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*Case Study*

# Association of Vitamin D3 and Laboratory Factors with Early Menopause: A Case-Control Study

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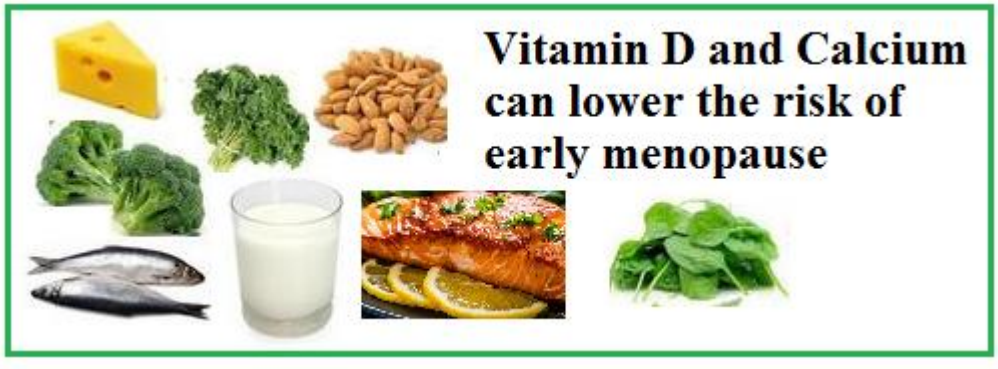
**ABSTRACT**

**Background:** Early menopause is defined as premature ovarian insufficiency (POI) before the age of 45. Some biochemical indices are known to alter hormonal responses in menopause like estrogen or progesterone levels. This study aimed to compare the association of vitamin D3 and laboratory factors with early menopause.
**Methods:** The present study was compared with a case and control group in early menopause and healthy women of the same age (50 Patients in each group), who referred to the obstetrics and gynecology clinic in Jahrom in 2021. Study groups were compared in terms of hormonal tests, ovarian reserve, vitamin D3 level, thyroid function, liver function, fasting blood glucose level, hemoglobin and alkaline phosphatase (ALP).
**Results**: AMH was lower in women in the early menopause group than in healthy women (P=0.001). Study groups had no significant difference in terms of age, occupation, location and economic status, and body mass index (P>0.05). Serum vitamin D3 levels as well as TSH, liver function tests, fasting blood glucose, hemoglobin, alkaline phosphatase (ALP) levels (P>0.05) were not different between study groups (P=0.191).
**Conclusion**: In this study, the results of examining laboratory factors in women with early and healthy menopause showed that serum levels of AMH hormone are very important in determining the time of early menopause. AMH levels were significantly lower in women with early menopause than in healthy. Therefore, early measurement of this hormone can prevent the complications of early menopause, but vitamin D3 and other factors were not associated with early menopause.

**GRAPHICAL ABSTRACT**

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## Introduction

Menopause before the age of 45 is called early menopause. Menopause before the age of 40 is called premature menopause. A spontaneous (natural) early menopause affects approximately 5% of the population before the age of 45 [1]. Amenorrhea, elevated gonadotropin levels, and estrogen insufficiency are all signs of early menopause. Regardless of cause, women who experience estrogen deficiency at an early age before the natural menopause are now recognized to be at increased risk for premature morbidity and mortality [2]. According to available reports, premature ovarian insufficiency has been documented in 1% of women [3]. In recent years, the prevalence of Premature or primary ovarian failure (POF) and early menopause in the general population of women in high-income nations was 1-2% and 5-10%, respectively [4]. A reduction in estrogen or progesterone is linked to several biochemical changes during menopause. Both hormones act through cytoplasmic receptors, and each steroid has two receptors, alpha and beta (ER-a and ER-b, respectively) are already known antagonists [5,6]. Strogen is involved in dilating blood vessels and helping blood flow [7]. Several studies have found that estrogen treatment lowers total cholesterol and low-density lipoprotein cholesterol (LDL) while increasing triglyceride and high-density lipoprotein (HDL) levels in postmenopausal women [8]. In addition, ovarian dysfunction during menopause causes the renin-angiotensin system to become activated, resulting in immunodeficiency, inflammation, and endothelial dysfunction [9]. Vitamin D3 is a fat-soluble vitamin that is known to contribute to inflammation, immune moderation, endothelial cells' function, and renin-angiotensin system; these characteristics have made it a valuable topic of research in the field of women's menstrual system [10]. Therefore, both the mentioned cases and the reduction of estrogen and progesterone hormones can make significant changes in biochemical factors in women with early menopause. This study aimed to compare the association of vitamin D3 and laboratory factors with early menopause

## Materials and Methods

This case study was conducted on 100 women with early menopause and healthy subjects referred to Jahrom women's clinic in 2021. The sample size was determined using G-power sampling software, taking into account the confidence interval of 95% and the test power of 80%; each group was 50 and a total of 100 patients were considered.

After approval of the ethics committee from the research deputy of Jahrom University of Medical Sciences (IR. JUMS. REC.1399.131), the researcher referred to Jahrom women's clinic, and by introducing themselves to the authorities and clarifying the purpose of the research to them, the subjects were included in the research on consecutive days and the eligible women selected the inclusion criteria.

Inclusion criteria included women with early menopause with amenorrhea symptoms (discontinuation of bleeding) for at least 4 months under the 45 years old and FSH > 25 IU/L or AMH<0.8 and healthy women with AMH >0.8. Exclusion criteria included a lack of cooperation of people to participate in the study and incomplete checklist information. The participants were assured about the confidentiality of the data collected. Data collection tools included demographic information including age, education, height, weight, body mass index (BMI), occupation status, marital status, place of residence, and economic status. From each individual, 5 mL of venous blood was taken using a disposable sterile syringe with strict compliance with standard blood sampling standards to measure serum levels of AMH, FBS, TSH, HB, SGOT, SGPT, ALK and vitamin D3.

Finally, the data were analyzed using SPSS software version 21. We applied both descriptive statistics, i.e. mean, standard deviation, frequency and percentage, and inferential statistics, namely Chi squire, T-test and Mann-Whitney, at a significant level of $P< 0.05$.

## Results and Discussions

One hundred women who referred to Jahrom women's clinic were divided into groups of women with early menopause (50) and healthy

(50), and participated in the study. Table 1 shows the frequency of demographic variables in the study groups. The results of statistical analysis with the Chi-square test showed that groups of women with early and healthy menopause were matched in terms of age, occupation, place of residence, and economic status (Table 1).

**Table1:** Frequency of demographic variables in women with early menopause and healthy

| | | Healthy | | Early menopause | | P-value |
|---|---|---|---|---|---|---|
| | | Frequency | Percent | Frequency | Percent | |
| **Age** | 15-35 years old | 25 | 50.0 | 25 | 50.0 | >0.99 |
| | 36-50 years old | 25 | 50.0 | 25 | 50.0 | |
| **Education level** | Middle school | 18 | 36.0 | 16 | 32.0 | 0.90 |
| | Diploma | 13 | 26.0 | 15 | 30.0 | |
| | Post-Diploma | 3 | 6.0 | 3 | 6.0 | |
| | Bachelor | 12 | 24.0 | 14 | 28.0 | |
| | Master's Degree | 4 | 8.0 | 2 | 4.0 | |
| **Occupation** | Housewife | 40 | 80.0 | 38 | 76.0 | 0.62 |
| | Employee | 10 | 20.0 | 12 | 24.0 | |
| **Marital status** | Single | 15 | 30.0 | 1 | 2.0 | 0.001 |
| | Married | 35 | 70.0 | 49 | 98.0 | |
| **Place of residence** | Urban | 33 | 66.0 | 39 | 78.0 | 0.181 |
| | Rural | 17 | 34.0 | 11 | 22.0 | |
| **Economic status** | Low | 0 | 0 | 2 | 4.0 | 0.222 |
| | Medium | 49 | 98.0 | 48 | 96.0 | |
| | High | 1 | 2.0 | 0 | 0 | |

Normal BMI in women of early menopause (56%) and healthy (48%) groups had the highest frequency. The frequency of overweight and obese women was lower in the women's group of early menopauses, but there was no statistically significant difference in BMI between early menopause and healthy groups (P=0.413) (Table 2).

**Table 2:** Frequency of BMI in women with early menopause and healthy ones

| | | Healthy | | Early menopause | | p-value |
|---|---|---|---|---|---|---|
| | | Frequency | Percent | Frequency | Percent | |
| Body Mass Index | Underweight | 4 | 8 | 1 | 2 | 0.413 |
| | Normal | 24 | 48 | 28 | 56 | |
| | Overweight | 19 | 38 | 16 | 32 | |
| | Obesity | 3 | 6 | 5 | 10 | |

The mean of vitamin D3 in women in early menopause groups (18.02±10.69) was lower than that of healthy group (21.51±8.80), but the results of the independent T-test showed that there was no significant difference between early menopause and healthy groups in terms of vitamin D3 (P=0.191) (Table 3).

**Table 3:** Comparison of Vitamin D3 in Women with Early Menopause and Healthy group

| | Healthy | | Early menopause | | P-value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Vitamin D3 | 21.51 | 8.80 | 18.02 | 10.69 | 0.191 |

The results of Mann–Whitney test showed there was a significant difference between the early menopauses and healthy groups in terms of AMH laboratory factor (P=0.001). The mean AMH factor in women in early menopause group was lower than that of healthy women. There was no

significant difference between the groups of early menopauses and healthy women in terms of other laboratory factors (P>0.05) (Table 4).

**Table 4:** Comparison of laboratory factors in early menopause and healthy women

| | Healthy | | Early menopause | | P-value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| AMH | 4.55 | 2.97 | 0.40 | 0.32 | 0.001* |
| TSH | 2.46 | 1.50 | 2.37 | 0.96 | 0.695 |
| FBS | 87 | 8 | 85 | 9 | 0.329 |
| HB | 13.03 | 1.48 | 12.73 | 1.83 | 0.375 |
| SGOT | 18 | 4 | 18 | 4 | 0.697 |
| SGPT | 19 | 6 | 19 | 5 | 0.833 |
| ALK | 177.86 | 63.77 | 179.10 | 54.52 | 0.917 |

* Mann-Whitney test and in other cases, independent t-test was used

Women's lifestyles alter dramatically throughout the premenopausal phase. These alterations can be seen in the biological, mental, social, and cultural realms. Hormonal alterations cause unfavorable changes in glucose and insulin metabolism, adipose tissue distribution, coagulation cascade problems, and endothelial dysfunction owing to the diminished hormonal activity of the ovaries and a significant fall in endogenous estrogen levels. Because of heredity, the intensity and kind of symptoms vary from person to person. Vasomotor and psychosomatic problems arise as a result of talents and environmental variablesHormonal imbalances increase body mass, alter adipose tissue distribution, lower energy consumption, and decrease insulin output and cell sensitivity to this hormone [14]. We sought to see how laboratory parameters differed between women in early menopause and healthy women. The study included 100 women who were referred to Jahrom Women's Clinic and were separated into two groups: Early menopausal women (50 individuals) and healthy women (50 people). The age, employment, location, and economic condition of the study groups were all matched. There was no statistically significant difference in BMI between early menopause and healthy groups (p=0.413). Because underweight and overweight women have experienced early menopause, the link between BMI and normal age appears to be nonlinear. Women with a lower BMI (less than 18.5 kg/m2) have insufficient fat storage, which may result in poor ovarian follicle quality [15-17]. Reduced BMI is not associated with a reduction in estrogen production in adipose tissue in skinny women, contrary to common belief, because estrogen synthesis in peripheral fats begins during postmenopausal periods [18]. According to Zhu *et al*. (2018), underweight women are more likely to have early menopause, while obese women are more likely to experience late menopause [19]. However, research has shown no significant link between body mass index and menopause age [21,20]. This is likewise supported by the findings of this investigation. Although normal BMI was higher in early menopausal groups (56%) than that of healthy women (48%) in the current investigation, the difference was not statistically significant. The influence of another factor on the incidence of early menopause, which cannot be precisely assessed as the effects of BMI on the incidence of early menopause, is one of the reasons for the inconsistent results in different research.The mean of vitamin D3 in women in early menopause groups (18.02±10.69) was lower than that of healthy group (21.51±8.80), but the results of the independent t-test showed that there was no significant difference between early menopause and healthy groups in terms of vitamin D3 (P=0.191). The ovary appears to be a target organ for 1,25-Dihydroxyvitamin D3, the active metabolite of vitamin D3, and vitamin D3 receptors are expressed in reproductive organs, including the ovaries, according to laboratory studies [22,23]. A study recently has been shown that plasma concentrations of 25-hydroxyvitamin (25 OHD) were favorably linked with ovarian reserve, adding to the growing body of evidence

for vitamin D3's protective function in ovarian aging [24]. In Smithe *et al.*'s (2017) study women with the greatest dietary vitamin D3 consumption (Mean of 528 IU/d) had a 17% reduced risk of early menopause than women with the lowest vitamin D3 intake after controlling for confounding variables such as age, smoking, and other factors [25]. Erosy *et al*. (2016) investigated serum vitamin D3 levels in patients with early ovarian failure. Serum levels of 25(OH)D3 were not significantly different between the group with early ovarian failure and the control group [26]. This is in line with the results of this study. In the present study, although serum vitamin D3 levels in the early menopause group were lower than those of the control group, this difference was not statistically significant. Vitamin D3 levels do not appear to have a significant effect on early menopause if they are not significantly reduced. The results showed that there was a significant difference between the groups of early menopauses and normal in terms of AMH laboratory factor (P=0.001). The mean AMH factor in women in the early menopause group was lower than that in healthy women. AMH hormone plays an important role in the growth of reproductive organs in both sexes during the embryonic period. In an adult woman, its role is probably in regulating folliculogenesis, mainly in inhibiting primary follicle uptake and reducing the sensitivity of small antral follicles to follicle-stimulating hormone (FSH) activity. To date, the main clinical application of AMH determination in women has been the evaluation of ovarian reserve in the diagnosis of infertility, premature ovarian failure, and hypogonadotropic hypogonadism [27]. According to various researches, measuring AMH is a useful predictor of menopause timing [28]. According to Bertone-Johnson *et al*. (2018), the link between AMH levels and early menopause was variable depending on the participant's characteristics, although this association was significant independent of changes in age, history of infertility, and smoking, or body weight. It was also shown that each 0.10 ng/mL decrease in AMH was linked to a 14 percent increased chance of early menopause [29]. In the present study, serum AMH levels were significantly lower in women with early menopause than those of healthy women. Then, examining the serum TSH level showed that there was no statistically significant difference between the early and normal menopausal groups in terms of serum TSH level ($p < 0.05$). Thyroid diseases are more common in middle-aged and elderly postmenopausal women. Diagnosis and interpretation of thyroid function tests, including estimating thyroid-stimulating hormone (TSH), tri-iodothyronine (T3), and tetra-iodothyronine (T4) activities in older adults is very difficult [30]. TSH levels were greater in postmenopausal women (2.80 UIU / mL) than those of premenopausal women (2.52 UIU / mL), according to Rojas *et al*. (2008). The difference between the groups, however, was not significant [31]. Kolanu *et al*. (2019) in their study stated that the mean serum level of TSH in older postmenopausal women (3.39 ±2.45) was higher than in premenopausal women (2.60 ±1.31). However, this difference was not statistically significant [32]. In the present study, serum levels of TSH were reported to be lower in women with premature menopause than those of healthy women, although this difference was not statistically significant. Then, examining the serum level of FBS showed that there was no statistically significant difference between the groups of early and normal menopause in terms of serum FBS (p-value> 0.05). Sekhar *et al*. (2015) showed that there is a significant difference between menopausal age between diabetic and non-diabetic women (p-value <0.01) and menopausal age was lower in diabetic women [33]. Another research in the United States discovered that type 1 diabetes women reach menopause 6 years sooner than non-diabetic women [34]. Even though none of the patients in this research had diabetes, blood glucose levels were not substantially different between the two groups. Finally, in the present study, the results showed that changes in liver enzymes in women with premature menopause and healthy women are not significantly different from each other. Several morphological changes occur with age in the liver; therefore, such characteristics are expected to develop in the

liver at an age of menopause. Such changes include a decrease in blood flow, liver volume as well as changes in liver regeneration capacity. The data have shown that liver volume, blood flow, and function decrease by approximately 1% per year after 40 to 50 years of age [35]. In general, by the time people reach old age, the liver volume will decrease by between 20-40%, and this decrease is more apparent in women [36]. Blood flow in the elderly is reduced by 35 - 50 % and may help reduce the volume of the liver seen with age [37]. In the present study, due to the mean age of the study population, no significant change was reported in liver enzymes SGOT, ALK, and SGPT in the two groups. Our recent study also confirmed the diagnostic role of the AMH for POF similar to what we found in this study [38].

## Conclusion

In this study, investigating laboratory factors in women with early and healthy menopause showed that serum levels of AMH hormone are very important in determining the time of early menopause. In the present study, the level of this hormone was significantly lower in women with early menopause than that of healthy group. Therefore, early measurement of this hormone can prevent the complications of early menopause.

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## Authors' contributions

All the authors met the criteria of authorship based on the recommendations of the international Committee of Medical Journal Editors.

## Conflict of Interest

There are no conflicts of interest in this study.

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