

# Vitamin D and infertility: a narrative review

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## ABSTRACT

**Background and purpose:** Vitamin D, in both women and men, has been shown to be involved in modulation of the reproductive process, due to expression of the vitamin D receptor and of 1-alpha-hydroxylase in reproductive tissues such as the ovaries, testes, uterus, placenta, pituitary gland, and in the hypothalamus. The authors provide an overview of clinical data on the role of vitamin D in conditions possibly associated with female infertility.

**Methods:** The PubMed database was searched for eligible studies published by May 10th 2020. The search was conducted by matching the term “vitamin D” with the following terms: “infertility”, “*in vitro* fertilization”/“IVF”, “polycystic ovary syndrome”/“PCOS” (and also “insulin-resistance”), “endometriosis”, “primary dysmenorrhea”, “uterine leiomyoma”, “ovarian reserve”.

**Results:** The final number of papers included in our review was 49. Findings were grouped under the headings: *in vitro* fertilization, polycystic ovary syndrome (PCOS), endometriosis, primary dysmenorrhea, uterine leiomyoma, ovarian reserve. Contrasting results were found regarding vitamin D levels in IVF and PCOS, as well as on the role of vitamin D in endometriosis. The literature provides scarce data on primary dysmenorrhea and uterine leiomyoma in relation to vitamin D. Although some studies showed no overall correlation between vitamin D and anti-Müllerian hormone (AMH) levels in the infertile population, vitamin D deficiency could be associated with lower ovarian reserve in women aged >40 years.

**Conclusions:** Vitamin D deficiency is very common in fertile and infertile women. This deficiency is correlated with a variety of adverse outcomes in different conditions associated with infertility.

While there are numerous conflicting studies on the relationship of vitamin D levels with AMH levels, PCOS and endometriosis, vitamin D, influencing endometrial thickness, plays a considerable role in intracytoplasmic sperm injection and in *in vitro* fertilization. It also plays an important role in the development of insulin resistance.

## KEYWORDS

Vitamin D, fertility, PCOS, *in vitro* fertilization, infertility, ovarian reserve, endometriosis, uterine leiomyoma.

## Introduction

Vitamin D is a steroid hormone. Around of 80-90% of our vitamin D is synthesized in the skin through sunlight exposure; the rest derives from food<sup>[1]</sup>. It is well established that vitamin D maintains calcium homeostasis and promotes bone mineralization<sup>[1]</sup>. However, increasing evidence suggests that there are also several non-skeletal benefits of vitamin D. Observational studies clearly demonstrated that low serum levels of vitamin D correlated with several chronic conditions including endocrine diseases<sup>[2-5]</sup>, with cancer development and progression<sup>[6,7]</sup>, and with autoimmune disorders<sup>[8,9]</sup>. Animal and human studies highlighted that vitamin D is also involved in modulation of the reproductive process in both women and men<sup>[10,11]</sup> due to expression of the vitamin D receptor (VDR) and of 1-alpha-hydroxylase in reproductive tissues such as the ovaries, testes, uterus, placenta, pituitary gland, and in the hypothalamus<sup>[11-13]</sup>.

When investigated, vitamin D deficiency is frequently diagnosed in women of reproductive age<sup>[14-16]</sup>. Its increasing prevalence seems to be linked to obesity, lifestyle, and reduced sun exposure<sup>[17]</sup>.

In humans, vitamin D is found in two isoforms: vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol)<sup>[18]</sup>. In the skin, ultraviolet-B radiation produces vitamin D3 from precursor

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7-dehydrocholesterol. A secondary way to get vitamin D3 is by eating foods such as fatty fish or egg yolk. Instead, vitamin D2 is derived from fungal sources, such as mushrooms and yeast. As mentioned, most of our vitamin D is produced in the skin through sunlight exposure, whereas only about 20% is derived from foods<sup>[17]</sup>. However, significant individual variation exists in the proportions obtained from dietary sources and skin metabolism.

In humans, 25-hydroxyvitamin D (25(OH)D) is produced by different 25-hydroxylase enzymes in the liver. Serum 25(OH)D has a traced half-life of 2-3 weeks. In the serum, about 85 to 90% of 25(OH)D is bound to vitamin D-binding protein (VDBP), while 10 to 15% is bound to albumin, and less than 1% circulates free<sup>[19]</sup>. Only the unbound fraction crosses the cell membrane and exerts effects in the cells. To produce 1,25-dihydroxyvitamin D (1,25(OH)2D), calcitriol, a hydroxylation step of 25(OH)D is required. Calcitriol has the highest

affinity for the vitamin D receptor (VDR). In the kidneys, the conversion of 25(OH)D to 1,25(OH)2D is catalyzed by 1-alpha-hydroxylase. The activity of this renal enzyme is regulated by parameters of mineral metabolism, stimulated by parathyroid hormone (PTH), and inhibited by fibroblast-growth factor-23. Instead, extra-renal 1,25(OH)2D production is highly substrate dependent. The downstream activity of dozens of genes is regulated by the interaction of 1,25(OH)2D with the VDR. This binding produces different biological effects. 24-hydroxylation starts the degradation of vitamin D, and calcitric acid is excreted in the bile and urine after several hydroxylation and oxidation steps [17,19]. A significant increase in vitamin D concentration has been observed during pregnancy and a rapid decrease after delivery. PTH concentration is lower in pregnant women compared with non-pregnant women. Some authors hypothesized the presence of some immune cells, such as macrophages in the kidneys, that produce vitamin D. The placenta also produces 1,25(OH)2D without significantly contributing to circulating serum 1,25(OH)2D levels [17,19].

The aim of this narrative review is to analyze the role of vitamin D in conditions frequently associated with female infertility.

## Methods

### Search strategy

We set out to provide an overview of clinical data on the role of vitamin D in conditions possibly associated with female infertility.

The PubMed database was searched for eligible studies published by May 10<sup>th</sup> 2020. The search was conducted by matching the term “vitamin D” with the following terms: “infertility”, “*in vitro* fertilization” / “IVF”, “polycystic ovary syndrome” / “PCOS” (and also “insulin-resistance”), “endometriosis”, “primary dysmenorrhea”, “uterine leiomyoma”, “ovarian reserve”.

We then analyzed randomized controlled trials (RCTs) in humans, retrospective, comparative, and observational studies, meta-analyses and reviews, excluding case reports and papers not written in English. We then evaluated the reference lists of all the considered papers with the aim of identifying possible additional eligible articles. The final number of papers included in the review was 49.

## Results

### *In vitro* fertilization

In 2012 Rudick *et al.* [20] performed a retrospective cohort study in 188 infertile women undergoing IVF, and evaluated the association between 25(OH)D levels and clinical pregnancy rates after IVF. They noticed a linear decline in pregnancy rate with decreasing vitamin D levels in non-Hispanic whites, whereas the opposite was found in Asian women. In this study, the odds ratio (OR) of clinical pregnancy was four times higher in non-Hispanic white women with sufficient vitamin D levels (>30 ng/ml) than in women showing a vitamin D deficiency

(< 20 ng/ml; P=0.01). Interestingly, in this study, vitamin D status was not significantly associated with ovarian stimulation parameters or with markers of embryo quality.

In another retrospective cohort study [21] the authors, seeking to “elucidate the role of vitamin D in reproduction”, examined “the relationship between recipient vitamin D levels and pregnancy rates in donor-recipient IVF cycles”. The study, conducted in 99 recipients, highlighted that clinical pregnancy rates were lower in vitamin D-deficient (<20 ng/ml) recipients than in vitamin D-sufficient (>30 ng/ml) women (37% *versus* 78%; P=0.004). The study also assessed effects of the vitamin on the endometrium, and concluded that a 25(OH)D level higher than 30 ng/ml should be achieved in women undergoing IVF.

A prospective observational study [14] examined the correlation of IVF outcomes with 25(OH)D levels in the follicular fluid and serum of 221 infertile women. The fertilization rates associated with vitamin D status were: 43.2% for women with vitamin D deficiency, 53.4% for those with vitamin D insufficiency, and 58.8% for women with vitamin D sufficiency (P=0.054), and the implantation rates were 17.3%, 15.3%, and 18.8%, respectively (P=0.579). No statistically significant correlation was found between pregnancy rate and serum vitamin D (P=0.094) or follicular vitamin D (P=0.170) levels. The absence of a statistically significant correlation could probably be due to the small proportion of women with sufficient vitamin D levels (7.2%).

Anifandis *et al.* and Ozkan *et al.* in 2010, Aleyasin *et al.* in 2011, and Firouzabadi *et al.* in 2014 found that vitamin D assays in follicular fluid or blood serum produce highly correlative results. Conveniently, vitamin D levels in blood serum could be measured before starting treatment with assisted reproductive technology (ART), and if necessary vitamin D levels could be corrected in women showing a deficiency [14,22-24].

In 2018, Chu *et al.* [25] found that the likelihood of achieving a positive pregnancy test after embryo transfer was higher in women with good stores of vitamin D. In a meta-analysis of seven studies (2026 participants in total), Chu and colleagues found a high prevalence of vitamin D deficiency. The meta-analyzed prevalence of vitamin D deficiency, insufficiency and repletion was 34.6% (95% CI 32.0-37.4), 45.3% (95% CI 42.4-48.5) and 25.7% (95% CI 23.4-28.2%), respectively. Moreover, they remarked that women who have good levels of vitamin D have a higher chance of achieving a live birth from ART compared with women showing vitamin D deficiency or insufficiency. The OR was 1.33 (1.08-1.65).

A study conducted by Asadi *et al.* [26] showed that vitamin D induces endometrial proliferation during an intrauterine insemination (IUI) cycle. They studied 110 infertile women with PCOS to investigate the effects of vitamin D on success rates of IUI.

In 1992, Rojansky *et al.* [27] noticed seasonal variations in conception rates, with highest conception rates in summer and autumn. A hypothesis could be that the sun exposure and greater sunlight luminosity increases the body's storage of vitamin D.

Vitamin D can immunomodulate the immune system within the endometrium with a resultant reduction of active inflammatory cytokines [1].

In 2018, Arabian and Raoofi studied the effects of serum vitamin D levels on endometrial thickness and parameters of

follicle growth in 153 infertile women undergoing ovulation induction<sup>[28]</sup>. They found that a correlation exists between both endometrial thickness and antral follicle count and different tertiles of vitamin D levels ( $p < 0.05$ ). Moreover, in this study, they found no correlation between BMI and different tertiles of vitamin D levels, and observed that BMI had no effects on pregnancy outcomes. The study results could not confirm the lack of a correlation between vitamin D and ovulation induction success rates, and was unable to show that vitamin D deficiency could have valid predictive value in ovulation induction. It is likely that endometrial thickness does not affect pregnancy rate, and that other factors are involved.

In 2016, Jiang *et al.* conducted a large retrospective observational cohort study in couples (including 1883 women and 1720 men) undergoing IVF/intracytoplasmic sperm injection (ICSI). They measured plasma 25-OH vitamin D levels before ovarian stimulation. The authors found no association between vitamin D levels (in men or women) and either embryo development in the cleavage (day 2 and day 3) and blastocyst (day 5/6) stages, or clinical outcomes. This, they explained, “may be because the threshold of vitamin D affecting the reproductive process is relatively low”<sup>[29]</sup>.

In 2017, Banker *et al.* conducted a prospective study involving two groups: Group A (target group) and Group B (donors)<sup>[30]</sup>. The participants were further categorized into subgroups on the basis of vitamin D levels: A1 and B1 with vitamin D deficiency ( $< 20$  ng/mL), and A2 and B2 with insufficient vitamin D (20 to  $\geq 30$  ng/mL). They found that vitamin D deficiency leads to lower reproductive results, although the difference was not statistically significant. It was therefore concluded that it does not negatively influence the results of IVF and ICSI.

In 2018, Zhao *et al.* explored the relationship between vitamin D levels and clinical outcomes of IVF and ICSI (the outcomes were clinical pregnancy, ongoing pregnancy, and live birth) in a meta-analysis<sup>[31]</sup>. Their results were the opposite of Banker’s findings. They showed that a vitamin D deficiency is associated with a decreased probability of a live birth after IVF/ICSI and concluded that vitamin D should be given to women with deficient levels of vitamin D.

In 2019, a prospective cohort study conducted by Chu *et al.* showed that vitamin D insufficiency and deficiency are common in patients who undergo assisted reproductive treatments, and they hypothesized that vitamin D deficiency could be an important parameter to consider when a woman undergoes such treatments<sup>[32]</sup>.

### Polycystic ovary syndrome

PCOS is an endocrine female disorder characterized by clinical or biochemical hyperandrogenism, polycystic ovarian morphology, and chronic anovulation. Vitamin D has an important role in PCOS, influencing aspects such as obesity, fertility, metabolic syndrome, impaired glucose tolerance, dyslipidemia, type 2 diabetes mellitus, and cardiovascular disease.

Numerous studies have been carried out, but no observational study has confirmed an association between PCOS and vitamin D deficiency.

In 2011, Wehr *et al.*<sup>[33]</sup> evaluated 57 PCOS women, examining the effects of weekly supplementation of 20000 IU

vitamin D over a period of 24 weeks. They reported an improvement of menstrual frequency in about 50% of the women.

In 2012, Ott *et al.*<sup>[34]</sup>, in a prospective cohort study of 91 anovulatory infertile women with PCOS, showed that BMI and 25(OH)D deficiency were significant predictive parameters. Above all, they noticed that 25(OH)D levels of less than 10 ng/ml reduced the chance of follicle development by 67% and reduced the possibility of becoming pregnant by 76%.

Vitamin D acts on the metabolism of cholesterol, triglycerides and very-low-density lipoprotein. This was confirmed by a RCT conducted in 50 PCOS women with vitamin D deficiency treated with three oral capsules of 50000 IU of vitamin D every 20 days over a period of 2 months<sup>[38]</sup>. The study also showed that vitamin D does not influence HDL, LDL, apolipoprotein AI, or high-sensitivity C-reactive protein concentrations.

Vitamin D and calcium supplementation is associated with a significant decrease of testosterone and androstenedione total levels, according to the results of the single-arm, open-label trial by Pal *et al.*<sup>[36]</sup>. The authors of this study also found that the supplementation was associated with a significant reduction in blood pressure, but they did not find effects on glucose and insulin metabolism.

In an Austrian study<sup>[37]</sup>, the authors found that 25(OH)D and calcium intake were independent predictors of androstenedione levels, and that calcium intake was an independent predictor of testosterone levels.

In a retrospective analysis of 50 overweight/obese PCOS women by Thomson *et al.*<sup>[15]</sup>, the authors noticed an increase in the cohort’s 25(OH)D levels in the summer, associated with greater reductions in waist circumference and cholesterol. Moreover, they showed that 98% of these PCOS women were vitamin D deficient ( $< 20$  ng/ml) and 2% were vitamin D insufficient (20-29.9 ng/ml). All this could explain the correlation between PCOS and fertility disorders. This study confirms the high prevalence of vitamin D deficiency among PCOS women and the general population.

Some authors demonstrated that vitamin D plays an important role in the development of insulin resistance<sup>[38-41]</sup>. They showed that 25(OH)D is associated with increased insulin receptor expression, increased insulin sensitivity (due to activation of the peroxisome proliferation-active receptor Delta (PPAR-Delta) gene), and increased insulin synthesis and secretion, and with a decrease of the production of pro-inflammatory cytokines involved in insulin resistance. Moreover, calcitriol shows an indirect effect on insulin sensitivity because there is a regulation of necessary intracellular calcium concentration for insulin-mediated intracellular signaling in insulin-responsive tissues like fat and muscle<sup>[42,43]</sup>.

Some studies reported an inverse correlation between vitamin D levels and BMI in both obese and non-obese PCOS patients and moreover, that vitamin D, BMI and HOMA-IR are independent predictors of development of metabolic syndrome in PCOS patients<sup>[16,44-48]</sup>.

There are contrasting findings regarding serum vitamin D levels in PCOS women.

Jia *et al.* showed that PCOS women had lower serum vitamin D levels compared with the control group<sup>[46]</sup>.

In 2015, He *et al.* conducted a meta-analysis of the corre-

lation between serum vitamin D levels and PCOS, comparing PCOS women with a control group. They found only a trend for higher prevalence of vitamin D deficiency in women with PCOS [45].

Tsakova *et al.* [49] reported that vitamin D deficiency was more common in obese PCOS women than in non-obese PCOS patients, a finding confirmed by Muscogiuri *et al.* [50] who found that total fat mass was associated with 25(OH)D levels and that obese PCOS women had lower 25(OH)D levels compared with non-obese PCOS patients. On the contrary, Mahmoudi *et al.* showed that patients with PCOS had a higher vitamin D level than the control group (29.3 ng/ml vs 19.4 ng/ml, respectively) [51].

In 2009, Wehr *et al.* reported lower vitamin D levels in hirsute patients with PCOS than in PCOS women without hirsutism [16].

Several studies showed an inverse association between 25-hydroxyvitamin D and testosterone, sex hormone-binding globulin, free androgen index, and dehydroepiandrosterone sulfate in PCOS women compared with control groups [16,44,48].

As a last datum, several studies investigated the effects of vitamin D supplementation on hyperandrogenism in PCOS women. These studies showed no effect on androgen levels [33,45,52,53]. However, most of them were not randomized and they were conducted in small patient cohorts. Therefore, these results are subject to several limitations.

## Endometriosis

Endometriosis affects around 10% of women of reproductive age. Inflammatory responses and an dysfunctional immune mechanism are involved in its pathogenesis [54]. Vitamin D is known to have some immunomodulatory and anti-inflammatory properties that could change this [8,9].

Evidence on the role of vitamin D in endometriosis is conflicting. In the human endometrium there are VDRs and enzymes that metabolize vitamin D.

In a cross-sectional study that included 133 healthy women, 132 women with endometriosis-related infertility, and 62 women with idiopathic infertility, Vilarino *et al.* showed that there was no association between VDR polymorphisms and infertility or endometriosis [55].

Agic *et al.* [56] studied expression of VDR and of 1-alpha-hydroxylase and found both to be higher in women with endometriosis than in controls. Moreover, in the same study, they showed that there was no difference between 25(OH)D levels in women affected by endometriosis and the control group.

The same results were obtained by Hartwell and colleagues [57]. They, too, observed that 25(OH)D levels were similar in women affected by endometriosis and the control group. However, they found a difference in 1,25(OH)D levels, which were higher in women with endometriosis [57].

On the contrary, Somigliana *et al.* [58] in a study conducted in 87 women with endometriosis and 53 controls, found a significant increase in 25(OH)D serum levels in patients compared with the control group ( $24.9 \pm 14.8$  vs  $20.4 \pm 11.8$  ng/ml); they also demonstrated that the advanced stages of the disease are associated with higher levels of 25(OH)D.

Conversely, Miyashita *et al.* [59] found that 25(OH)D levels in serum were significantly lower in women with severe endo-

metriosis. This discrepancy could be due to different population distributions or groupings.

Another important role in the pathogenesis and progression of endometriosis is played by VDBP, although the literature reports contrasting results in this regard.

A study conducted by Faserl *et al.* showed that VDBP was significantly higher in ectopic endometrial tissue than in normal tissue [64]. Also, they observed a 3-fold increase in VDBP levels in all studied women with endometriosis compared with the control group [60].

On the other hand, Ferrero *et al.* reported lower VDBP concentrations in peritoneal fluid in women with untreated endometriosis than in women who use oral contraceptives and in the control group [61].

## Primary dysmenorrhea

Dysmenorrhea is a condition characterized by excessive uterine production of prostaglandins. It has been suggested that vitamin D might have a role in the treatment of dysmenorrhea since vitamin D inhibits synthesis of prostaglandins. Lasco *et al.* observed a reduction of pain in vitamin D group with severe pain at baseline and no analgesic was recorded [62]. They used a single loading dose of vitamin D (300 000 UI).

## Uterine leiomyoma

In the only study evaluating the association of uterine leiomyoma with vitamin D, the authors showed that women with low levels of vitamin D developed uterine leiomyoma more frequently. In this case-control study, conducted by Paffoni *et al.* in 128 women with leiomyoma and 256 age-matched controls, the authors observed that 25(OH)D levels were significantly lower in the leiomyoma group than in the control group. Women with vitamin D deficiency (<10 ng/ml) had a higher OR (2.4,  $p=0.016$ ) than women with sufficient vitamin D levels (> 20 ng/ml) [63].

## Ovarian reserve

The role of anti-Müllerian hormone (AMH) is to preserve the ovarian reserve by inhibiting the initial recruitment of follicles for growth and by reducing the sensitivity of the primordial follicles to FSH. Merhi *et al.* observed that calcitriol promotes follicle maturation [64].

Although some studies showed no correlation between vitamin D in the infertile population, in a cross-sectional study including 388 premenopausal women with normal menstrual cycles, a positive independent association was found between 25(OH)D levels and AMH in 40-year-old women. Therefore, vitamin D deficiency could be associated with lower ovarian reserve in advanced reproductive age [65].

Another small study conducted by Dennis *et al.* [66] in 33 premenopausal women showed that 25(OH)D serum levels were correlated with AMH levels, and that levels of both 25(OH)D and AMH showed a seasonal variation. Moreover, the authors found that AMH decrease can be prevented by vitamin D supplementation.

Shapiro and colleagues, in a retrospective cohort study of 457 infertile women between the ages of 21 and 50, showed that 25(OH)D levels were poor predictors of AMH [67].

## Discussion

Clinical studies show that vitamin D deficiency is very common both in fertile and in infertile women. This deficiency is correlated with a variety of adverse outcomes in women affected by infertility.

There are numerous contrasting findings on the association of vitamin D levels with AMH, PCOS, and endometriosis.

Vitamin D plays an important role in ICSI and *in vitro* fertilization and seems to be directly correlated to endometrial thickness. Vitamin D levels could be measured in blood serum before starting an ART treatment and, if necessary, corrected. All women undergoing IVF or ICSI who are found to have a vitamin D deficiency or insufficiency should have a supplementation of vitamin D. The desired levels of vitamin D is at least 30 ng/ml according to most authors.

There are some inconsistencies in PCOS and endometriosis studies, maybe due to a lack of uniform distribution of populations. Also, in most of these studies, the PCOS and endometriosis women showed vitamin D deficiency or insufficiency.

Vitamin D also plays an important role in the development of insulin resistance, which is associated with increased insulin receptor expression, insulin sensitivity (due to activation of the PPAR-Delta gene), and insulin synthesis and secretion, and decreased production of pro-inflammatory cytokines involved in insulin resistance.

Vitamin D has some immunomodulatory and anti-inflammatory properties that are probably involved in the pathogenesis of endometriosis. VDR and 1-alpha-hydroxylase expression could be higher in women with endometriosis. VDBP is significantly higher in ectopic endometrial tissue than in normal tissue.

In the future, vitamin D determination should be introduced as a routine test for women with PCOS, endometriosis, or undergoing IUI or ICSI.

Those found to have a deficiency or an insufficiency could be supplemented with vitamin D, the dose being dictated by the degree of deficiency.

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