

## SPECIAL ARTICLE

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# Vitamin D deficiency and gynecological pathologies in women of reproductive age

## Deficiencia de vitamina D y patologías ginecológicas de la mujer en edad reproductiva

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### ABSTRACT

Vitamin D is currently under investigation in many fields of medicine. It is known to have fundamental functions in calcium metabolism and bone modeling. Vitamin D deficiency defined as 25-hydroxycholecalciferol concentration < 20 ng/mL and is frequently observed in patients with gynecological pathologies. In the last two decades there is evidence on the association of low serum vitamin D concentrations with disorders such as diabetes mellitus and metabolic syndrome. There are increasing reports of the impact of vitamin D metabolism on the development of disorders of the female reproductive system. Vitamin D receptor and 1 $\alpha$ -hydroxylase are present in the reproductive organs, suggesting that vitamin D may have some effect in modulating cellular functions. The detrimental effects of deficiency have been shown in patients diagnosed with polycystic ovarian syndrome, endometriosis, and leiomyomatosis. Vitamin D supplementation should be added to the treatment schemes of most gynecologic pathologies in patients with deficiency, both for the improvement of insulin resistance (as in patients with polycystic ovarian syndrome) and for the outcomes of infertility treatment. The aim of this review was to establish effects of vitamin D deficiency on pathologies in women of reproductive age.

**Key words:** Vitamin D, Polycystic ovary syndrome, Uterine leiomyomatosis, Endometriosis, In vitro fertilization.

### RESUMEN

La vitamina D está actualmente en el ámbito de la investigación en muchos campos de la medicina. Es conocido que tiene funciones fundamentales en el metabolismo del calcio y modelado óseo. La deficiencia de vitamina definida como la concentración de 25-hidroxicalciferol < 20 ng/mL es observada con frecuencia en pacientes con patologías ginecológicas. En las últimas dos décadas existe evidencia sobre la asociación de concentraciones séricas bajas de vitamina D con trastornos como diabetes mellitus y síndrome metabólico. Cada vez hay más informes que plantean el impacto del metabolismo de esta vitamina en el desarrollo de trastornos del sistema reproductor femenino. El receptor de vitamina D y la 1 $\alpha$ -hidroxilasa están presentes en los órganos reproductivos, lo que sugiere que la vitamina D puede tener algún efecto en la modulación de las funciones celulares. Se ha comunicado los efectos perjudiciales de la deficiencia en pacientes con diagnóstico de síndrome de ovarios poliquísticos, endometriosis y leiomiomatosis. La suplementación de vitamina D debería agregarse a los esquemas de tratamiento de la mayoría de las patologías ginecológicas en pacientes con deficiencia, tanto por la mejora de la insulinoresistencia (como en las pacientes con síndrome de ovarios poliquísticos) como por los resultados del tratamiento de la infertilidad. El objetivo de esta revisión fue establecer los efectos de la deficiencia de vitamina D en patologías de la mujer en edad reproductiva.

**Palabras clave.** Vitamina D, Síndrome de ovarios poliquísticos, Leiomiomatosis uterina, Endometriosis, Fertilización *in vitro*.

### INTRODUCTION

Epidemiological studies suggest that global vitamin D (VitD) deficiency is about 90%. Despite indications for supplementation, deficiency is still important and includes women of childbearing age. Deficiency is defined as 25-hydroxyvitamin [25(OH)D; main circulating form] concentrations below 20 ng/mL; suboptimal values correspond to 20 and 30 ng/mL, whereas serum concentrations of 30 to 50 ng/mL are considered optimal to ensure pleiotropic effects<sup>(1)</sup>. There are few data on VitD con-



centrations in the Latin American population. However, studies in different adult populations have shown a high prevalence of moderate deficiency in the world population<sup>(2)</sup>.

In the last three decades, several investigations have evaluated the therapeutic effects of VitD other than bone metabolism. It has beneficial effects on autoimmune, infectious, cardiovascular, insulin resistance and malignant neoplasms<sup>(3)</sup>. However, studies evaluating the effects on gynecological pathologies are scarce<sup>(4)</sup>. Since both VitD receptors and 1 $\alpha$ -hydroxylase are present in reproductive tissues (ovaries, uterus and pituitary), the potential association between VitD deficiency and gynecological pathologies is evident<sup>(5)</sup>. The objective of this review was to establish the effects of vitamin D deficiency on pathologies in women of reproductive age.

## VITAMIN D METABOLISM

VitD is an essential fat-soluble vitamin and its pleiotropic effects are closely related to health and disease<sup>(1)</sup>. Its biological cycle begins when 7-dehydrocholesterol is transformed by the effects of ultraviolet B radiation (wavelength 290 to 315 nm) in epidermal keratinocytes and dermal fibroblasts into previtamin D. Less than 10% comes from food sources or dietary supplements. In the liver and kidneys it is converted into two main metabolically active forms: cholecalciferol (VitD3) and ergocalciferol (VitD2). This process is extremely efficient, since a brief daily exposure to sunlight of the surface of the hands and face is equivalent to the intake of 200 units of VitD<sup>(6)</sup>.

It is difficult to determine the duration of daily exposure to sunlight necessary to achieve the amount provided by supplements in individual patients and depends on skin type, latitude, season and time of day<sup>(7)</sup>. Prolonged exposure to sunlight does not produce toxic concentrations of VitD, mainly due to photoconversion to inactive metabolites (lumisterol, tachysterol, 5,6-transVitD and supra-sterols). In addition, sunlight induces melanin production, which contributes to decrease its production<sup>(8)</sup>.

## VITAMIN D IN GYNECOLOGICAL PATHOLOGIES AND REPRODUCTIVE MEDICINE

### POLYCYSTIC OVARY SYNDROME

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women of reproductive age with heterogeneous clinical manifestations. In addition to menstrual alterations, ovaries with polycystic changes, hyperandrogenism and/or hyperandrogenemia, a group of patients present obesity - overweight (20% and 85%), insulin resistance and cardiovascular and metabolic disorders<sup>(9-11)</sup>.

A meta-analysis showed that a 1 kg/m<sup>2</sup> increase in body mass index (BMI) correlated with a greater than 1% decrease in VitD concentrations. Similarly, a 10% increase in BMI was associated with a greater than 4% decrease in serum concentrations. These observations confirm that overweight-obesity, present in most PCOS patients, leads to VitD deficiency. The main pathophysiological mechanism proposed is sequestration by adipose tissue<sup>(9)</sup>.

There is no clear evidence indicating the possible association between low VitD concentrations and the pathogenesis of PCOS, especially in patients with normal weight<sup>(10,11)</sup>. There is evidence of correlations between VitD concentrations and androgen, luteinizing hormone and follicle stimulating hormone values<sup>(12)</sup>. However, other investigations have not confirmed these findings<sup>(13,14)</sup>. Other studies have found an association between low serum VitD concentrations and insulin resistance, impaired glucose tolerance, dyslipidemia, obesity and hypertension in these patients<sup>(13-15)</sup>.

VitD may have beneficial metabolic effects by stimulating insulin receptor expression, leading to improved glycemic metabolism. Activation of the insulin promoter gene produces changes in extra- and intracellular calcium stores that modulate insulin secretion. The Apa-I polymorphism of the VitD receptor gene may contribute to the development of PCOS<sup>(16)</sup>. Other polymorphisms (Cdx-2, Taq-I, Bsm-I) appear to be associated with alterations in glycemic metabolism, hyperandrogenemia, increased concentrations of luteinizing hormone and follicle stimulating hormone with decreased sex hormone binding globulin<sup>(17,18)</sup>.



The therapeutic efficacy of VitD supplementation in PCOS patients has been evaluated by several studies. VitD and calcium supplementation produced normalization of menstrual cycles after initiation of treatment<sup>(19)</sup>. Another study showed regularization of menstrual cycles in half of the cases, as well as improvement of insulin resistance, without significant changes in BMI<sup>(15)</sup>. Two other studies showed that supplementation improved insulin sensitivity and lipid profile, without other significant metabolic effects<sup>(20,21)</sup>. An investigation of VitD and calcium supplementation found significant decreases in testosterone and androstenedione concentrations, accompanied by a decrease in blood pressure, with no effect on fasting glycemia and insulin concentrations<sup>(22)</sup>. Other studies have provided evidence that supplementation can repair folliculogenesis alterations and induce spontaneous ovulations<sup>(23)</sup>.

There is still controversy about the effects of VitD supplementation on metabolic disorders in PCOS patients. One investigation showed improvement of lipid profile with no effect on inflammatory markers<sup>(24)</sup>. Meanwhile, VitD supplementation alone or combined with metformin did not produce changes in insulin resistance despite normalization of blood pressure values<sup>(25)</sup>. Finally, other research has shown beneficial effects of VitD supplementation on ovulation stimulation with clomiphene citrate and increased success rate of in vitro fertilization (IVF) procedures in infertile PCOS patients<sup>(26)</sup>.

## ENDOMETRIOSIS

The presence of VitD receptors and metabolic enzymes in human endometrium and myometrium has been confirmed. Due to the immunomodulatory, antiproliferative and anti-inflammatory properties of VitD, there is growing interest in the possible etiopathogenesis of endometriosis<sup>(27,28)</sup>.

A case-control study showed that serum VitD concentrations were elevated in patients with endometriosis<sup>(27)</sup>. Subsequent studies showed overexpression of VitD receptors and 1 $\alpha$ -hydroxylase in peritoneal foci and endometrium of patients with endometriosis compared with healthy controls. This could indicate that there is immune hypersensitivity at normal concentrations in patients with endometriosis and

immune overstimulation at elevated peritoneal VitD concentrations. These effects would be auto- and/or paracrine within the implants<sup>(28)</sup>. Another investigation of serum from endometriosis patients found increased expression of VitD-binding protein<sup>(29)</sup>. Similar results have also been obtained in ectopic endometrial tissue<sup>(30)</sup>.

Some authors suggest that the elevated serum VitD concentrations and receptor overexpression in endometriotic foci may be the result of inadequate selection of the control groups, which included patients with uterine myomas and idiopathic infertility, conditions characterized by VitD deficiency<sup>(31)</sup>. In addition, these studies have small sample groups, great heterogeneity and retrospective design.

Investigations of the association between VitD intake and serum concentrations in patients with endometriosis confirmed that serum concentrations correlated negatively with the presence of endometriosis foci. In addition, patients with the highest VitD concentrations had a 24% lower risk of developing endometriosis compared to the group of patients with lower concentrations. On the other hand, women with higher dietary intake had 21% lower risk than those patients with lower concentrations<sup>(32)</sup>. These findings were confirmed by research with elocalcitol (a selective VitD receptor agonist) by inhibiting the development of endometriotic foci and reducing inflammatory markers<sup>(33,34)</sup>.

## INFERTILITY AND ASSISTED REPRODUCTION

Several in vitro and in vivo studies document the association between VitD deficiency and ovarian dysfunction. VitD regulates the expression of receptors for follicle-stimulating and antimüllerian hormone, controlling both folliculogenesis and granulosa cell differentiation. It also increases the expression of steroidogenic enzymes and stimulates progesterone-estrogen production, controlling corpus luteum development<sup>(35)</sup>.

Mice lacking the VitD receptor gene have impaired folliculogenesis, anovulation and uterine hypoplasia. In addition, VitD-deficient diet causes decreased fertility<sup>(36)</sup>. Clinical studies of the association between VitD deficiency and infertility, response to ovulation stimulation and efficacy of IVF methods are scarce



and offer contradictory data. Some publications indicate high rates of deficiency (between 20% and 100%) in patients undergoing IVF programs<sup>(37-39)</sup>. A prospective investigation showed a positive correlation between VitD concentrations and the percentage of pregnancies achieved in an IVF program<sup>(10)</sup>. Higher nidation rates were achieved in women whose follicular fluid VitD concentrations were higher<sup>(37)</sup>.

One study found that serum VitD concentrations affect the efficacy of IVF procedures. Linear decreases in concentrations were associated with decreased pregnancy rates. But concentrations did not affect ovulation stimulation or resulting embryos<sup>(38)</sup>. Other research showed that higher VitD concentrations were associated with higher pregnancy rates and live births (37% vs. 78%)<sup>(39)</sup>. Other research that evaluated single blastocyst transfer on day 5 found lower pregnancy rates in VitD-deficient women (41% compared with 54%). The probability of achieving a pregnancy in the deficiency group was 40% lower compared to the control group<sup>(40)</sup>. In contrast, the absence of association between the efficacy of blastocyst transfer on day 5 with VitD deficiency was shown by a later study<sup>(41)</sup>.

Although most data indicate an association between VitD deficiency and IVF failure, other studies have not confirmed this relationship. One group showed adverse effects of high VitD concentrations on embryo quality<sup>(42)</sup>. No effects on IVF efficacy have been observed either, regardless of the determination of total or available VitD<sup>(43)</sup>.

These contradictory findings are probably due to confounding factors, different definitions of deficiency and methodologies of VitD determination and transfer of different numbers of embryos. Nevertheless, most of the available studies suggest a possible causal relationship. Given the prevalence of VitD deficiency in infertile women and low cost of supplementation, the current recommendation is the routine determination of concentrations and the use of supplementation before initiating any IVF program<sup>(31)</sup>.

## UTERINE LEIOMYOMAS

Several investigations have shown that VitD deficiency may be a risk factor for the development of uterine leiomyomas, regardless of ethnicity<sup>(44)</sup>. One study found that serum concentrations were significantly lower in patients with leiomyomas. After adjustment for BMI, ancestry, and ethnicity, this association remained significant<sup>(45)</sup>.

The antiproliferative effects of VitD on human myometrial and leiomyoma-derived cells have been documented in *in vitro* studies<sup>(46,47)</sup>. It inhibits both Wnt4/ $\beta$ -catenin and signal transduction of the target pathway of rapamycin in mammalian cells, key pathways in the etiopathogenesis of leiomyomas. The potential therapeutic effect during the formation and/or growth of leiomyomas has also been documented in *in vivo* animal models<sup>(48)</sup>.

## CONCLUSION

VitD deficiency is a public health problem. Available evidence indicates that it is related to potential health complications in women of reproductive age. Deficiency appears to be related to endocrine and gynecological diseases. Differences in study methodologies, geographic location, season of the year and exposure to sunlight may explain the discrepancies between different population groups. Patients with proven deficiency may benefit from supplementation.

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