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Original Article

Evaluation of the Relationship Between Serum Vitamin D Levels and First-Trimester Miscarriage: A Case-Control Study

Soheila Akbari[1], MD; Arian Karimi Rouzbahani[2,3], Medical Student; Masoumeh Ghaffarzadeh[1], MD; Golnaz Mahmoudvand[3], MD; Leila Fathi[4], MSc; Shaghayegh Mapar[2,3], MD; Parsa Namdari[5], Medical Student; Fatemeh Yari[1,3]*, PhD

[1]Department of Obstetrics and Gynecology, School of Medicine, Lorestan University of Medical Sciences, Khorramabad, Iran
[2]Student Research Committee, Lorestan University of Medical Sciences, Khorramabad, Iran
[3]USERN Office, Lorestan University of Medical Sciences, Khorramabad, Iran
[4]Midwifery Department, School of Nursing and Midwifery, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[5]Faculty of Medicine, University of Debrecen, Hungary

Corresponding author:* Fatemeh Yari, Associate Professor of Reproductive Health, Lorestan University of Medical Sciences, Khorramabad, Iran. **Tel: +98 9163613621; **Email:** yariacademic@gmail.com

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Abstract

Background: Vitamin D deficiency/insufficiency can be regarded as a crucial public health obstacle that affects about 50% of the world's population. Pregnant women are at a relatively high risk of developing deficient concentrations of vitamin D, which can result in detrimental pregnancy outcomes. This survey was designed to evaluate the correlation between serum vitamin D concentrations and first-trimester spontaneous abortion.
Methods: This was a case-control study conducted at the Asalian Referral Gynecological Hospital in Khorramabad, Iran, from April 2021 to March 2022. Forty-two women hospitalized due to spontaneous pregnancy loss in the first trimester were recruited as cases, and 100 individuals referred for routine pregnancy care constituted the control group. Demographic and clinical data were recorded for all subjects, and blood samples were taken from both groups to determine serum vitamin D levels. The data were recorded on a researcher-made checklist. The chi-squared test and logistic regression were used for analysis in SPSS version 22.
Results: The frequency of vitamin D deficiency/insufficiency was higher in the case group (n=10, 23.8%) than in the control group (n=21, 21%), although this difference was not significant (P=0.899). Logistic regression revealed a significant link between vitamin D deficiency/insufficiency and age (P<0.001), gestational age (P=0.005), and body mass index (P<0.001).
Conclusion: The results suggested no significant association between vitamin D deficiency/insufficiency and miscarriage during the first trimester.

Keywords: Vitamin D deficiency, Spontaneous abortion, Pregnancy outcome, Hypovitaminosis

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1. Introduction

Vitamin D (calciferol) is an important steroid hormone that plays a pivotal role in preserving bone tissue and regulating calcium levels. Vitamin D3, which is derived from animal sources, is produced in the skin through non-enzymatic processes influenced by ultraviolet B. However, vitamin D2 is mostly produced by plants (1, 2). Vitamin D deficiency, diagnosed by a 25(OH)D level below 20 ng/ml in the serum sample, is a common global disorder with a prevalence ranging from 17.31% to 53.5% in different populations (3-6). Many reasons have been identified for vitamin D deficiency, including inadequate vitamin D in the daily diet, an indoor lifestyle, as well as hepatic, renal, and skin disorders (7). Beyond skeletal metabolism, evidence suggested the probable activities of vitamin D in several tissues and organs (2). A link between deficient amounts of vitamin D and different conditions such as obesity, insulin resistance, cardiovascular diseases, and immune disorders has been elucidated (1). Additionally, deficient levels of vitamin D are assumed to be a risk factor for various unpleasant consequences during pregnancy, such as gestational diabetes mellitus, preeclampsia, and premature labor (8). The possible role of lower amounts of vitamin D in miscarriage has been reported by previous research, but it is still controversial (9). Miscarriage, which is defined as a pregnancy loss prior to the 20th week or at a fetal weight of <500 g, is considered the most frequent complication of early pregnancy, with an estimated risk of 15.3% (10, 11). Vitamin

D is a significant factor in having a successful pregnancy by participating in immunoregulation and trophoblast invasion (12). In a meta-analysis in Iran, vitamin D deficiency was extremely prevalent (60.45%) (13). Due to the marked frequency of vitamin D deficiency in Iran and the scarcity of data on the relationship between this condition and pregnancy complications in our region, this research was implemented to inspect the link between vitamin D status and first-trimester miscarriages in subjects admitted to Asalian Hospital, Khorramabad, Iran.

2. Methods

2.1. Study Design and Participants

The current study is a case-control study conducted at the Asalian referral gynecological hospital in Khorramabad, Iran, from April 2021 to March 2022. The inclusion criteria for cases were as follows: women aged 20-40 years with confirmed intrauterine pregnancy by ultrasound, regular menstruation, no intake of vitamin D supplements in the preceding three months, no history of chronic underlying disease, infectious diseases (such as rubella, toxoplasmosis, herpes simplex virus, and cytomegalovirus), smoking or alcohol consumption before and during pregnancy, uterine abnormality, in vitro fertilization, use of teratogenic drugs during pregnancy, and no familial relationship with their spouse. The inclusion criteria for the control group were healthy women aged 20-40 years with confirmed intrauterine pregnancy by ultrasound, regular menstruation, no intake of vitamin D supplements in the preceding three months, and no history of chronic underlying diseases or abortion. The exclusion criteria were a history of underlying chronic diseases (such as heart diseases, kidney disorders, kidney stones, rheumatoid arthritis, atherosclerosis, thyroid, parathyroid, and adrenal disorders, and type 1 diabetes), infertility, recurrent miscarriages, malignancy, malabsorption syndrome, Cushing's syndrome, any disease diagnosed during routine pregnancy examinations, a body mass index (BMI) above 35, or non-consent to participate in the study.

2.1.1 Sample Size Calculation and Recruitment

Based on the formula below, and considering power=80%, 1-α=95%, a ratio of controls to cases=2, a percentage of controls exposed=86%, and a percentage of cases exposed=100%, as reported by Sharef and co-workers (14), the number of cases was calculated to be 42 individuals.

$$n = \frac{\left[z_{\alpha/2}\sqrt{(r+1)\overline{pq}} + z_{1-\beta}\sqrt{rp_1q_1 + p_2q_2}\right]^2}{r(p_1 - p_2)^2}$$

where: n=sample size Z1-α/2=Z value for confidence level 1-α/2 Zβ=Z value for power 1-β p1=proportion in the control group p2=proportion in the case group n1=sample size of the control group n2=sample size of the case group

Therefore, 42 women hospitalized due to spontaneous abortion within the first trimester (until the end of the 13th week of gestation) were recruited as cases, and 100 pregnant individuals referring for routine pregnancy care were recruited as the control group. Sampling was performed using the convenience method.

2.2. Data Collection

Demographic and clinical information, including age, gestational age, gravidity, parity, desired or unwanted pregnancy, education level, and BMI, were obtained and recorded in a researcher-made checklist. Then, 5 to 10 cc of patients' venous blood samples were taken and transferred to the laboratory department for measuring 25(OH)D concentrations.

2.3. Data Analysis

The obtained data were analyzed using IBM SPSS Statistics for Windows, Version 22.0 by IBM Corp. in Armonk, NY. Descriptive statistics tools, including contingency tables, frequency, and percentage, as well as mean±standard deviation (SD), were utilized to describe the data. Analytical tools, including odds ratio (OR) with a 95% confidence interval (CI), were employed. Furthermore, Chi-squared test was applied to monitor differences between categorical variables in the two groups. Logistic regression modeling was employed to analyze the determinants of vitamin D deficiency/insufficiency. The significance level was considered to be less than 0.05.

3. Results

The mean age of the subjects was 31.85±6.16 years in the case group and 33.18±4.46 in the control group. Other demographic and clinical features of the studied groups are listed in Table 1. 59.5% of the cases and 51% of the controls were over 30 years old, and statistical analysis showed no significant difference between cases and controls regarding age (P=0.228). In terms of education, the most common educational level in the case group was a college or university degree with a frequency of 57.1%, and in the control group, both diploma and university degrees were at 41%. However, the studied groups were not significantly different in terms of education (P=0.207). Regarding gravidity, the frequency of gravid 1 was greater in the cases (45.2%), and in the control group, gravid 1 and 3 were the most frequent (35% each). Still, this difference did not appear to be significant (P=0.092). In both case and control groups, the frequency of first pregnancy (0 deliveries) was the highest (45.2% and 35%, respectively), and we observed no significant difference between the groups regarding the number of births (P=0.185). In the cases, the mean gestational week at the time of miscarriage was 8.76. The most frequent gestational age was ≤8 in the case group and 8-16 weeks in the control group, indicating a significant difference (P=0.001). Concerning BMI, 9.5% of the cases were obese, but in the control group, 35% were obese, and the frequency of overweight in the case group was lower than in the control group; analysis also revealed a significant difference between the BMI in the two groups (P=0.009).

According to the results of Table 2, 25(OH)D levels in the serum sample were above 30 ng/ml in 79% of the controls and 76.2% of the cases, but this difference was not significant (P=0.899).

As shown in Table 3, the chance of suffering from vitamin D deficiency/insufficiency for cases was about 1.09 times that of the control group, meaning that vitamin D deficiency in the case group does not increase the chance of miscarriage, OR (CI): 1.17 (0.499-2.77).

In the case group, vitamin D deficient/insufficient levels were more prevalent among the age group 30-40 years than 20-30 years (32% vs. 11.8%), but this difference was not significant (P=0.435) (Table 4).

As can be seen in Table 5, concerning BMI, the frequency of vitamin D deficient/insufficient status was most frequent in people with a BMI of 18.6-24.9 kg/m2 (27.3%) than in other groups, but this difference appeared to be insignificant (P=0.941).

Furthermore, logistic regression with backward elimination was performed to discover the

Table 1: Frequency distribution of demographic and clinical features in the studied groups

Characteristic		Cases		Controls		P value*
		Frequency	%	Frequency	%	
Age group (years)	20-30	17	40.5	49	49	0.228
	31-40	25	59.5	51	51	
Educational level	Primary or secondary degree	5	11.9	18	18	0.207
	High school diploma	13	31	41	41	
	College or university degree	24	57.1	41	41	
Gravida	1	19	45.2	35	35	0.092
	2	16	38.1	30	30	
	3≤	7	16.7	35	35	
Number of deliveries	0	19	45.2	35	35	0.185
	1	16	38.1	30	30	
	2	6	14.3	29	29	
	3≤	1	2.4	6	6	
Gestational age (weeks)	≤8	25	59.5	28	28	0.001
	8-16	17	40.5	40	40	
	16≤	0	0	32	32	
BMI	≤18.5	0	0	1	1	0.009
	18.6-24.9	11	26.2	25	25	
	25-29.9	27	64.3	39	39	
	30-35	4	9.5	35	35	

*Chi-square test, BMI: Body Mass Index

Table 2: Contingency table of 25(OH)D concentrations based on the studied groups

Group		Serum 25(OH)D (ng/ml)				P value
		<10	10-20	21-30	30≤	
Control	N	1	10	10	79	0.899
	%	1	10	10	79	
Case	N	0	4	6	32	
	%	0	9.5	14.3	76.2	

Table 3: Odds ratio and 95% confidence interval for first-trimester miscarriage according to serum vitamin D status

	Controls	Cases	OR (95% CI)
Vitamin D deficiency/ insufficiency	21	10	1.17 (0.499-2.77)
	21%	23.8%	
Vitamin D sufficiency	79	32	-
	79%	76.2%	

OR: Odds Ratio

Table 4: Contingency table of the frequency of vitamin D deficiency/ insufficiency according to age in the case group

Age group (years)		Vitamin D deficiency/ insufficiency	Vitamin D sufficiency	P value
20-30	N	2	15	0.435*
	%	11.8	88.2	
31-40	N	8	17	
	%	32	68	

*Chi-square test

Table 5: Contingency table of the frequency of vitamin D deficiency/ insufficiency based on BMI in the cases

BMI		Vitamin D deficiency/ insufficiency	Vitamin D sufficiency	P value
18.6-24.9	N	3	8	0.941*
	%	27.3	72.7	
25-29.9	N	6	21	
	%	22.2	77.8	
30-35	N	1	3	
	%	25	75	

*Chi-square test, BMI: Body Mass Index

Table 6: Logistic regression to discover the influence of age, BMI, and gestational age on the likelihood of vitamin D deficiency/insufficiency

Model	β	Standard error	P value	OR
Age (20-30 vs. 31-40 years)	-5.663	1.276	<0.001	0.003
BMI (≤18.5 vs. 18.5<)	5.192	1.165	<0.001	179.786
Gestational age (≤8 vs. 8< weeks)	-1.373	0.484	0.005	0.253

BMI: Body Mass Index, OR: Odds Ratio

influence of different variables on the chance that subjects had vitamin D deficiency/insufficiency and indicated that age, BMI, and gestational age were connected with vitamin D deficient/insufficient status (Table 6).

4. Discussion

In this case-control study, which aimed to investigate the connection between serum vitamin D status and first-trimester miscarriage, we found no significant difference between women with first-trimester miscarriage and controls. Existing studies have reported conflicting results. Christoph and colleagues, in a survey of 1382 pregnant women, observed that vitamin D status was not linked to miscarriage in early pregnancy (15). Additionally, Grossmann and colleagues conducted a study on 118 nulliparous women with miscarriages and 162 controls and reported that decreased serum vitamin D was not correlated with miscarriage (16). In contrast, a link between the deficient status of calcifediol and miscarriage has been suggested in the literature. Andersen and co-workers reported a connection between first-trimester miscarriage and 25(OH)D amounts, suggesting that vitamin D played a protective role against miscarriage (17). Radzinsky and colleagues, in a cohort of 178 subjects, concluded that insufficient amounts of vitamin D were more frequent in women with first-trimester miscarriage compared to the control group (18).

Vitamin D might diminish the risk of miscarriage because of its specific biological characteristics. Several pathways have been suggested through which these effects are exerted, but the exact mechanisms remain unclear (19). In pregnancy, vitamin D plays various roles, such as adjusting extravillous trophoblast cell invasion and immunomodulatory effects. A local decrease in the activated form of vitamin D may contribute to the etiology of miscarriage. Increased mRNA levels of the vitamin D receptor and CYP24A1 and decreased mRNA levels of CYP27B1 in the decidual tissue of patients with miscarriage have been reported (12).

Overall, there is no standardized guideline for evaluating vitamin D and supplementation during pregnancy or for those planning to establish a pregnancy at this time. However, due to the great safety of vitamin D supplementation and its affordable cost, even a slight effect would be of value in these groups (20).

4.1. Limitations

The findings of the current research should be interpreted in light of some limitations. First, the 25(OH)D concentrations were checked at only a single time point. Additionally, the number of cases with miscarriages who had decreased vitamin D levels was low, which might limit the power of the study.

5. Conclusion

Vitamin D deficiency and miscarriage in the first trimester did not appear to be associated. However, future studies with larger sample sizes are recommended to investigate the possible association.

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Ethical Approval

This study was approved by the ethics committee of Lorestan University of Medical Sciences with the code of IR.LUMS.REC.1400.210. Also, written informed consent was obtained from the participants.

Conflict of Interest: None declared.

References

1. Bikle DD. Vitamin D metabolism, mechanism of action, and clinical applications. Chem Biol. 2014;21(3):319-29. doi: 10.1016/j.chembiol.2013.12.016. PubMed PMID: 24529992; PubMed Central PMCID: PMC3968073.
2. Saponaro F, Saba A, Zucchi R. An Update on Vitamin D Metabolism. Int J Mol Sci. 2020;21(18):6573. doi: 10.3390/ijms21186573. PubMed PMID: 32911795; PubMed Central PMCID: PMC7554947.
3. Mogire RM, Mutua A, Kimita W, Kamau A, Bejon P, Pettifor JM, et al. Prevalence of vitamin D deficiency in Africa: a systematic review and meta-analysis. Lancet Glob Health. 2020;8(1):e134-e142. doi: 10.1016/s2214-109x(19)30457-7. PubMed PMID: 31786117; PubMed Central PMCID: PMC7024961.
4. Olmos-Ortiz A, Avila E, Durand-Carbajal M, Díaz L. Regulation of calcitriol biosynthesis and activity: focus on gestational vitamin D deficiency and adverse pregnancy outcomes. Nutrients. 2015;7(1):443-80. doi: 10.3390/nu7010443. PubMed PMID: 25584965; PubMed Central PMCID: PMC4303849.
5. Riaz H, Finlayson AE, Bashir S, Hussain S, Mahmood S, Malik F, et al. Prevalence of Vitamin D deficiency in Pakistan and implications for the future. Expert Rev Clin Pharmacol. 2016;9(2):329-38. doi: 10.1586/17512433.2016.1122519. PubMed PMID: 26582317.
6. Sahota O. Understanding vitamin D deficiency. Age Ageing. 2014;43(5):589-91. doi: 10.1093/ageing/afu104. PubMed PMID: 25074537; PubMed Central PMCID: PMC4143492.
7. Aparna P, Muthathal S, Nongkynrih B, Gupta

SK. Vitamin D deficiency in India. J Family Med Prim Care. 2018;7(2):324-330. doi: 10.4103/jfmpc.jfmpc_78_18. PubMed PMID: 30090772; PubMed Central PMCID: PMC6060930.
8. Dovnik A, Mujezinović F. The Association of Vitamin D Levels with Common Pregnancy Complications. Nutrients. 2018;10(7):867. doi: 10.3390/nu10070867. PubMed PMID: 29976852; PubMed Central PMCID: PMC6073751.
9. Ganguly A, Tamblyn JA, Finn-Sell S, Chan SY, Westwood M, Gupta J, et al. Vitamin D, the placenta and early pregnancy: effects on trophoblast function. J Endocrinol. 2018;236(2):R93-R103. doi: 10.1530/joe-17-0491. PubMed PMID: 29109081.
10. MacWilliams K, Hughes J, Aston M, Field S, Moffatt FW. Understanding the Experience of Miscarriage in the Emergency Department. J Emerg Nurs. 2016;42(6):504-512. doi: 10.1016/j.jen.2016.05.011. PubMed PMID: 27507550.
11. Quenby S, Gallos ID, Dhillon-Smith RK, Podesek M, Stephenson MD, Fisher J, et al. Miscarriage matters: the epidemiological, physical, psychological, and economic costs of early pregnancy loss. Lancet. 2021;397(10285):1658-1667. doi: 10.1016/s0140-6736(21)00682-6. PubMed PMID: 33915094.
12. Hou H, Zhang JY, Chen D, Deng F, Morse AN, Qiu X, et al. Altered decidual and placental catabolism of vitamin D may contribute to the aetiology of spontaneous miscarriage. Placenta. 2020;92:1-8. doi: 10.1016/j.placenta.2020.01.013. PubMed PMID: 32056782.
13. Tabrizi R, Moosazadeh M, Akbari M, Dabbaghmanesh MH, Mohamadkhani M, Asemi Z, et al. High Prevalence of Vitamin D Deficiency among Iranian Population: A Systematic Review and Meta-Analysis. Iran J Med Sci. 2018;43(2):125-139. doi: 10.30476/ijms.2018.40519. PubMed PMID: 29749981; PubMed Central PMCID: PMC5936844.
14. Sharef AA-R, Hussien SS, Noori FM. Vitamin D3 deficiency and early pregnancy loss. World Family Medicine. 2020;18(01):76-80. doi: 10.5742MEWFM.2020.93732.
15. Christoph P, Challande P, Raio L, Surbek D. High prevalence of severe vitamin D deficiency during the first trimester in pregnant women in Switzerland and its potential contributions to adverse outcomes in the pregnancy. Swiss Med Wkly. 2020;150:w20238. doi: 10.4414/smw.2020.20238. PubMed PMID: 32502277.
16. Grossmann M, Hoermann R, Francis C, Hamilton EJ, Tint A, Kaitu'u-Lino T, et al. Measuring thyroid peroxidase antibodies on the day nulliparous women present for management of miscarriage: a descriptive cohort study. Reprod Biol Endocrinol. 2013;11:40. doi: 10.1186/1477-7827-11-40. PubMed PMID: 23672306; PubMed Central PMCID: PMC3655833.
17. Andersen LB, Jørgensen JS, Jensen TK, Dalgård C, Barington T, Nielsen J, et al. Vitamin D insufficiency is associated with increased risk of first-trimester miscarriage in the Odense Child Cohort. Am J Clin Nutr. 2015;102(3):633-8. doi: 10.3945/ajcn.114.103655. PubMed PMID: 26178723.
18. Radzinsky VE, Ramazanova FU, Khamoshina MB, Azova MM, Orazov MR, Orazmuradov AA. Vitamin D insufficiency as a risk factor for reproductive losses in miscarriage. Gynecol Endocrinol. 2021;37(sup1):8-12. doi: 10.1080/09513590.2021.2006451. PubMed PMID: 34937516.
19. Subramanian A, Steiner AZ, Weinberg CR, Doss GL, Jukic AMZ. Preconception vitamin D and miscarriage in a prospective cohort study. Hum Reprod. 2022;37(10):2465-2473. doi: 10.1093/humrep/deac155. PubMed PMID: 35834313; PubMed Central PMCID: PMC9527460.
20. Tamblyn JA, Pilarski NSP, Markland AD, Marson EJ, Devall A, Hewison M, et al. Vitamin D and miscarriage: a systematic review and meta-analysis. Fertil Steril. 2022;118(1):111-122. doi: 10.1016/j.fertnstert.2022.04.017. PubMed PMID: 35637024.