



# Polycystic Ovarian Syndrome and Its Association with Vitamin D

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## Keywords

Vitamin D; Polycystic Ovarian Syndrome; PCOS; Diabetes; Pregnancy; Ovulation

## Introduction

The polycystic ovarian syndrome (PCOS) is generally characterized by hyperandrogenism, irregular menses, and polycystic ovaries. The clinical presentation of the PCOS may include acne, hirsutism, acanthosis nigricans, weight gain, and insulin resistance. The prevalence of PCOS, although varied by diagnostic criteria, is estimated to be as high as 15% to 20% [1]. In the United States, PCOS is the most common cause of an ovulatory infertility (90% to 95%) and infertility affects about 40% of PCOS women [1-3]. There is an increased risk of gestational diabetes mellitus (GDM) and type II diabetes mellitus (DMII) in women with PCOS. In a large Danish study, the total event rate of DMII was 4 times higher in the PCOS group compared to the controls and diagnosis of DMII occurred at a median age of 31 in the PCOS group versus 35 years in the control group [4]. Considering the prevalence of PCOS and its long-term implications, it has become important to explore recent therapeutic findings involving the association between PCOS and vitamin D.

## PCOS and Vitamin D

Vitamin D may serve as a key in preventing and attenuating the insulin resistance. In one study, PCOS women (not on insulin sensitizers and hormone therapy) were divided into two groups based on their vitamin D status: vitamin D <30 ng/mL or normal vitamin D [5]. It was found that the body mass index (BMI), body fat, and testosterone were higher in the vitamin D <30 ng/mL cohort compared to the normal vitamin D cohort [5]. In a Saudi women study, the age and BMI matched PCOS and non-PCOS women were assessed for fasting serum levels of vitamin D, hyperinsulinemic factors, and hormones of interest [6]. It was found that the vitamin D levels were lower (<30 ng/mL) in the PCOS group than the control group, 77.8% vs. 12.3%, respectively [6]. Furthermore, there was a positive correlation between vitamin D levels with adiponectin and FSH levels, and an inverse relationship between the vitamin D levels and follistatin, HOMA-IR, fasting plasma glucose (FPG), LH, testosterone, and androstenedione [6].

Number of interventional studies with vitamin D has shown promising results. Kardag et al. [7] started PCOS and non-PCOS women with vitamin D deficiency (<20 ng/mL) on vitamin D 1500 IU/day for 4-weeks and 50,000 IU/week for 8 weeks. In the PCOS group, the insulin sensitivity increased, and serum androstenedione and total testosterone decreased; in contrast, these values didn't change significantly in the non-PCOS group [7]. This may imply that vitamin D may be beneficial in promoting insulin sensitivity only in PCOS women; however, multiple studies on non-PCOS women with GDM have found improvements in insulin sensitivity with vitamin D supplementation [8-12].

In another study, 180 women with PCOS and vitamin D levels <30 ng/mL were randomized to receive either the vitamin D 20,000 IU/week or placebo for 24 weeks [13]. It was found that the vitamin D supplementation led to a decrease in plasma glucose after one-hour oral glucose tolerance test (OGTT) of mean -10 mg/dL compared to the placebo [13]. Seyyed et al. [14] found that women with PCOS who were given Vitamin D 50,000 IU/week versus placebo had significant change in FPG of -7.67 mg/dL versus -1.71 mg/dL, and improvements in the homeostatic model of assessment-estimated B cell function (HOMA-B) and adiponectin. Another study illustrated that the PCOS women who were given vitamin D 4,000 IU, 1,000 IU, or placebo daily for 12 weeks had significantly reduced total testosterone (TT), free androgen index (FAI), and increased sex-hormone binding globulin (SHBG) on high-dose of vitamin D supplementation compared to the low-dose or placebo group [15]. In a similar study, PCOS women were randomized to either the

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vitamin D 4,000 IU/day, 1,000 IU/day, or placebo group for 12 weeks of intervention [16]. This study also found that within the vitamin D 4,000 IU/day group, there were significant decreases in the fasting plasma glucose, serum insulin concentrations, and homeostatic model of insulin resistance (HOMA-IR) [16]. In a double-blind placebo-controlled study, PCOS women were started on vitamin D 60,000 IU weekly or placebo for 12 weeks [17]. In the vitamin D group, there was a significant improvement in insulin resistance and sensitivity [17]. Overall, multiple studies indicate a significant improvement in insulin resistance and androgenic factors in PCOS women supplemented with high dose vitamin D.

## Fertility in PCOS Women and Vitamin D

Some clinical studies have demonstrated an improvement in fertility status in PCOS women who have better vitamin D status. A cross-sectional study in 1,102 African American women illustrated that doubling of vitamin D levels from median of 14.7 ng/mL to 29.4 ng/mL was associated with half the odds of having long menstrual cycles [18]. A retrospective study assessed vitamin D status in PCOS women and their reproductive outcomes after ovulation induction. It was found that the live birth rate was 40% reduced in women with vitamin D <30 ng/mL; furthermore, improvements in live birth success were noted at thresholds  $\geq 38$  ng/mL (OR 1.42) and  $\geq 45$  ng/mL (OR 4.46) [19]. Consequently, the study points out that the vitamin D status was an independent predictor of ovulation and live birth post induction [19]. In a randomized placebo-controlled trial, PCOS women with fertility issues undergoing intrauterine insemination (IUI) were treated with either vitamin D or placebo [20]. The women in vitamin D group had significant improvements in their endometrial thickness [20].

A study assessing impact of vitamin D on the success of ovarian stimulation in women with PCOS or unexplained infertility found that in the PCOS women group, those with vitamin D deficiency (<20 ng/mL) had lower chance of ovulation and a 40% decrease in the rate of live birth [21]. Wong et al. [22] found that in women with PCOS, serum anti-mullerian hormone levels were positively and independently correlated with the vitamin D levels. In the obese PCOS women started on weight loss intervention plus 50,000 IU/week vitamin D or weight loss intervention plus placebo for 12 weeks, there were no significant differences found between the groups, fat mass, waist and hip circumference, DHEAS, total testosterone, weight, BMI, fat mass, waist and hip circumference, waist-to-hip ratio, DHEA-S, TT, FAI, and SHBG [23]. However, there was a significant improvement in menstrual frequency in women on vitamin D [23].

## Conclusion

Multiple studies have illustrated an inverse association between the vitamin D status, and hyperandrogenism and insulin resistance. Consequently, intervention with vitamin D at doses as high as 50,000 to 60,000 IU/week have provided improvements in the hyperinsulinemia, and androgenic and fertility factors in PCOS women. Overall, high dose vitamin D supplementation has shown promising results in improving the treatment of the PCOS patients.

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