link between maternal vitamin D status and birth anthropometric measurements. However, their results were not consistent [27–29]. Studies have produced conflicting data with respect to the correlation between maternal vitamin D status and development of fetal-child skeleton. Two studies showed that impaired fetal skeleton development was linked to maternal vitamin D status [30,31]. Conversely, another study did not show any correlation between feto-maternal vitamin D status and infant bone mineral content (BMC) [32]. A longitudinal study by Javaid et al. demonstrated a link between reduced maternal vitamin D in the last trimester and lower mineral content of the lumbar spine bone and the whole body in children at the age of nine [33]. However, a recent study was not in line with the previous study [34]. In a clinical trial, 26 weeks pregnant teenage mothers received 200 IU vitamin D plus 600 mg calcium daily throughout their pregnancy. Results of this study did not show significant differences between the intervention and placebo groups, in terms of infant BMD and BMC [35].

On the other hand, pregnancy can have a negative effect on maternal bone mass. Olausson et al. compared BMC, bone area (BA), areal bone mineral density (aBMD), and BA-adjusted BMC at the whole-body, lumbar spine, radius, and hip before pregnancy and 2 weeks postpartum.

Significant reductions (between 1 and 4%) in the bone mass criteria were observed. These recently pregnant women had lower BA-adjusted BMC compared to non-pregnant and non-lactating women [36]. The clinical trial by Diogenes et al. demonstrated the positive effect of 200 IU vitamin D, plus 600 mg calcium daily throughout pregnancy on maternal bone mass at 5 and 20 weeks postpartum [37].

Institute of Medicine of The USA (IOM) has recommended 400–600 IU/day vitamin D intake during pregnancy, while the Endocrine Society [38] and the Canadian Pediatric Society recommended 1500–2000 IU/day [39]. Recently, a number of clinical trial studies have shown a further improvement in maternal-fetal vitamin D status with high dose vitamin D supplementation than what was recommended by IOM [40,41]. To the best of our knowledge, there has been no clinical trial on the benefits of 2000 IU/day vitamin D supplementation during pregnancy on fetal-infant growth and maternal-neonate bone mass. Therefore, we conducted this study to examine whether such higher dose of vitamin D supplementation in late pregnancy can improve anthropometric measures of infant or maternal-neonate bone mass in pregnant women residing in Shiraz, Iran.

2. Material and methods

2.1. Design and data collection

This randomized clinical trial was carried out from November 2014 until early October 2015 in pregnant women, both nulliparous and multiparous, who were under prenatal care in Hafez teaching hospital in Shiraz, Iran. This hospital is affiliated to the Shiraz University of Medical Sciences. The inclusion criteria were mothers aged 18 years or older, no history of mental illness and internal diseases such as hyper/hypothyroidism, no addiction to any kind of narcotic drugs or alcohol, not divorced or widowed, no pregnancy complications such as preeclampsia, gestational diabetes, ruptured membranes and suspicion of preterm birth, no previous cesarean sections, with a live fetus singleton pregnancy, and gestational age of 26–28 weeks based on ultrasound results. Exclusion criteria were unwillingness to cooperate during the study, consumption of <8 weeks of vitamin D_3 supplements. Also, exclusion criteria for infants were gross congenital malformations and chromosomal disorders.

According to a previous study [42], considering $\alpha = 0.05$ and power of 90%, the sample size was set at 134 individuals. Initially, mothers who were under prenatal care were invited to participate in the study. Then, the aims were explained and if they were willing, a written informed consent was obtained from each participant. The eligible pregnant women were referred to the lab of Endocrine and Metabolism Research Center to provide blood samples to determine serum 25(OH)D concentrations, total calcium and phosphorus levels after they were assigned to the control or vitamin D groups, using block randomization strategy. The serum was separated within 1 h of sampling by centrifugation. All the serums were then coded, frozen at −70 °C and remained intact in the site until the end of the sampling.

The study participants were asked to complete a questionnaire to collect their demographic data, their supplements usage, and dairy product consumption. Maternal weight and height were measured using a standard scale while the subjects were dressed in light clothing. Body mass index was calculated as weight (in kilograms) divided by height squared (in meters).

According to the Canadian Pediatric Association recommendation, a daily amount of 2000 IU of vitamin D for pregnant and breast-feeding women is required [39,43]. Therefore, the intervention group received two 1000-unit vitamin D_3 pills (totally 2000 IU) daily from the 26–28 weeks of gestation until childbirth. The pills were manufactured by the Jalinous pharmaceutical company in Tehran, Iran. The control group received two placebo pills from 26 to 28 weeks of gestation until childbirth. The two study groups also received routine prenatal care. We monitored the consumption of vitamin D and placebo in later prenatal care visits and over the phone. If a mother had consumed the pills irregularly or in general or if the duration of consumption was <8 weeks, the mother was excluded from the study. The participants were followed up until delivery. The second stage of blood samplings were done at delivery.

After two stages of blood sampling, total calcium and phosphorus levels were measured by spectrophotometer and maternal serum 25(OH)D concentrations were measured using the Chemiluminescence immunoassay (CLIA) [44]. The lab technicians were blind to group allocations.

In order not to deprive the participants from antenatal supplements, all participating mothers were allowed to use the prescribed supplementation outside this study's protocol. However, we recorded how much vitamin D and calcium they had received through supplements. We also estimated daily dietary calcium intake of the participants according to the Clinician's Guide to Prevention and Treatment of Osteoporosis [45]. Then, the variable of total calcium intake was calculated using the sum of daily dietary calcium intake and daily calcium supplements.