

Association of serum vitamin D levels with ectopic pregnancy

Golnaz Abedini¹, Hamideh Parsapour², Elham Khanlarzadeh³, Aida Alizamir⁴

¹School of Medicine, Clinical Research Development Unit of Fatemeh Hospital, Hamadan, Iran, ²Department of Obstetrics and Gynecology, Clinical Research Development Unit of Fatemeh Hospital, Hamadan, Iran, ³Department of Community Medicine Faculty of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran, ⁴Department of Pathology, School of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran

ABSTRACT

Background and Aim: A few studies have addressed the possible role of vitamin D in decrement of ectopic pregnancy. Therefore, because of the widespread of vitamin D deficiency, especially among Iranian women, in this study, the association of serum vitamin D levels and ectopic pregnancy in pregnant women during the first trimester of pregnancy was investigated. **Methods:** This study is a cross-sectional study that has a control group. The cases group consisted of 51 pregnant women with ectopic pregnancies, and the control group consisted of 51 pregnant women with normal pregnancies. From all pregnant women participating in the study, 5 cc of blood samples were taken to determine the concentration of vitamin D serum. Serum vitamin D level was measured using enzyme-linked immunosorbent assays. The collected data were statistically analyzed using SPSS Statistical Software Package Version 16.0. *P* value less than 0.05 was considered as statistically significant level. **Results:** The differences between the two groups based on the demographic characteristics, including mean age, body mass index, and number of deliveries, were not statistically significant. The level of vitamin D in blood (ng/ml) was significantly higher in the control group (34.31 ± 7.32) compared to the participants with ectopic pregnancy (20.95 ± 20.68) (<0.001). Based on the results of the present study, women with inadequate serum levels (less than 30 ng/ml) are 6.40 times more likely to have an ectopic pregnancy than normal pregnant women (OR = 6.40; 95% CI; 3.260–15.834). **Conclusion:** Based on the results of this study and considering the association of serum vitamin D levels and ectopic pregnancy, it seems necessary to measure the level of serum vitamin D in women before their pregnancy.

Keywords: Ectopic pregnancy, pregnancy, serum vitamin D

Introduction

Ectopic pregnancy is a type of pregnancy disorder in which the fetus is formed outside of the uterus.^[1] Abdominal pain and vaginal bleeding are symptoms of ectopic pregnancy.^[2] The prevalence of this type of disorder in developed countries is about 1–2% among pregnant women, which has been reported to be the main

cause of death of pregnant women (10%) in the first trimester of pregnancy.^[3] The main risk factors that cause this disorder include pelvic inflammatory disease, smoking, having a history of surgery and infertility, history of ectopic pregnancy, and using assisted reproductive technology.^[2] Although ectopic pregnancy can occur in the cervix and ovaries, in more than 90% of cases, it happens in the fallopian tube.^[4] Prostaglandins, integrins, growth factors, cytokines, lectins, and modulatory proteins have been introduced as impressive physiological factors that cause this disorder.^[5] Measuring beta-human chorionic gonadotropin (β -hCG) in the blood and vaginal ultrasonography are among the methods that could be used in ectopic pregnancy differential diagnoses.^[5] During this disorder, the level of β -hCG in the blood increases almost twice as much as in a normal pregnancy.^[2]

Address for correspondence: Dr. Aida Alizamir, Department of Pathology, School of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran.
E-mail: aidaalizamir@yahoo.com

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Vitamin D is a fat-soluble vitamin that has a significant role in the absorption and metabolism of calcium and phosphorus.^[6] Along with the major role of vitamin D in the metabolisms of calcium and phosphorus, some nonspecific roles of vitamin D have also been in the body such that, the deficiency of vitamin D will lead to metabolic syndromes, cardiovascular disease, immunocompromisation, and depression.^[7,8] Because of the presence of vitamin D receptors in the female reproductive system, including the uterus, endometrium, ovaries, and placenta, the possible role of this vitamin in female reproduction has been suggested.^[9] It has been reported that vitamin D deficiency is associated with gestational diabetes, endometriosis, polycystic ovary syndrome, preterm labor, and preeclampsia.^[10] The results achieved from studies have showed that there is a direct relationship between insufficient levels of vitamin D in the blood and the incidence of ectopic pregnancy.^[11,12] Therefore, because of the limited number of studies conducted on this issue on the one hand, and the widespread of vitamin D deficiency, especially among Iranian women on the other hand, in the present study, the association of serum vitamin D levels and ectopic pregnancy during the first trimester was evaluated.

Materials and Methods

The present study as an analytical cross-sectional study with a control group was performed in the period of September 2020 to September 2021 in Fatemiyeh Hospital, Hamedan University of Medical Sciences, Hamedan, Iran. Based on the study of Bahat *et al.*^[11] and according to the following parameters (type I error of 5%, test with power 80%, and medium effect size of 0.5) and by G*Power software version 3.1, the sample size was determined to be 102. Therefore, after conducting ultrasonography test on referrals to this hospital, 51 ectopic pregnant women and 51 pregnant women with normal pregnancy conditions were randomly selected and studied in two groups. Written consent was obtained from all patients to participate in the study. The research protocol was approved by the Ethics Committee of the Medical School of Hamadan University of Medical Sciences according to the Declaration of Helsinki. Inclusion criteria were pregnant women in the age range of 18–40 years and the results of ultrasonography for screening process in the first trimester of pregnancy. However, women with multiple pregnancies, pregnant women with chronic kidney disease, pelvic inflammatory disease, diabetes, hypertension, endocrine, and cardiovascular diseases were excluded from the study.

Besides, women with a history of infertility, cesarean section, abortion, using intrauterine device, smoking, history of surgery and hospitalization during the past year, and taking vitamin D supplements for at least the last 3 months were excluded from the study. Age, number of deliveries, maternal body mass index, and education level were assessed as demographic variables of participants in this study. From all pregnant women participating in the study, 5 cc of blood samples were taken to determine the

concentration of vitamin D serum. Serum vitamin D level was measured using enzyme-linked immunosorbent assays.

Serum vitamin D levels less than 30 ng/ml were considered as insufficient levels and more than 30 ng/ml as adequate levels. The collected data were statistically analyzed using SPSS Statistical Software Package Version 16.0 to determine the frequency, mean, and standard deviation. Quantitative variables were examined using independent *t*-test and Mann–Whitney tests, and qualitative variables were examined using Chi-square test. *P* value less than 0.05 was considered as statistically significant level. The degree of correlation was determined by estimating the odds ratio (OR) and 95% confidence interval.

Results

In this study, 51 pregnant women with normal pregnancy status and 51 other pregnant women with ectopic pregnancy status were compared based on their demographic characteristics and serum vitamin D level. There was no significant difference between the two groups in terms of demographic characteristics, including mean age, body mass index, and number of deliveries [Table 1]. As could be seen from Table 1, women in higher education were significantly more likely to have ectopic pregnancies (*P* = 0.001). The level of vitamin D in blood in the control group (34.31 ± 7.32 ng/ml) was significantly higher than the women with ectopic pregnancy (15.95 ± 20.68 ng/ml) (*P* < 0.001) [Table 2].

Comparison of two groups based on serum vitamin D levels revealed that 94.1% of ectopic pregnant women had insufficient serum vitamin D levels and 45.1% of normal pregnant women had insufficient serum vitamin D levels (*P* = 0.008) [Table 3]. According to the results of this study, women with insufficient serum levels (less than 30 ng/ml) are 6.4 times more likely to have an ectopic pregnancy than normal pregnant women (OR = 6.40; 95% CI; 3.260–15.834).

Table 1: Demographic characteristics of the study groups

Characteristic	Ectopic pregnancy (n=51)	Normal pregnancy (n=51)	P
Age (year), mean±SD	28.50±5.78	27.54±5.26	0.26
Parity, mean±SD	1.92±0.95	2.21±1.06	0.14
BMI (kg/m ²), mean±SD	26.12±5.10	24.98±5.37	0.63
Educational Level, n (%)			
Elementary	19 (37.3)	16 (31.4)	0.001
High school	21 (41.2)	34 (66.7)	
College	11 (21.5)	1 (1.95)	

Table 2: The mean serum levels of vitamin D in two groups

Variable, mean±SD	Study groups		P
	Ectopic pregnancy (n=51)	Normal pregnancy (n=51)	
Vitamin D level (ng/ml)	15.95±20.68	34.31±7.32	<0.001

Table 3: Odds ratios and 95% confidence intervals for ectopic pregnancy according to maternal serum levels of vitamin D

Vitamin D level	Study groups		P	OR (95% CI)
	Ectopic Pregnancy (n=51)	Normal Pregnancy (n=51)		
Sufficient (>30 ng/ml), n (%)	3 (5.9)	28 (54.9)	0.008	6.40 (3.260-15.834)
Insufficient (<30 ng/ml), n (%)	48 (94.1)	23 (45.1)		

Discussion

According to the results of the present study, about 94% of women with ectopic pregnancy had insufficient serum levels of blood vitamins. Bassir *et al.*^[13] reported that serum vitamin D level in 85% of Iranian women with preterm delivery was less than 25 ng/ml (insufficient level). Inadequate serum vitamin D in women is directly associated with reduced fertility and pregnancy complications.^[14] In the present study that was carried out to investigate the association of serum vitamin D levels with the incidence of ectopic pregnancy, it was revealed that the level of vitamin D in healthy pregnant women was significantly higher than the women with ectopic pregnancy, which is consistent with the result of the Sahhaf *et al.*^[12] study. Besides, Bahat *et al.*^[11] found that women with ectopic pregnancy had inadequate serum levels of vitamin D, calcium, and magnesium compared with healthy pregnant women. Adequate increase of serum levels of vitamin D in women increases the capability of egg *in vitro* fertilization, and ultimately increases pregnancy after embryo transfer.^[15] In addition to ectopic pregnancy, it has been reported that inadequate serum vitamin D levels in pregnant women are directly associated with preterm delivery.^[16]

Although the exact mechanism of the association of serum vitamin D levels with ectopic pregnancy is not clear, animal model studies revealed that blocking vitamin D receptors in mice leads to gonadal dysfunction, shortage of functional aromatase, and uterine hyperplasia.^[17] In fact, vitamin D and calcium regulate physiological function and improve transfer of the fetus into the uterus by binding to their receptors on the surface of the fallopian tube.^[15] Vitamin D may also facilitate implantation process of fetus in endometrial tissue through an immunological interaction between the placenta and maternal tissue.^[18] Inflammatory factors, including cytokines, interleukins, and prostaglandins, can disrupt the process of replacement of fetus.^[19] It has been reported that Vitamin D could prevent ectopic pregnancy by reducing inflammation at the surface of the fallopian tubes and uterus.^[11]

Conclusion

Bases on the results of this study, women with insufficient serum blood levels are 6.40 times more likely to have an ectopic pregnancy compared with normal pregnant women. Therefore, using vitamin D supplements in the pre-pregnancy stage in women with insufficient serum vitamin levels is recommended. Therefore, in addition to doing more in this area, it is necessary to measure the serum level of vitamin D in women in the pre-pregnancy stage.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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