

# The impact of vitamin D supplementation on reproductive outcomes in women with polycystic ovary syndrome: a randomized controlled study

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## ABSTRACT

**Aims:** This study aims to evaluate the effectiveness of vitamin D supplementation treatment on reproductive outcomes in women with polycystic ovary syndrome (PCOS).

**Methods:** The study involved 235 women aged 20-40 with PCOS who were seeking treatment at Private infertility Clinic in Türkiye. The participants were divided into two groups: 123 in the control group and 115 in the intervention group, chosen at random. Their age, body-mass index (BMI), education level, employment status, and PCOS symptoms were assessed. Statistical significance between the case and control groups was compared using the chi-squared and Fisher's exact tests.

**Results:** There were no significant differences in age, BMI, education level, employment status, and PCOS symptoms such as menstrual irregularity, amenorrhea, hirsutism, hair loss and acne between the intervention and control groups (p-value>0.05). There were significant differences in clinical pregnancy rates (CPR) between the intervention and control groups (p-value<0.05). The two groups showed no significant differences in live birth rates and clinical miscarriage rates (p-value>0.05).

**Conclusion:** Based on the findings, it has been revealed that supplementing with vitamin D has a positive impact on CPR. Vitamin D supplementation may support the improvement of fertility in women with PCOS, although the exact mechanisms and effectiveness are still under study.

**Keywords:** PCOS, vitamin D supplementation, pregnancy rates, reproductive outcomes

## INTRODUCTION

The most common endocrine disorder in females at the age of childbearing is considered to be polycystic ovary syndrome (PCOS).<sup>1</sup> PCOS is highly prevalent among women as its prevalence is reported to be 9.2% worldwide (95% CI: 6.8–12.5%).<sup>2</sup> This disorder is the most relevant cause of hyperandrogenism, hirsutism and anovulatory infertility in the developed countries.<sup>3,4</sup> The most prevalent symptom of PCOS is suggested to be infertility, approximately 75% women diagnosed with PCOS suffer from infertility due to anovulation, which makes PCOS by far the most relevant cause of anovulatory infertility.<sup>5</sup> It is a heterogeneous androgen excess disorder with various severities of metabolic and reproductive dysfunctions.<sup>6</sup> Treatment of women who are diagnosed with PCOS is reliant on their symptoms. Current therapies available for infertility caused by PCOS generally involve ovulation induction, monitoring ovulation, assisted reproduction technologies and ovarian perforation. additionally, the use of some nutrients

such as minerals, unsaturated fatty acids, vitamins, etc. has seen a fair amount of attention as an adjunction.<sup>7</sup>

Vitamin D (“serum concentrations of 25-hydroxycalciferol [25-(OH)D3]”) plays a crucial role in regulating calcium and phosphate levels, essential for the health of muscles, bones, and teeth.<sup>8</sup> Additionally, it may help reduce the risk of diabetes, cancer, autoimmune disorders, and migraines.<sup>9</sup> Vitamin D insufficiency is the most common medical issue worldwide. According to studies, over 1 billion individuals worldwide suffer from Vitamin D deficiency, with nearly half of the world's population experiencing some level of insufficiency.<sup>10</sup> Compared to the general population, women with PCOS are more likely to be vitamin D deficient. Numerous studies suggest a connection between Vitamin D deficiency and the development and symptoms of PCOS.<sup>11</sup> Noticeably, 67-85% of individuals with PCOS also experience vitamin D



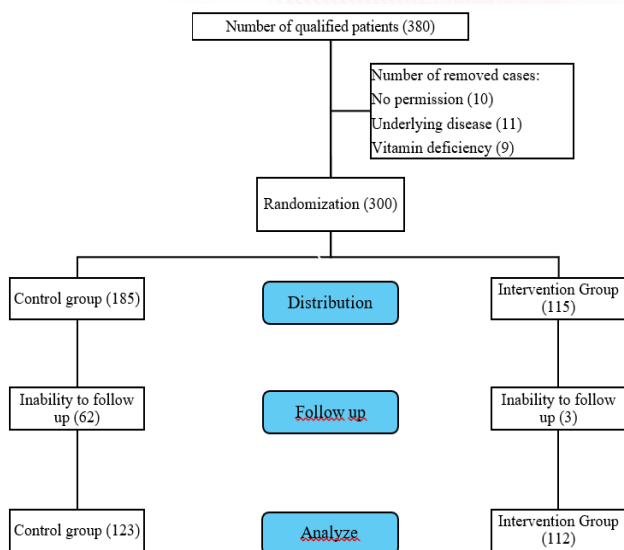
deficiency.<sup>12,13</sup> Additionally, this deficiency may play a role in the development of insulin resistance and metabolic syndrome associated with PCOS.<sup>14</sup>

Due to the role of vitamin D in ovulation dysfunction as well as the anti-inflammatory benefits of vitamin D, it is expected for vitamin D supplementation to have a positive effect in regulating the growth of follicles and therefore ovulation and ultimately fertility.<sup>15</sup> Recently, supplementation has drawn considerable attention for its potential benefits in preparing PCOS patients for pregnancy. Its protective effects against oxidative stress and its role in maintaining calcium ion levels may enhance fertilization, cleavage, implantation, and placental development. However, findings on the impact of vitamin D supplementation on pregnancy rates remain inconsistent. Some studies indicate that it can improve pregnancy rates in PCOS patients, while others show no significant effect.<sup>16</sup> Consequently, this study aims to evaluate the impact of vitamin D supplementation on reproductive outcomes in women with PCOS. The main goal of this study is to assess the effects of vitamin D in infertility of Turkish women diagnosed with PCOS.

## METHODS

This randomized controlled study was conducted in 2023-2024 on 235 PCOS patients referred to Women's Clinics of Bezmialem Hospital. The study was conducted in accordance with the Declaration of Helsinki. Ethics Committee Approval The study was conducted with the permission of Bezmialem Vakif University Ethics Committee (Date: 31.12.2024, Decision No: 2024/432).

**Figure** shows the flowchart of patient selection. Block method was used for randomization. First, blocks were created with the combination AAABBB and then all possible permutations were made for this combination. Finally, a number was assigned to each composition. This study was a single-blind study. The drug intervention in two groups was the same in terms of the shape, color or appearance of the drugs. The patients of both groups were unaware of the type of the group they were in, while the doctor and researcher were aware of the type of groups or therapeutic intervention.



**Figure.** Women with polycystic ovary syndrome selection flowchart

The present study was a single-blind clinical trial study. Inclusion criteria included: women aged 20-40 with PCOS diagnosis, patients without celiac disease, patients without vitamin D deficiency, and those who consented to participate in the study.

Exclusion criteria included: patients with underlying disease, previous use of ovulation induction, previous use of metformin, patients who lacked consent, and those with vitamin D deficiency. The cut-off value <20 ng/ml was considered vitamin D deficiency. The sample size included 235 patients with PCOS. After collecting basic information including age, marital status, education, body-mass index (BMI), presence of PCOS symptoms such as acne, menstrual irregularity, amenorrhea, hirsutism and hair loss at the time of visit was checked and the patients with a serum level greater than or equal to 30 ng/ml of vitamin D (25-hydroxyvitamin D3) were included in the study and then they were divided into two groups based on the random number table. The other group was prescribed metformin 500 mg daily plus vitamin D 50 thousand units weekly (intervention group) orally for 36 weeks. Then the reproductive outcomes information of the two groups was compared in two groups.

The sample size was equal to 235 people by considering error=0.05 and 80% power and using the sample size formula. SPSS statistical software (version 22) was used to data analysis and descriptive statistics methods including frequency and percentage. Fisher's exact test and chi-squared test were used to test whether two categorical variables are related to each other. p value less than 0.05 was considered as significant.

## RESULTS

The mean age of women with PCOS in the intervention group was 29.39±5.30 years, and their mean BMI upon entering the group was 27.01±3.23 kg/m<sup>2</sup>. The mean age of PCOS patients in the control group was 30.41±6.02 years, and their mean BMI upon entering the group was 27.25±3.39 kg/m<sup>2</sup>.

There were no significant differences in age between the intervention and control groups at the time of enrolment (p-value>0.05). No significant BMI differences existed between the intervention and control groups at enrollment (p-value>0.05). There were no significant differences in the rates of education level and job status between the intervention and control groups (p-value>0.05) (**Table 1**).

PCOS symptoms including menstrual irregularity, amenorrhea, hirsutism, hair loss and acne were not significantly different in both intervention and control groups (p-value>0.05). The clinical pregnancy rates (CPR), clinical miscarriage rates (CMR) and live birth rates (LBR) were compared between the two groups (**Table 2**).

As illustrated in **Table 2**, CPR was (39.3%), CMR (32.0%) and LBR was (90.0%) in women in the intervention group. CPR was (27.6%), CMR (35.3%), and LBR was (91.0%) in the control group. There were significant differences in CPR between the intervention and control groups (p-value<0.05). The two groups had no significant differences in live birth rate (p-value>0.05). There were no meaningful differences in CMR between the two groups (p-value>0.05).



**Table 1.** The patients' demographic characteristics between the two groups

		“Intervention mean±SD (min–max) n (%)” n=112	“Control mean±SD (min–max) n (%)” n=123	p-value
Female age (years)		29.39±5.30 (20–40)	30.41±6.02 (20–40)	.170*
BMI (kg/m <sup>2</sup> )		27.01±3.23 (20–38)	27.25±3.39 (20–37)	.573*
Education level	High school	47 (42.0)	56 (45.5)	.655*
	Bachelor	50 (44.6)	55 (44.7)	
	Master	15 (13.4)	12 (9.8)	
Job status	Employed	44 (39.3)	56 (45.5)	.582*
	Housewife	68 (60.7)	67 (54.5)	
Menstrual irregularity	No	22 (19.6)	27 (22.0)	.664*
	Yes	90 (80.4)	96 (78.0)	
Amenorrhea	No	111 (99.1)	121 (98.4)	.617**
	Yes	1 (0.9)	2 (1.6)	
Hirsutism	No	27 (24.1)	25 (20.3)	.531*
	Yes	85 (75.9)	98 (79.7)	
Hair loss	No	35 (31.3)	35 (28.5)	.640*
	Yes	77 (68.8)	88 (71.5)	
Acne	No	57 (50.9)	68 (55.3)	.500*
	Yes	55 (49.1)	55 (44.7)	

BMI: Body mass index, Min: Minimum, Max: Maximum, \*Chi-squared test \*\*Fisher's exact test

**Table 2.** The patients' outcomes between two groups

		Intervention n (%) n=112	Control n (%) n=123	p-value
CPR	No	68 (60.7)	89 (72.4)	.004*
	Yes	44 (39.3)	34 (27.6)	
CMR	No	30 (68.0)	22 (64.7)	.671*
	Yes	14 (32.0)	12 (35.3)	
LBR	No	3 (10.0)	2 (9.0)	1.000**
	Yes	27 (90.0)	20 (91.0)	

\*Chi-squared test \*\*Fisher's exact test. CPR: Clinical pregnancy rates, CMR: Clinical miscarriage rates, LBR: Live birth rates

## DISCUSSION

The current randomized controlled trial study examined the impact of vitamin D supplementation on reproductive outcomes in women with PCOS. The findings indicate that the use of vitamin D supplementation significantly affects CPR in women with PCOS. However, vitamin D did not have a statistically significant effect on CMR and LBR. This section compares and discusses the current study's findings with previous studies' results. Limited research was done on the role of vitamin D supplementation in increasing the chance of getting pregnant in women with PCOS. Most performed investigations focus on the effect of vitamin D supplementation on “assisted reproductive technology” (ART) outcomes such as in vitro fertilization (IVF) in women with PCOS.<sup>13,17-19</sup>

Rashidi et al.<sup>20</sup> found that calcium-vitamin D plus metformin improving CPR in patients with PCOS. This study was to assess the impacts of calcium-vitamin D and metformin on regularity of menses, number of large follicles and pregnancy rates. Pal et al.<sup>21</sup> found that vitamin D is relevant for procreative success for getting pregnant in infertile PCOS patients. They showed that vitamin D status associates to reproductive outcome. Varbiro et al.<sup>22</sup> in a comprehensive review reported the positive effects

of vitamin D supplementation on CPR in PCOS women. Nosseir et al.<sup>23</sup> showed that vitamin D supplementation improved pregnancy rates in infertile women with PCOS in a randomized, controlled clinical preliminary investigation. Zhuang et al.<sup>24</sup> reported that combined metformin, clomiphene, vitamin D could significantly improve endocrine conditions and clinical symptoms and enhance CPR and ovulation rates. Yang et al.<sup>15</sup> found that vitamin D supplementation donate to the higher ovulation and CPR. According to Khalifa et al.<sup>25</sup> women who have sufficient levels of 25(OH)D are significantly more likely to achieve clinical pregnancies compared to those deficient in 25(OH)D. According to Katyal et al.<sup>26</sup>, inositol and vitamin D were shown to alleviate symptoms, boost fertility, enhance metabolic control, and reduce long-term health risks. Piao et al.<sup>27</sup> found that vitamin D supplementation can enhance pregnancy rates and alleviate fundamental hormonal disorders. The results of these studies are compatible with our findings. However, contradictory results have been reported in some studies.

Sulaiman et al.<sup>28</sup> conducted comprehensive research on the positive effects of vitamin D on the reproductive system of women. They found doubts and suspicions regarding the correlation between vitamin D intake and improved PCOS symptoms. The studies conducted across multiple laboratories did not yield definite findings. Firouzabadi et al.<sup>29</sup>, compared two groups to examine pregnancy rates, PCOS symptoms, and menstrual regularity. Group 1 received daily metformin, while group 2 was treated with calcium, vitamin D, and metformin for a duration of six months. The study suggests that calcium and vitamin D supplementation may lead to improvements in weight reduction, follicular development, symptoms related to androgen excess, and menstrual regularity in PCOS patients. Interestingly, the study found no significant difference in pregnancy rates between the two groups. Shojaieian et al.<sup>30</sup> in a systematic review and meta-analysis examined calcium and vitamin D supplementation effects on follicular responses, menstrual cycles, and metabolic factors in women with PCOS.

Studies have shown that prescribing calcium and vitamin D supplementation along with metformin improved follicular maturation, pregnancy rate had no significant difference in different groups after treatment with calcium and vitamin D supplementation. Regarding the effect of vitamin D supplementation on the CMR and LBR not many studies were found to compare the findings.

While a few limited studies have not found a link between vitamin D supplementation and increased CPR, the majority of previous research has demonstrated a direct impact of these supplements on CPR. As a result, it is advised that both patients and healthcare professionals be informed about these effects.

### Limitations

This study has several limitations. One significant limitation is the sample size collected from single center. Thus, it is required to conduct further studies with larger sample sizes to understand better the effect of Vitamin D supplementation on reproductive outcomes in PCOS patients.

## CONCLUSION

In conclusion, the present proof indicated that vitamin D supplementation may enhance the CPR of women with PCOS based on standard medicine, supplying a specific basis for the clinical usage of vitamin D supplementation in patients in the future. Nevertheless, more valuable studies are still required because of the heterogeneity and quality of the contained examinations.

As a consequence of our study with a randomized control group and a one-year follow-up period followed that the use of vitamin D supplementation in women with PCOS was statistically significant in increasing the CPR. There were no significant differences in LBR and CMR between the intervention and control groups. Future examinations are required to systematically evaluate these concepts because the public health, clinical, and financial implications of such a easy, secure, and cheap technique can be effective.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was carried out with the permission of Bezmialem Vakif University Ethics Committee study (Date: 31.12.2024, Decision No: 2024/432).

### Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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