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Does Vitamin D Level Cause Recurrent Miscarriages? A Cross-Sectional Study on Pregnant Women in Isfahan, Iran

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Abstract

Introduction: Recurrent miscarriage is one of the most common problems during pregnancy and one of these factors that has been recently studied by researchers is vitamin D deficiency in pregnant women. Therefore, this study was performed to compare vitamin D levels in women with recurrent miscarriage and women with normal pregnancies.

Methods: The present study is a descriptive-analytical and cross-sectional study conducted in 2020 on 120 pregnant women referred to infertility centers in Isfahan in two groups of women with at least one successful pregnancy and women with recurrent miscarriage. Vitamin D blood levels of women were extracted from the information in their file. Data were analyzed using SPSS software.

Results: The mean concentration of vitamin D in the case group was 19.92±5.07 and in the control group was 23.33±4.20 showing a statistically significant difference between the two groups (P <0.05). Mean vitamin D was also significantly different between the two groups in terms of the number of previous children, number of pregnancies, abortion, and stillbirth (P <0.05).

Conclusion: Serum vitamin D levels in women with recurrent miscarriage are lower than women with normal pregnancies. Therefore, low levels of vitamin D in the blood can be one of the causes of recurrent miscarriage in pregnant women.

Keywords: Vitamin D, Pregnancy, Recurrent Miscarriage, Mothers, Hospitals

Introduction

Vitamin D is a fat-soluble vitamin with a steroidal structure that is essential for calcium absorption, development, and maintenance of the bone structure. The most important source of vitamin D in the body is made by the sun's ultraviolet rays from the 7 hydrocholesterol in the skin.[1,2] Age, season, latitude, sun exposure, skin type, type of coverage, and use of sunscreen are some of the factors that can affect the production of vitamin D.[3,4] Animal source foods including egg yolks, animal liver, and cod liver oil are other sources of vitamin D. The most important form of vitamin D in the bloodstream is 25-hydroxyvitamin D (25-OH-D), and its blood level is the best indicator of the total vitamin D level.[5,6]

Cases such as urbanization and low exposure to sunlight due to occupational, social, and geographical conditions of people lead to a decrease in vitamin D levels in the body.[7] One of the comprehensive problems of the 21st century is lower than normal levels of vitamin D in individuals. Some people are more prone to vitamin D deficiency than others, most notably pregnant women, whose vitamin D deficiency is almost common and may be more severe in the second and third trimesters of pregnancy.[8,9]

As pregnancy increases the need for vitamins,[10] vitamin D deficiency is also observed significantly during this period and it is referred to as a pandemic so that the prevalence of this deficiency in pregnant women is estimated to be between 20 and 85%.[11,12] Previous studies have shown that maternal vitamin D deficiency during pregnancy can have detrimental consequences for both mother and fetus, such as gestational diabetes, maternal hypertension, skeletal growth disorders, and brain development as well as

fetal immune system function.[13-17] In other words, low levels of vitamin D during pregnancy are associated with health problems and various consequences such as implantation of eggs to adult diseases.[18]

Recurrent miscarriage is one of the most common problems during pregnancy, in which various factors are involved. In recent studies, researchers have linked vitamin D deficiency in pregnant women to recurrent miscarriage, thus it is necessary to examine the relationship between vitamin D deficiency and pregnancy outcomes more closely so that if strong relationships are found in this regard, basic measures must be taken to improve pregnancy outcomes

Materials and Methods

The present study is a descriptive-analytical and cross-sectional study conducted in 2020 in case and control groups. The control group included women with at least one successful pregnancy and the case group included women with recurrent miscarriages. The study population consisted of women referring to specialized infertility centers in Isfahan, Iran with a history of recurrent miscarriage and the control group included women referring to specialized obstetrics and gynecology hospitals in Isfahan, Iran with at least one successful pregnancy. Using the following formula, 63 individuals were estimated as research samples. By simple random sampling method, 60 individuals in the case group and 60 in the control group were included in the study based on the inclusion and exclusion criteria.

$$n=\frac{(Z_1+Z_2)^2(2S^2)}{d^2}$$

$$n=\frac{(1.96+0.84)^2(2S^2)}{0.25S^2}\approx 63$$

Inclusion criteria included being in the age range of 18-41, not taking vitamin D with a level of more than 411 international units, and not having certain diseases such as cardiovascular diseases, kidney diseases, liver diseases, and thyroid diseases. Also, in the control group having at least one successful singleton pregnancy, and in the case group having repeated abortions (at least three abortions) were considered as the inclusion criteria. The exclusion criteria include an unwillingness to cooperate in the project, consumption of alcohol, cigarettes, and other drugs, and sunbathing.

Information was collected about mothers such as age, education levels, number of pregnancies, number of children, vitamin D intake, number of stillbirths, number of abortions, sunbathing, smoking, drinking alcohol or taking other drugs, as well as specific diseases. To determine the serum level of vitamin D in the participants, the enzyme-linked immunosorbent assay (ELISA) method with Immunodiagnostic Systems (IDS) kit and Elisa Reader at 451 nm was used. The sensitivity of this kit is 5 nmol/l, equivalent to 2 ng/ml, 100 percent specificity with external variation coefficient in 10 samples of 5.3, 5.6, 6.7%, and internal coefficient of variation in 10 samples, respectively 6.4, 4.6, and 7.8%. In addition, laboratory equipment for blood sample testing was validated and calibrated.[19]

Results

This study aimed to investigate the relationship between serum vitamin D levels and recurrent miscarriage in which 120 individuals participated in two groups of 60 (successful pregnancy and recurrent miscarriage). The mean age of the participants was 34±4.2 years, the mean systolic and diastolic blood pressure was 75±3 mm Hg and 113±6 mm Hg, respectively, and the mean BMI was 24±1.

Table 1. Mean of Vitamin D, Age, BMI, and Blood Pressure (systolic and diastolic) in Case and Control Groups

Groups / Statistical Index	Case		Control	
	Mean	SD	Mean	SD
Vitamin D	19.92 P=0.0001	5.07	23.33	4.20
Age	34.36 P=0.402	4.16	34.13	4.35
BMI	25.02 P=0.329	1.93	24.61	1.87
Blood Pressure (Systolic)	113.33 P=0.891	6.28	113.66	6.36
Blood Pressure (Diastolic)	76.16 P=0.864	3.36	75.83	2.93

According to Table 1, there was a significant difference between the mean of vitamin D in the two groups (P <0.05). The results also showed that there was no significant difference between the case and control groups in terms of age, body mass index, and blood pressure (systolic and diastolic) (P >0.05). The results obtained from Table 2 showed that the mean of vitamin D in terms of age, body mass index, systolic blood pressure, and diastolic blood pressure was significantly different between the two groups (P <0.05).

Table 1. Mean of Vitamin D, Age, BMI, and Blood Pressure (systolic and diastolic) in Case and Control Groups

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Table 2. Mean Vitamin D in Case and Control Groups by Age, BMI and Self-pressure

Vitamin D		Case			Control		
		N (%)	Mean	SD	N (%)	Mean	SD
Sex	Less than 34 years	30 (50)	19.96	5.35	29 (48.3)	22.55	4.15
	More than 34 years	30 (50)	19.87	4.87	31 (51.7)	24.05	4.18
	P=0.039						
BMI	Thin	1 (1.6)	30	0	1 (1.6)	20.20	0
	Normal	29 (43.4)	18.98	4,48	43 (71.4)	23.51	4.43
	Overweight	30 (50)	20.49	5.32	15 (25)	22.97	3.80
	Fat	0	0	0	0	0	0
	P=0.391						
Blood Pressure (Systolic)	Less than 113	60 (100)	19.92	5.07	60 (100)	23.33	4.20
	More than 113	0	0	0	0	0	0
	P=0.001						
Blood Pressure (Diastolic)	Less than 75	38 (63.3)	19.56	5.16	44 (73.3)	22.94	4.41
	More than 75	22 (36.7)	20.53	4.98	16 (26.7)	24.41	3.45
	P=0.0001						

Table 3. Distribution of the Number of Pregnancies, Number of Children, Abortion, and Stillbirth in Case and Control Groups

Groups / Statistical Index		Case		Control	
		N	Percent	N	Percent
Number of Pregnancies	1 Pregnancy	0	0	1	1.7
	2 Pregnancy	0	0	36	60
	3 Pregnancy	33	55	23	38.3
	4 Pregnancy	25	41.7	0	0
	5 Pregnancy	2	3.3	0	0
	P=0.0001				
Number of Previous Children	Does not have	60	100	0	0
	1 Child	0	0	11	18.3
	2 Children	0	0	40	66.7
	3 Children	0	0	9	15
	P=0.0001				
Abortion	1 Time	0	0	12	20
	2 Time	0	0	40	66.7
	3 Time	40	66.7	8	13.3
	4 Time	20	33.3	0	0
	P=0.0001				
Stillbirth	Does not have	52	86.7	58	96.7
	1 Fetus	7	11.7	2	3.3
	4 Fetuses	1	1.7	0	0
	P=0.128				

Based on the obtained results from Table 3, there was a significant difference between the case and control groups in terms of the number of pregnancies, the number of previous children, and abortion (P <0.05). Also, there was no significant difference between these two groups in terms of stillbirth (P >0.05).

According to the results obtained from Table 4, there was a significant difference between the mean of vitamin D in terms of the number of pregnancies, the number of previous children, abortion, and stillbirth between case and control groups (P <0.05).

Table 4. Mean of Vitamin D in Case and Control Groups by the Number of Pregnancies, Number of Children, Abortion, and Stillbirth

Groups	Statistical Index	Women with Recurrent Miscarriages		Women with Successful Pregnancies	
		Mean	SD	Mean	SD
Number of Pregnancies	1 Pregnancy	0	0	20.20	0
	2 Pregnancy	0	0	23.77	4.31
	3 Pregnancy	20.38	5.09	22.78	4.09
	4 Pregnancy	18.73	4.54	0	0
	5 Pregnancy	27.15	6.85	0	0
	P =0.014				
Number of Previous Children	Does not have	19.92	5.07	0	0
	1 Child	0	0	23.96	3.25
	2 Children	0	0	22.96	4.68
	3 Children	0	0	24.20	2.82
	P =0.039				
Abortion	1 Time	0	0	23.95	3.10
	2 Time	0	0	23.02	4.71
	3 Time	20.18	5.35	23.97	2.92
	4 Time	19.40	4.55	0	0
	P =0.046				
Stillbirth	Does not have	19.83	4.67	23.27	4.26
	1 Fetus	21.37	7.75	24.90	1.55
	4 Fetuses	14.30	0	0	0
	P =0.0001				

Discussion

Abortion is one of the most common complications of pregnancy and one of the few problems that affect the lives of young couples.[20] Many studies have been performed on the role of vitamin D in reproductive health to examine the prevalence of vitamin D deficiency and the possible side effects of vitamin D deficiency in pregnant women and women of childbearing age with different results.[21-29]

In the present study, there was no significant difference between the two groups participating in the reaction in terms of mean age, blood pressure, and body mass index. In Moghadas Inanloo's study, both groups were similar in terms of mean age and body mass index of participants, but the blood pressure of participants was not measured.[19] According to the results of the present study, there was a significant difference between the two groups in terms of the number of pregnancies and the number of previous children. In the study of Moghadas Inanloo et al., there was no statistically significant difference between the two groups in terms of the number of pregnancies and the number of previous children.[19]

According to the results of this study, there was a significant difference between the two groups in terms of the number of abortions, but the two groups did not differ significantly in terms of stillbirth. The results of this study showed that the mean concentration of vitamin D in women who had recurrent miscarriages was 19.92 and in women who had at least one successful pregnancy was 23.33, which according to statistical analysis, there was a significant difference between the mean of vitamin D in the two groups. In the study of Moghadas Inanloo et al.,[19] and the study of Hou et al., there was a significant difference between the mean of vitamin D in the two groups.[30] However, in the study of Chen et al., there was no significant difference between the mean of vitamin D between the two groups of pregnant and infertile women, and the level of vitamin D was low in both groups.[31]

The results of this study showed that the mean of vitamin D in terms of abortion was statistically significant between the two groups (P <0.05). A review by Sharif et al. also showed that due to the role

of vitamin D in modulating the function of the immune system in maternal-fetal communication and creating a more suitable environment for pregnancy, its deficiency is associated with abortion.[32] A study by Kwak-Kim et al. also found that vitamin D deficiency was common in women with RPL, and those women with vitamin D deficiency had increased autoimmune and cellular immune abnormalities compared to women with normal vitamin D levels.[33]

The study by Yan et al. also showed that women with recurrent miscarriage had lower levels of vitamin D receptor expression in placental villi, decidua, and serum than normal pregnant women, indicating a decrease in vitamin D receptor expression in pregnancy may be associated with recurrent miscarriages.[34] However, in this study, the effect of expression or non-expression of receptor on vitamin deficiency and recurrent miscarriage was not investigated.

A study by Irani et al.[35] and Moukhah et al.[36] showed that vitamin D prepares the endometrium for pregnancy and that vitamin D deficiency reduces fertility by affecting the endometrium, while in this study, the effect of vitamin D on the endometrium was not studied independently and only the role of vitamin D on abortion was investigated. A study by Ji et al. showed that the use of vitamin D supplementation in women with recurrent miscarriage after two months improved the imbalance of Treg/Th17 ratio in vitro and the use of vitamin D could be an alternative treatment for recurrent miscarriage caused by vitamin D deficiency.[37] These findings were also consistent with the results of this study.

Finally, in this study, it was found that vitamin D deficiency is common in women of childbearing age in Isfahan, Iran, which is consistent with studies conducted in Iranian cities such as Isfahan,[38] Zahedan [39] and Tehran.[40]

Conclusion

According to findings, it seems that vitamin D deficiency in pregnant women can be one of the causes of recurrent miscarriage; therefore, evaluation of vitamin D levels in pre-pregnancy and during pregnancy examinations and vitamin D consumption in case of low levels of vitamin D compared to the normal can improve the outcome of the pregnancy and as a result can reduce recurrent miscarriage. However, for conclusive conclusions about the effect of this vitamin on recurrent miscarriage, it is necessary to conduct more extensive control studies.

Ethical Approval

This study was committed to the Helsinki principles and an informed consent was obtained from all participating patients. Patient information was kept confidential and no additional costs were imposed on patients. This study was approved by Najafabad Branch, Islamic Azad University Ethics Committee with the code of IR.IAU.NAJAFABAD. REC.1398.029.

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