



Review Article

Role of Vitamin D in the treatment of polycystic ovarian syndrome: A systematic review

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ABSTRACT

8–13% of women in the reproductive age group are affected by Polycystic ovary syndrome (PCOS) and around 70% of cases stay undiagnosed worldwide. It is one of the most common causes of infertility nowadays. Polycystic ovarian morphology, hyperandrogenism, and ovulatory dysfunction are traits of PCOS. Insulin resistance is the primary finding in the pathophysiology of PCOS.

Vitamin D is a fat-soluble vitamin that can be found as a dietary supplement. Hypovitaminosis is a risk for glucose intolerance so it has been found that supplementing vitamin D in females with PCOS lowers insulin resistance, total testosterone, and androstenedione levels and improves pressure profiles. Obese PCOS patients have been found to have lower vitamin D levels than PCOS patients who are not obese. This review aims at the pathophysiology of PCOS and the role of Vitamin D supplementation in PCOS patients. A literature search was performed to identify all relevant studies on PubMed, Google Scholar, Crossref, Medline, and Cochrane. The keyword used were; “Vitamin-D”, “Polycystic ovary syndrome (PCOS)”, “fertility”, “insulin resistance”, and “androgen hormones”. All relevant articles including review articles, original articles, case series, and case reports were reviewed.

It was found that Vitamin D supplementation has beneficial effects on reproductive outcome, metabolic abnormalities and regulating menstrual cycle in PCOS patients. Understanding importance of Vitamin D level in treating PCOS patient is of great clinical significance in preventing disease progression.

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1. Introduction

An endocrine disorder called polycystic ovary syndrome (PCOS) is frequently observed in women of reproductive age. First described by Stein and Leventhal in 1935 as triad of polycystic ovaries, amenorrhea, and hirsutism in women of reproductive age. Polycystic ovarian morphology, hyperandrogenism, and ovulatory dysfunction are traits of PCOS.¹ Depending on the diagnostic criteria used and the populations investigated in various geographic areas, PCOS affects up to one-sixth of women with a prevalence that may approach or even exceed 10-15%.^{2,3} According to the World

Health Organization 8–13% of women in the reproductive age group are affected by PCOS and around 70% of cases stay undiagnosed worldwide. It is one of the most common causes of infertility nowadays.⁴

PCOS being a multisystemic illness is characterized by oligomenorrhea or anovulation as well as the emergence of hyperandrogenism as a result of elevated levels of circulating luteinizing hormone (LH) and an altered LH: FSH (follicle-stimulating hormone) ratio.⁵ Evidence points to a multifactorial basis, with expression evident in women with a genetic predisposition.⁶ Insulin resistance is the primary finding in the pathophysiology of PCOS.⁷ Strong links exist between this development and weight gain, an increase in waist circumference, and ovarian dysfunction.⁸

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Hyperandrogenaemia is aggravated by obesity and insulin resistance.⁹ In women with PCOS, increased adipose tissue and hyperandrogenaemia are associated with an increased risk of cardiovascular disease, type 2 diabetes mellitus, hypertension, endometrial cancer, and inflammation-related disorders.^{10–12}

A fat-soluble vitamin known as vitamin D (also known as "calciferol") can be found as a dietary supplement. Additionally, it is created internally when ultraviolet (UV) rays from sunshine strike the skin and start the production of vitamin D.¹³ It is also known as steroid hormone as it maintains a balance between calcium phosphate and mineralization of bone.

A major public health issue on a global scale is vitamin D deficiency.¹⁴ With a prevalence rate of 67–85% vitamin D deficiency, can exacerbate hyperandrogenaemia and insulin resistance and is highly common in individuals with PCOS.¹⁵ Previous research has shown that vitamin D may help prevent cancer, autoimmune diseases, hypertension, diabetes, and obesity.¹⁶

Obese PCOS patients have been found to have lower vitamin D levels than PCOS patients who are not obese. According to the literature, Vitamin D can also lower inflammatory responses and control the physiological balance between oxidation and antioxidants.¹⁶

Also, vitamin D receptors (VDR) are found in the pancreas and ovaries and they play an important role in pathogenesis. By increasing PPAR expression, which increases insulin synthesis and release, vitamin D may contribute to the development of insulin resistance. Additionally, vitamin D may encourage the expression of the insulin receptor or prevent the production of pro-inflammatory cytokines.¹⁷

This article aims to compile the PCOS data and also the role of Vitamin D in the treatment of PCOS.

2. Method of Literature Search

Systematic literature research used PubMed, Google Scholar, Crossref, Medline, and Cochrane. The following keywords were used; "Vitamin-D", "Polycystic ovary syndrome (PCOS)", "fertility", "insulin resistance", and "androgen hormones". All relevant articles including review articles, original articles, case series, and case reports were reviewed. The research was conducted in September 2023. We have mostly selected publications listed in the last 20 years but did not exclude the older publications, which are commonly referenced.

2.1. Inclusion and exclusion criteria

Study included women enrolled with strict diagnosis of PCOS as per diagnostic criteria by the Rotterdam European Society of Human Reproduction and Embryology and the American Society of Reproductive Medicine.

The exclusion criteria were studies reporting other chronic or metabolic disease like diabetes, Cushing's syndrome, hyperthyroidism, history of autoimmune disease, pregnancy, coronary artery disease, hyperlipidemia or other hormone disorders; studies including other treatments as calcium or metformin.

2.2. Causes of PCOS

The most common reason behind PCOS is hormonal abnormality. Some hormones in patients with PCOS are on a higher side than in normal women. In normal women, the level of estrogens which is called the female hormone is on the higher side, and in small quantities, the male hormones known as androgens are also found. But in the patients of PCOS, an imbalance between these hormones is found and they are found to have higher androgen levels which affects the normal functioning of the body. These abnormal levels cause:

1. Anovulatory cycles as the signals from the brain for ovulation are impaired.
2. Impaired follicle growth¹⁸
3. Symptoms^{19,20}

Other causes which are believed to cause PCOS are:

1. Genetic predisposition- it has been found that PCOS runs in families.^{21,22}
2. Insulin resistance- It is one of the causes of PCOS as in patients with insulin resistance the production of insulin is decreased which in turn triggers the ovaries to produce male hormones.²³

2.3. Pathophysiology of PCOS

To this day, the precise etiology of PCOS is still poorly known. The ovaries, the hypothalamus, genetic predisposition, metabolic syndrome, and other components all play a role in the pathophysiological picture of PCOS, which is intricate and multifaceted. In recent years, Insulin Resistance and hyperandrogenism have assumed important roles in the development of this illness.²⁴ The first shortcoming is undoubtedly functional ovarian hyperandrogenism (FOH), which is brought on by steroidogenic hyperactivity and interferes with the ovarian process of producing androgens and estrogens.²⁵ Increased GnRH secretion by the hypothalamus and subsequent pituitary gland release of LH are thought to be the primary causes of FOH. An increased LH/FSH ratio is a symptom of this incorrect secretion.

As a result, there will be an increase in the thecal release of androgens, which is reflected in the presence of small and numerous antral follicles that are actively expanding. These follicles are more resistant to the hormonal action of FSH, and as a result, the elevated level of LH will prevent

the growth of granulosa cells, resulting in an early stage of luteinization. This anomaly, which is accompanied by decreased FSH sensitivity, prevents follicular maturation, which results in oligo-/anovulation.²⁶ Insulin, which works directly through the insulin receptor or indirectly through the growth factor 1 (IGF-1) receptor, exacerbates theca cells' overstimulation by LH.²⁷

2.4. Symptoms in patients with PCOS

Menstrual cycle abnormality is the most common symptom of PCOS. The cycles are irregular, infrequent, missed, or prolonged. Other features include:

1. Oily skin or Acne
2. Hair growth at abnormal parts due to excess androgens (male-like growth pattern)
3. Hair loss in some (male pattern baldness)
4. Skin tags on neck and armpits
5. Weight gain
6. Mood swings
7. Unusual aches
8. Infertility^{28–30}

Up to 80% of PCOS-afflicted women are obese or overweight. Both PCOS and obesity result in elevated blood sugar levels, high blood pressure, lower levels of HDL (high-density lipoproteins) "good" cholesterol, and higher levels of LDL (low-density lipoproteins) "bad" cholesterol. The combination of these elements is known as metabolic syndrome, and it raises the risk of diabetes, heart disease, and stroke.²⁸

3. Role of Vitamin D in PCOS

According to studies, the 1,25(OH)₂D₃ molecule controls the production and release of human chorionic gonadotropin, placental lactogen, and endometrial decidualization. In granulosa and cumulus oophorus cells of human ovarian tissue, VDR has reportedly been found. Also discovered was VDR expression in the decidua and placenta. Additionally, human-cultured syncytiotrophoblasts were found to contain VDR and vitamin D metabolism enzymes. In vitro, production of progesterone, estradiol, and estrone may be induced by 1,25(OH)₂D₃ due to vitamin D's role in the manufacture of estrogen in females.^{31,32}

Patients with PCOS frequently have hirsutism and high serum testosterone levels. In PCOS, there was additional evidence of a negative correlation between 25(OH)D levels and the degree of hirsutism brought on by high testosterone.³³ Vitamin D's impact on testosterone levels, however, was debatable.

According to certain research, supplementing with vitamin D had no discernible impact on the serum testosterone level. A very distinct voice, though, was heard

saying that vitamin D supplementation enhanced insulin sensitivity and lowered serum testosterone levels. The varied vitamin D supplementation dose and duration could be the cause of this disparity.

According to certain reports, Anti Mullerian hormone (AMH) plays a significant part in ovarian dysfunction and folliculogenesis. Serum AMH levels were higher in PCOS patients than in healthy women, and AMH has been used to diagnose and assess the prognosis for PCOS. Vitamin D supplementation reduced the serum AMH level in PCOS patients, suggesting that vitamin D aids PCOS folliculogenesis.³⁴ Additionally, research has shown that PCOS patients' follicular fluid vitamin D concentration is lower than that of the control group. Due to the small number of studies, additional research that focuses on the connection between vitamin D and folliculogenesis is still needed.

Endometrial hyperplasia which was a side consequence of PCOS that was brought on by persistent anovulation, estrogen's unopposed stimulatory impact, and the absence of progesterone's inhibitory effects. Additionally, increased endometrial thickness was a result of PCOS patients' metabolic inefficiencies. Vitamin D therapy has been suggested to raise endometrial thickness in intrauterine inseminated women with PCOS and hence helps in fertility.³⁵ Increasing evidences showed that low vitamin level was associated with an increase risk of developing breast cancer, endometrial, and ovarian cancer.³⁶

When compared to women with mild vitamin D deficiency, women with severe vitamin D deficiency have higher body weight, BMI, and waist circumference. Low blood levels of 25-hydroxyvitamin D are also associated with obesity in PCOS individuals.³³ The greatest predictors of low 25(OH)D among all metabolic indicators, including sex hormone binding globulin (SHBG), free androgen index (FAI), and glucose absorption were shown to be greater BMI and total body fat mass.

Menstrual cycle problems, infertility, and physical abnormalities such as hirsutism, obesity, and acne that are caused by PCOS might encourage psychological abnormality manifested as loss of self-esteem, emotional stress, and increased depressive symptoms. These symptoms affect the mental health of females to avoid this a supplementation of Vitamin D also helps to reduce the symptoms of PCOS and also acts as a relaxant in these females as they are taking medication for their illness.

3.1. Diagnosing PCOS

In 2003, the European Society of Human Reproduction and Embryology (ESHRE) established Rotterdam criteria for diagnosing PCOS.^{37–39} As per this criterion for diagnosing PCOS at least two of three clinical features should be present:

1. Clinical or biochemical signs of androgen excess.
2. Ovarian dysfunction which includes oligomenorrhea/anovulation
3. Ultrasound examination suggestive of polycystic disease (Necklace appearance).

This criterion helps in classifying women with PCOS into 4 different groups:⁴⁰

1. Group 1- The most prevalent one with Hyperandrogenism, menstrual dysfunction, and ultrasonographic findings suggestive of polycystic ovaries.
2. Group 2- Hyperandrogenism, and menstrual dysfunction (oligo/amenorrhea).
3. Group 3- Hyperandrogenism and polycystic ovarian morphology.
4. Group 4- Oligomenorrhea, polycystic ovarian morphology, and normal androgens.

4. Conclusion

It's being outlined that Vitamin D affects PCOS related metabolic abnormalities, enhance reproductive ability and improve mental wellness. Though to fully understand the relationship of vitamin D and PCOS, research in advance form like cell culture, animal models and Off course more human studies are indeed required but nevertheless, it is well-established fact that providing vitamin D supplementation for women from identified deficiency areas can reduce the risk of PCOS. In PCOS patients, Vitamin D supplementation improve women's ability to conceive via regulating menstrual cycles and folliculogenesis and does positively affect their metabolic syndrome profile. Therefore, vitamin D supplementation for treating PCOS in combination might be a novel therapeutic approach.

5. Summary

The current investigation discovered that vitamin D administration could influence lipid metabolism, insulin resistance, lower endometrial thickness, and, to some extent, hyperandrogenism in patients with PCOS despite various limitations which would enhance PCOS patients' menstrual cycles and folliculogenesis. As a result, vitamin D should be taken into consideration as a PCOS treatment.

6. Source of Funding

None.

7. Conflict of Interest

None.

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