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Comparing the Effect of Different Doses of Vitamin D Supplementation During Pregnancy on Prevention of Adverse Pregnancy Outcomes; a Randomized Clinical Trial

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ABSTRACT

Aims Repeated pregnancy loss (RPL) is commonly considered as ≥3 fetal losses previously 20 weeks of gestation. Vitamin D has an important role on immune inflection at the maternal-fetal part. Though, vitamin D can be utilized as a useful approach to treat patients with repeated pregnancy loss. There was lack of consensus on prescribing Vitamin D during pregnancy to prevent pregnancy complications. However, the present study was conducted to compare the effect of low and high dose of Vitamin D on to prevent pregnancy complications.
Materials & Methods We conducted a single-blinded, randomized controlled trial in Yasuj, Iran, to assess the influence of different doses of vitamin D supplement through pregnancy in women on pregnancy and birth outcomes (preterm births and stillbirths, pre-eclampsia, gestational diabetes and low birth weight.
Findings Patients (n=150) in their first trimester were enrolled and randomized to two groups of vitamin D supplementation; 500IU/day (group A; n=70) and 2000IU/day (group B; n=70). 131 patients completed the intervention. Maternal vitamin D supplementation 2000IU/day had a positive effect only on gestational diabetes mellitus, spontaneous miscarriage and preeclampsia and preterm births but there was no statistically significant difference between two groups (p>0.05).
Conclusion Increasing dose from 500 units to 2000 units per day does not increase the effectiveness of vitamin D to decrease pregnancy complications. Vitamin D supplementation (500 IU/day) appeared sufficient to reduce the risk of pregnancy complications as well as the higher dose.

Keywords Vitamin D; Spontaneous Miscarriage; Neonate Birth; Preterm Labor

CITATION LINKS

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Introduction

Some observational studied were indicated that vitamin deficiency during pregnancy increase risks of, Preterm labor, recurrent pregnancy losses, gestational diabetes, spontaneous miscarriage, preeclampsia, and low birth weight are common in pregnant mothers [1]. Preterm labor is considered one of the major causes of neonatal mortality and neonatal complications after fetal malformations. Preterm labor pain occurs when contractions and changes in the cervix begin before week 37 [2]. Preterm labor is relatively common and occurs in 5 to 18% of the labors around the world Preterm birth occurs spontaneously in 70 to 80% of the cases. Maternal or fetal problems that endanger the health of the mother or fetus, for example, preeclampsia, placenta previa, placental abruption, fetal growth restriction, and multiple pregnancy complications can also result in spontaneous preterm labor Preterm labor is the most common cause of neonatal mortality at present [1-3].

Miscarriage is defined as the termination of pregnancy before the week 22 of pregnancy. More than 80% of spontaneous miscarriages occur within the first 12 weeks of pregnancy. Based on the statistics presented by the Ministry of Health and Medical Education, 80000 miscarriages occur annually in Iran [3]. Many risk factors are associated with increasing the risk of pregnancy loss. The most important risk factors for spontaneous miscarriage are increased maternal age, previous spontaneous miscarriage, and maternal smoking [4]. Approximately 50% of all spontaneous miscarriages include chromosomal abnormalities and the remaining 50% are related to environmental and dietary factors that may be preventable. Vitamin D plays a key role in pregnancy safety [5].

Vitamin D is one of the fat-soluble vitamins essential for normal bone metabolism. Various non-bone-related metabolic processes also require this vitamin. Vitamin D is an essential and unique micronutrient whose main function is to maintain calcium and phosphorus hemostasis. As a result of this vitamin deficiency, only 10-15% of calcium and 60% of phosphorus in the food are absorbed, while the calcium absorption increases to 30-40% and phosphorus absorption increases to 80% with the presence of the Vitamin D. Some people also argue that the serum level needed in an individual with healthy bones is needed for potentially beneficial non-calcium effects should be at least 75nmol/lit [6]. This vitamin plays a significant role in human health, survival, and fertility [7]. The National Institute of Medicine has recommended its serum level to be 50nmol/lit. Its daily intake has been also recommended to be 600 units in the general population [8]. Vitamin D regulates the protein related to the parathyroid hormone, which is a muscle relaxant. This vitamin reduces gene expression and may be involved in stimulating uterine contractions [9, 10]. Vitamin D deficiency is a common pregnancy problem in different parts of the world. There is a strong correlation between Vitamin D deficiency and different consequences of pregnancy. However, the role and metabolism of this vitamin in pregnancy have not been still clarified [11].

Based on a study conducted by Samimi *et al*. the results revealed that the intake of Vitamin D3 and finally adequate serum level of Vitamin D3 in the mother's body led into reduced serum level of interleukin-23 and miscarriage in mothers with a history of recurrent miscarriage [4]. Moreover, in a study conducted by Ghaedi *et al*., the results showed that the serum level of Vitamin D was in the range of 11.5ng/ml in women with a history of two miscarriages. It was concluded that vitamin D deficiency plays a major role in unexplained miscarriage in women with recurrent miscarriage (due to a defect in the inflammatory-immune response). Hence, the routine test of Vitamin D3 and the administration of Vitamin D supplementations are important in pregnant women with a history of recurrent miscarriage [12]. However, In a study conducted to evaluate the relationship between serum level of 25-hydroxy Vitamin D and gestational diabetes in pregnant women, Hosseini *et al.* found that The mean values of 25-hydrozxy-vitamin D level were 29.4±19 and 24.13±13.3 in the case and control groups The results was a revealed a significant difference between the two groups (p=0.042) [13].

As Vitamin D can have different effects on human health, it is necessary to study the relationship of vitamin D deficiency with the consequences of pregnancy more closely in order to take necessary steps, if a strong associated is found between them. The present study was conducted to compare the effect of low and high dose of Vitamin D on pregnancy outcomes including Preterm labor pain, spontaneous miscarriage, and low birth weight.

Materials and Methods

This Single-blind randomized clinical trial study was conducted on pregnant women that referred to obstetric and gynecological clinics in Yasuj, Iran in March 2016 to January 2017. In the present study, the interventions were taking Vitamin D in different doses including Vitamin D 500IU/day and Vitamin D 2000IU/day supplements. Moreover, primary outcomes were premature labor, spontaneous miscarriage, and Birth weight, and secondary outcome were preeclampsia, diabetes, and Labor type.

The sample size is based on the formula of comparing two ratios by considering α%=05.0, β=1-80%, p1=12 p2=30% [14], the sample size in each group estimated 77, and including 10% drop, it increased to 85 people in each group. 130 subjects entered in the study by presenting written consent. Then subjects were

assigned into two groups A and B using block randomization sampling method.

The research inclusion criteria consisted pregnant women aged 20-37, and gestational age less than 12 weeks. However, exclusion criteria were no history of diabetes and high blood pressure, and any critical illness such as chronic diseases, cardiovascular disease, cancer, and depression.

The data was gathered by a form including age, BMI, number of pregnancies, education, labor type, premature labor, spontaneous miscarriage, Preeclampsia, diabetes, and Birth weight

Group a received Vitamin D 500IU/day supplements and group B received Vitamin D 2000IU/day supplement from the 12th week of pregnancy until delivery. All participants were fallowed from 12th week of pregnancy till delivery. Both interventions were conducted by one of researcher (gynecologist), however, the intervention was single-blind (participants).

Data were analyzed using SPSS 23 software by independent t-test for quantitative variables. Means were compared between groups through an analysis of variance (ANOVA) test for continuous variables and were adjusted for confounders and Chi-square test for qualitative and ranking variables.

Findings

Patient (n=150) in their first trimester were enrolled and randomized to two groups of vitamin D supplementation: 500IU/day (group A; n=66), 2000IU/day (group B; n=65) completed the intervention. During the study, about 10 patients were excluded from both groups. They were evaluated in terms of spontaneous miscarriage, low birth weight, and preterm labor. During the study, about 10 patients were excluded from both groups. Characteristics were similar between both groups in terms of maternal age, education and Number of pregnancies and did not significantly differ between two groups (Table 1).

Table 1) Demographic information of women participating in the study

Parameter		Group A (n=66)	Group B (n=65)	p Value
Age (year)		28.7±4.9	29.1±5.0	0.3
BMI (kg/m^2)		25.3±4.0	25.6±4.8	0.55
Number of pregnancies	First	36 (54.5%)	39 (60%)	0.77
	second	17 (25.7%)	13 (20%)	
	third	13 (19.6%)	13 (20%)	
Education	Bachelor or less	62 (93.7%)	60 (91.6%)	0.22
	Higher than bachelor	4 (6.3%)	5 (8.4%)	

Although normal vaginal labor was more common in both study groups than caesarean section births, and in the Vitamin D 500 intervention group, the percentage of normal vaginal labor was higher than the Vitamin D 2000 intervention group (41 vs. 36). However, these differences between the groups were not significant. There were no statistically significant differences between the two groups in the variables of labor, preterm labor, spontaneous miscarriage, preeclampsia, diabetes, and birth weight (Table 2).

Table 2) Comparison of the frequency of pregnancy outcomes in study groups (The numbers in parentheses are percentage)

Parameter		Group A	Group B	p Value
Labor type	Normal	41 (62.1)	36 (55.4)	0.434
	Cesarean	25 (37.9)	29 (44.6)	
Premature labor	No	58 (87.9)	57 (87.7)	0.974
	Yes	8 (12.1)	8 (12.3)	
Spontaneous miscarriage	No	58 (87.9)	63 (96.9)	0.051
	Yes	8 (12.1)	2 (3.1)	
Preeclampsia	No	63 (95.5)	65 (100)	0.082
	Yes	3 (4.5)	0 (0)	
Diabetes	No	60 (90.9)	61 (93.8)	0.527
	Yes	6 (9.1)	4 (6.2)	
Birth weight	No	8 (4/36)	12 (46.2)	0.226
	Yes	14 (63.6)	14 (53.8)	

Discussion

There is a strong correlation between Vitamin D deficiency and different consequences of pregnancy. However due to lack of efficient study to compare the effect of different dose of vitamin D on pregnancy outcomes this study was to compare the effect of 2 vitamin D doses of Vit D on pregnancy outcomes in Yasuj city, Iran.

In the present study, there was no significant relationship between the type of labor between the Vitamin D 500 Group and Vitamin D 2000 Group. Increasing the dose did not affect the type of labor. Some studies have indicated that Vitamin D deficiency is a factor involved in reducing uterine contractions, which has led to an increase in cesarean section. However, the effective and positive dose of this vitamin has not been clarified yet [14]. Strong association was observed between vitamin D deficiency and cesarean section type of labor [15, 16]. In line with this study, in a randomized trial study on Vitamin D supplementation, no difference was found between the control group and the group received Vitamin D in the rate of cesarean section [17]. The reason for the difference in the results of the studies may be due to the difference in the sample size.

Our study showed there was no significant difference between two groups as preterm labor. Also, in a study to evaluate preterm labor in patients with Vitamin D deficiency, a significant relationship was found between Vitamin D deficiency and the prevalence of preterm labor [18, 10]. But In a study conducted by Mojebian *et al.* to evaluate the effects of Vitamin D and its role on neonates and mothers, Vitamin D 400units/day were compared with Vitamin D 50000units/every 2wk in preterm labor revealed no significant difference between high doses and low doses of Vitamin D that similar to our study [19].

The present study was indicated, there was no significant difference between two groups in spontaneous miscarriage. In the meta-analysis study conducted by Kofi Amegah *et al.* in 2017, 18 studies

were reviewed and no association was found between Vitamin D deficiency and spontaneous miscarriage [20].

Although the present study also revealed a higher rate of preeclampsia in the group receiving Vitamin D 500 than in the group receiving Vitamin 2000 D, no significant relationship was reported between these two groups in this regard. People with hypertension had a low Vitamin D level, increased prevalence of preeclampsia in pregnant women can be justified [9]. Moreover, the results of studies by Fogacci *et al*. and Dahma *et al*. indicated that vitamin D supplementation probably useful in preventing preeclampsia [21, 22]. In a study carried out by Bodnar *et al*. in 2015, a significant relationship was reported between preeclampsia and low level of Vitamin D in women with the gestational age of less than 22 weeks [18]. In contrast to the mentioned research, in a study conducted by Behjat Sasan *et al* to examine Vitamin D levels in the first trimester and pregnancy complications at the end of pregnancy, no significant relationship was found between decreased Vitamin D levels and increased preeclampsia at the end of pregnancy [23]. The reason for the difference in the results of the studies may be due to difference dose of vitamin D can utilized.

In the present study, there was no significant relationship between the group receiving Vitamin D 500 and the group receiving Vitamin D 2000 incidence of diabetes. Reviewing 7 studies in a meta-analysis study by Poel *et al*., it was concluded that the incidence of gestational diabetes is negatively and directly associated with low levels of Vitamin D [24-26]. Moreover, Wang and *et al*. in a meta-analysis study indicated that vitamin D supplementation in GDM women can control blood sugar and reduce adverse maternal-infant outcomes. In a study by Mojibian, a significant difference was found between the incidence of diabetes and Vitamin D intake in two different doses of 400 units daily and 50000 units once every two weeks, so that the incidence of gestational diabetes was low in the group receiving Vitamin D 50000 units once every 2wk [20, 27]. One reason for non-significant differences between the two study groups might be the minimum dose of vitamin D to reduce the incidence of diabetes in pregnant women is 500 units/day, and its increase has no much effect. However, further studies are needed in this area.

No significant difference was found between low birth weight and Vitamin D intake in two different doses. This result is in line with the study conducted by Mojebian that no significant difference was found between the group receiving Vitamin D 400 units per day and the group receiving Vitamin D 50000 units every 2wk [19]. However, in a study conducted by Lapillonne *et al*., a significant association was reported between low birth weight and low Vitamin D level [28]. Due to the lack of studies comparing different doses of vitamin D in low birth weight one meta-analysis showed that vitamin D supplementation improves growth and vitamin D level in low-birth-weight infants [29].

Vitamin D supplementation 2000IU/day might may reduce the risk of pregnancy complications and vitamin D deficiency in pregnant women and neonatal disorders, but in the present study there was no significant difference between 500 and 2000IU/day dosage in complications of pregnancy. However, it cannot be said that only vitamin D determines the occurrence of pregnancy outcomes and complications, because other factors besides this vitamin affect the occurrence of these outcomes. On the other hand, WHO and Institute of Medicine guidelines on vitamin D supplementation during pregnancy (200–600 IU/day) could be revised for populations of women at risk of deficiency in order to improve their vitamin D status. On the other hand, the WHO and Institute of Medicine guidelines for vitamin D supplementation during pregnancy are that 200-600 IU of vitamin D per day can be recommended for pregnant women at risk of vitamin D deficiency to improve their vitamin D intake. Based on this and the results of the present study, it can be said that the dose of 500 IU vitamin D can be recommended to pregnant women and there is no difference with the dose of 2000 IU in terms of pregnancy complications.

The present study had some limitations. The role of other confounding and influencing variables on the occurrence of these consequences has not been considered, controlled and investigated. The second limitation is that randomization was not done and it would have been better to compare a control group without vitamin D intervention with two intervention groups, but it was not possible due to ethical considerations.

Based on the results of the present study and if the results are confirmed in other clinical trial studies, this vitamin can be prescribed even with a dose of 500 to prevent pregnancy complications. But it should be noted that in prescribing vitamin D dosage for pregnant women, not only pregnancy complications are considered, but also the need to increase calcium and vitamin D to prevent physical disorders of the mother. However, it is suggested that in future studies, the control group without vitamin D should be considered in order to compare the effect of vitamin D on pregnancy c and maternal complications. In addition, the study should be conducted with a clinical trial method on a larger sample by controlling or examining other confounding variables.

Conclusion

Increasing dose from 500 units to 2000 units per day does not increase the effectiveness of vitamin D to decrease pregnancy complications.

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Ethical Permissions: The Ethics Committee of Yasouj 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 Ethics Committee of Yasouj University of Medical Sciences approved. (IR.YUMS.REC.1396.191)

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

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