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Comparison of the Effect of Two Doses of Vitamin D (Vit D-Ca and Vit D-Ca+Vit D) from the 16th Week on Preterm Labor in Pregnant Women

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ABSTRACT

Aims Preterm labor (delivery earlier than 37 weeks) is one of the most common problems with midwifery. Recently, vitamin D deficiencies have been reported with adverse maternal outcomes such as pregnancy toxicity, intrauterine growth limitation, and preterm labor. The aim of this study was to compare the effect of 2 doses of vitamin D (Vit D-Ca and Vit D-Ca+Vit D) from the 16th week on preterm labor in pregnant women.

Materials & Methods The present single-blind randomized clinical trial was conducted on 202 pregnant women referred to 5 obstetric and gynecological clinics in Bandar Abbas, Hormozgan province, Iran during January 2016 to March 2017. The subjects were selected by randomization sampling method and were randomly assigned into group A (n=150) and group B (n=152). Group A received Vit D-Ca supplements, containing 400 IU/day, and group B received Vit D-Ca supplement plus Vit D (with D3 brand), containing 1000 IU/day from the 16th week of pregnancy until delivery. The subjects were examined from the 16th week of pregnancy until delivery. The data were analyzed by SPSS 21 software, using independent t-test, Mann-Whitney U test and Chi-square test.

Findings The incidence of preterm labor in the group receiving Vit D-Ca+Vit D (group B) was 24 (16.0%) and in the group receiving Vit D-Ca alone was 25 (16.7%). There was a significant difference between the two groups in terms of preterm labor (p=0.01).

Conclusion Vit D-Ca plus Vit D intake reduces preterm labor in pregnant women more than Vit D-Ca alone intake.

Keywords Vitamin D; Preterm Labor; Pregnancy

CITATION LINKS

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Introduction

Preterm labor (delivery earlier than 37 weeks) is one of the most common problems with midwifery, resulting in death of over 1 million newborns worldwide, and it is the second leading cause of death in children younger than 5 years [1]. The detection of high-risk individuals to prevent preterm labor is considered a health priority [1-3]. Recently, vitamin D deficiencies have been reported with adverse maternal outcomes such as pregnancy toxicity, intrauterine growth limitation, and preterm labor; however, their results are contradictory. Based on some studies, vitamin D deficiency during pregnancy is associated with an increased risk of preterm labor. Wagner *et al*. have reported that vitamin D serum levels lower than 20ng/ml increase the risk of preterm labor 3.81 times more than vitamin D serum levels more than 40ng/ml [4]. Bodnar *et al*. reported that the risk of preterm labor with vitamin D serum level of 36ng/ml is reduced and, then, reaches to a constant level [5]. Zhou *et al*. reported that vitamin D deficiency is associated with lower risk of preterm labor. They found that the prevalence of preterm labor was higher in 25(OH)D (25-hydroxy vitamin D)≥30ng/ml than the low level (≤20ng/ml) and medium level (20-30ng/ml) in southern China [6]. However, Flood *et al*. and Rodriguez *et al*. reported that vitamin D deficiency during pregnancy is not associated with preterm labor [7, 8].

Vitamin D is a unique and essential micronutrient, whose main and important function is maintaining calcium homeostasis and skeletal well-being. With the deficiency of this vitamin, only 10% to 15% of calcium and 60% of phosphorus can be absorbed [9]. Low levels of vitamin D (lower than normal) are one of the problems of the community in the 21st century [10, 11]. Serum levels of 25(OH)D more than 30ng/ml and less than 20ng/ml were considered ideal and deficient statuses, respectively [12]. Levels of 25(OH)D less than 25ng/ml during pregnancy in pregnant women were 17% to 18% in Caucasus, 61% in New Zealand, 32% to 42% in India, 59% to 84% in Kuwait, 84% in Iran, and 75% in UAE [13-17]. Low levels of vitamin D during pregnancy have been effective on maternal and fetal calcium homeostasis and are expected to affect bone development [18].

Currently, the recommendations for daily intake of vitamin D vary from 400 to 600 IU (Medical Association), 1500 to 2000 IU (Endocrinology Association), and 2000 IU (Canadian Association) [19]. According to the Royal College of Obstetricians and Gynecologists, in terms of vitamin D supplementation intake, people are divided into 3 groups: Normal people, 400 IU should be available to all pregnant women, high-risk people, 1000 IU such as obese or dark-skinned women, and 2000 IU involved with the Cholecalciferol treatment at least taking 4 to 6 weeks for those who have deficiency. Many specialists agree to 1000 to 2000 IU/day, and it is suggested that even up to a dose of 4000 IU/day is safe in pregnancy and lactation [20].

The prevalence of vitamin D deficiency in the Middle East is much higher than in the United States and Europe; it seems that how to wear is a significant factor in the incidence of vitamin D deficiency in the Muslim and Middle Eastern countries [12]. Hormozgan province is one of the deprived southern provinces of Iran that, based on the Ministry of Health, is in an unfavorable situation in terms of malnutrition and food insecurity [21]. The shortage of micronutrients and all types of vitamins in high-risk groups, including pregnant women, is on the rise. Regarding the mentioned issues and lack of research on the relationship between vitamin D and preterm labor in Iran, the aim of this study was to compare the effect of 2 doses of vitamin D (Vit D-Ca and Vit D-Ca+Vit D) from the 16th week on preterm labor in pregnant women.

Materials and Methods

The present single-blind randomized clinical trial was conducted on pregnant women referred to 5 obstetric and gynecological clinics in Bandar Abbas, Hormozgan province, Iran during January 2016 to March 2017. After approving the research at the Ethics Committee of Hormozgan University of Medical Sciences, the subjects were selected by randomization sampling method by computer generation.

At first, 420 people were evaluated, of whom 10 were not eligible. Therefore, 410 subjects entered the study by presenting written consent. They were randomly assigned into group A and group B (205 people in each group), using homogeneous and similar envelopes. Of group A, 45 subjects and of group B, 41 subjects left the study for personal reasons. In the next step, 10 subjects in group A and 12 subjects in group B were excluded due to fear of side effects and Ca-D intolerance. Finally, 150 subjects in group A and 152 subjects in group B remained. Considering 50% loss, the sample size was estimated at least 150 people per group [4].

Inclusion criteria consisted of gestational age less than 10 weeks, no history of diabetes and blood pressure, Iranian nationality, no history of polycystic ovaries, no history of diabetes and blood pressure in first-degree relatives, willingness to participate in the study, body mass index (BMI) between 19 to 26Kg/m^2, no intake of vitamin D in the last 6 months, single pregnancy, and vitamin D levels ranged between 30-70ng/ml. Exclusion criteria consisted of embryos with anomalies, reluctance to participate in the study, thyroid and parathyroid diseases, kidney disease (Creatinine>2), known liver disease, sarcoidosis, tuberculosis, consumption of anticonvulsant medications or drugs such as corticosteroids that affect metabolism of vitamin D and calcium.

The researcher did not know about the allocation of

subjects to the studied groups. Group A received Vit D-Ca supplements, containing 400 IU/day from the 16th week of pregnancy until delivery, and group B received Vit D-Ca supplement plus Vit D (with D3 brand), containing 1000 IU/day (Zahravi; Tabriz, Iran) from the 16th week of pregnancy until delivery. The subjects were examined from the 16th week of pregnancy until delivery. The care intervals were based on the guideline of Ministry of Health and the measures taken were listed (Table 1).

The data were analyzed by SPSS 21 software, using Kolmogorov-Smirnov test to examine the normal distribution of data, independent t-test for quantitative variables (age, educational level of the pregnant women and husbands), and Mann-Whitney U test and Chi-square test for qualitative and ranking variables (gravid, parity, number of children, abortion, and stillborn).

Table 1) Measures taken at each visit of pregnant women in group A (n=150) and group B (n=152)

Weeks 10-15
- Mother information: age, Body Mass Index, educational level and occupation
- Weight and blood pressure measurement
- Common tests include FBS, CBC/Diff, BUN/Cr, and UA/UC
–PUQE index for evaluating nausea and vomiting
Weeks 16-20
- Weight and blood pressure measurement
- PUQE index for evaluating nausea and vomiting
- Cervical incompetence measurement
- Request preterm delivery ultrasonography at weeks 16-18
-(Formulation, evaluation of amniotic fluid volume)
Weeks 26-30
- Weight and blood pressure measurement
- Common tests include FBS, CBC/Diff, BUN/Cr, and UA/UC
Weeks 31-34
- Weight and blood pressure measurement
Request preterm delivery ultrasonography at weeks 31-34 (evaluation of amniotic fluid volume, fetal growth and placenta evaluation)
Weeks 35-37
- Weight and blood pressure measurement

Findings

The two groups (A and B) did not significantly differ in terms of age, educational years of women and their husbands, gravid, parity, abortion, number of children, stillborn, and first-trimester visit (Tables 2, 3, and 4).

The incidence of preterm labor in the group receiving Vit D-Ca+Vit D (group B) was 24 (16.0%) and in the group receiving Vit D-Ca alone was 25 (16.7%). There was a significant difference between the two groups in terms of preterm labor (p=0.01).

Table 2) Comparison of the mean age and educational level of pregnant women and their husbands in group A (n=150) and B (n=152)

Group A	Group B	t	P.value
Age (years)			
26.84±4.71	26.14±4.72	1.48	0.13
Educational level (years)			
12.50±2.97	12.45±3.17	0.18	0.85
Educational level of husband (years)			
14.33±2.42	14.44±2.51	0.43	0.66

Table 3) Comparison of the absolute and relative frequency of (numbers in parentheses are percentages) variables related to pregnancy in group A (n=150) and group B (n=152)

Variables	Group A	Group B	P.value
Gravid (pregnancy)			
First	84 (56.0)	82 (53.9)	
Second	36 (24.0)	50 (32.9)	0.99
Third	30 (20.0)	20 (13.2)	
Parity (pregnancy date to week 20)			
Zero	76 (50.7)	103 (67.8)	
One	27 (18.0)	40 (26.3)	0.79
Two	47 (31.3)	9 (5.9)	
Abortion			
Zero	117 (78.0)	120 (78.9)	0.92
One	33 (22.0)	32 (21.1)	
Number of children			
Zero	114 (76.0)	119 (78.3)	
One	30 (20.0)	24 (15.8)	0.43
Two	6 (40)	9 (5.9)	
Number of stillborn			
Zero	141 (94.0)	136 (89.5)	0.6
One	9 (6.0)	16 (10.5)	

Table 4) Comparison of the levels of biochemical variables in the first visit (first trimester) between groups A (n=150) and B (n=152)

Variables	Group A	Group B	t	P.value
Hb (g/dL)	11.07±1.43	11.35±1.42	1.98	0.7
Platelet ($\times 10^9$/L)	277.37±48.35	279.17±50.02	0.37	0.71
MCV (femtoliter)	80.77±4.76	81.81±4.43	2.25	0.6
FBS (mg/dl)	79.11±6.54	79.40±6.25	0.46	0.64
BUN (mg/dl)	14.24±2.59	14.15±2.67	0.32	0.74
Cr (mg/dl)	0.68±0.60	0.63±0.13	1.04	0.290

Discussion

The aim of this study was to compare the effect of 2 vitamin D doses (Vit D-Ca and Vit D-Ca+Vit D) on preterm labor in pregnant women in Hormozgan province, Iran. The effect of the deficiency and inadequate level of vitamin D-Ca on the consequences of pregnancy has been controversial; although observational research studies have reported limited results, there are currently few guidelines on the management of vitamin D in pregnancy. The present study showed that the prevalence of preterm labor in the Vit D-Ca plus Vit D was significantly lower than Vit D-Ca alone.

Due to the well-known association of vitamin D deficiency and inflammatory symptoms, some studies have suggested vitamin D in preventing preterm labor. Some studies have shown that the level of 25(OH)D in pregnancy has a negative correlation with the risk of preterm labor or reduces the gestational age [22, 23]. However, some studies have not shown such an association [24, 25]. Previous studies were conducted in twin pregnancy on American Pregnant women [22] and Tanzanian mothers infected with the HIV virus [19]. In a study in North Carolina, in women with preterm labor and lack of chorioamnionitis, there was no association between the first-trimester vitamin D level and per se preterm labor [26].

There are also few research studies on the effects of vitamin D and preterm labor. Only one study has

shown that vitamin D did not affect preterm labor before 37 weeks in doses of 2000-4000 IU from 12th to 16th weeks of pregnancy until delivery. However, this study was designed to assess safety and lacked sufficient statistical power to evaluate the effect of Vit D supplement on adverse pregnancy outcomes [27].

To date, the pathophysiological mechanisms involved in preterm labor have been important. In fact, preterm labor is a syndrome, but there is strong evidence showing that intrauterine infection is a common mechanism for this type of labor. It has been suggested that vitamin D affects the physiological pathways involved in the preterm labor pathogenesis, such as inflammation, immunomodulation, and the translation of the genes involved in the pair function [28-30]. The differences in the current research and earlier studies may be due to racial differences affecting the vitamin D function that has already been proven [31] and includes heterozygosity in parathyroid function, expression of vitamin D receptor, protein bounded to vitamin D, or enzymes involved in the metabolism of vitamin D [32].

One of the limitations of the present study is not measuring other symptoms involved in the metabolism of vitamin D. The concentration of protein bounded to vitamin D affects bioavailability of 25(OH)D. Because 25(OH)D is bounded to the vitamin D binding protein and the serum level of 25(OH) D alone is an inadequate indicator of vitamin D function [27]. The 2000 IU/day dose was not available in Iran and 1000 IU/day pill was selected due to poor compliance and poor financial condition of pregnant women in Hormozgan province. Also, the random selection of the present research population may not be true for the whole Hormozgan province and limit the generalizability of the findings. It is suggested to conduct clinical trials with larger sample sizes.

Conclusion

Vit D-Ca plus Vit D intake reduces preterm labor in pregnant women more than Vit D-Ca alone intake.

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Ethical Permissions: The Ethics Committee of Hormozgan University of Medical Sciences approved this study. Informed consent was obtained from all subjects. According to the ACOG guidelines, receiving 4000 IU/day vitamin D during pregnancy is safe. The registration code on the international clinical trial site is RCT2016121430612N2.

Conflict of Interests: The authors declare that there is no conflict of interests.

Authors' Contribution: Mosallanejad N.S. (First author), Introduction author/ Methodologist/ Original researcher/ Discussion author (20%); Taghavi A.V. (Second author), Methodologist/ Assistant (20%); Saadat M. (Third author), Methodologist/ Assistant (20%); RaJaii M. (Fourth author), Introduction author/ Methodologist/ Discussion author (20%); Bazarganipour F. (fifth author), Introduction author/ Methodologist / Statistical analyst/ Discussion author (20%)

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