Polycystic Ovary Syndrome and Vitamin D, Where do We Stand?

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ABSTRACT

In recent years, a correlation between vitamin D deficiency (VDD) and polycystic ovary syndrome (PCOS) has been suggested. Our attention has been drawn to vitamin D having effects other than those related to calcium homeostasis, specifically those concerning the reproductive process.

In this article we discuss the role of vitamin D on women with PCOS and the recommendations on vitamin D supplementation for these women.

Keywords: Vitamin D, Fertility, Polycystic Ovary Syndrome

Introduction

Vitamin D has been known to play an essential role in calcium-phosphorus homeostasis [1] but during the last years there is an increasing interest regarding its effects on the reproduction process.

The aim of this article is to review the current state of knowledge on vitamin D and Polycystic ovary syndrome (PCOS) and whether dietary supplementation in women suffering from PCOS should be provided.

A revision of the articles published in PubMed during the last five years was carried out, using the following search criteria: “vitamin D”, “polycystic ovary syndrome” and “fertility”. Twenty-two articles were found, of which three were excluded (one due to irrelevance to the topic, and the other two due to not having access to the full article).

Vitamin D

Vitamin D, conceptually, acts more as a hormone rather than a vitamin as it does not need dietary intake in order to be present in the organism and it carries out its actions in tissues that may be far away from its origin. It can therefore be described as a steroid hormone, which is mostly (80-90%) synthesized in the skin after sunlight exposure, and only 10-20% of total serum levels come from the diet. [2]

The endogenous synthesis of vitamin D starts after photolysis induced by ultraviolet light B (UV-B) on 7-dehydrocholesterol, located in dermis fibroblasts and epidermic keratinocytes, producing colecalciferol (also known as vitamin D3). [3]

Vitamin D coming from the diet is very efficiently absorbed in the intestine as colecalciferol (or vitamin D3) and

ergosterol, a biological precursor of vitamin D2. Vitamin D3 is mostly from animal origin and it can be found in fatty fish (such as salmon, tuna, sardines and mackerel), eggs and veal liver, whereas ergosterol comes from vegetables such as yeast and mushrooms. Ergosterol requires UV-B for its conversion to vitamin D2. [4]

Both colecalciferol and ergosterol, regardless of their origin, act as pro-hormones and must be metabolized in the liver by 25-hydroxylase (CYP27A1) and transformed into 25-hydroxivitamin D (25-(OH)-D). It is then converted into its active form, 1,25-dihydroxivitamin D (1,25-(OH)-D) by the enzyme 1-alpha hydroxylase, present in the kidney. [5]

Vitamin D metabolites circulating in the blood stream have different kinetics. 25-(OH)-D has a 2-3 week half-life and thus its serum quantification is used to assess the vitamin D deposits in the body.

The biological actions of vitamin D and its metabolites are mediated through its union to a nuclear and cytoplasmic receptor that belongs to the same gene superfamily as steroid and thyroid hormones. [6,7]

Although its role in calcium-phosphorous metabolism is widely known [1], it is also known that its activity is important for a wide range of physiological functions such as cellular differentiation, inflammatory, apoptotic and antiproliferative phenomena, immunosuppression [8,9] and female fertility. [10]

The renal enzyme alpha-1-hydroxylase has been isolated in other tissues such as ovaries, brain, breast, prostate and colon, inferring that the active form of vitamin D can also be produced in these organs. Moreover, vitamin D receptor

(VDR) has been found in ovarian tissue, placenta, testes, hypothalamus and pituitary gland. [11, 12, 13, 14]

The relationship between vitamin D and fertility is relatively new and there are studies both in animal models and humans that sustain the importance of adequate serum levels of vitamin D and its metabolites in the reproductive physiology of both women and men.

As previously stated, the longer half-life (2-3weeks) of 25-(OH)-D compared to that of 1,25- (OH)-D (4-6 hours) makes the first essential to evaluate vitamin D deposits in the organism. [15]

Vitamin D deficiency (VDD) is defined as 25-(OH)-D serum levels under 20ng/dL. Insufficiency is considered when serum levels are between 20 and 30ng/dL. [16]

Many authors consider VDD as a global health issue, which is derived from a decrease in the intake of certain foods, an increase the population's obesity index, environmental pollution and a decrease in sunlight exposure. [17]

Polycystic Ovary Syndrome

PCOS is amongst the most common causes of female infertility. [18]

It is the most frequent endocrine disorder in women, affecting 5-20% of women in reproductive age. It results in an excess of androgens, menstrual dysfunction and chronic anovulation. Women with PCOS are at greater risk of developing type 2 diabetes mellitus, cardiovascular diseases and endometrial adenocarcinoma. [19]

Regarding its etiology, an autosomal dominant mode of inheritance was first proposed, with a prevalence of 51-67% and a high penetrance of up to 90%. [20] However, later studies suggested an X-linked or polygenic inheritance, with more than 70% heritability. [21]

Even though its definition has been revised on multiple occasions, it was in a consensus meeting in 2012, sponsored by the National Institutes of Health (NIH), where the use of its broadest definition was suggested ie. Rotterdam 2003 criterion (2 out of 3 of: 1. Oligo and/or anovulation, 2. Clinical and/or biochemical signs of hyperandrogenism, and/or 3. Polycystic ovaries in ultrasonography) [22], alongside stating the phenotype of the disorder (Phenotypes A through D) as the latter is associated with the risk for metabolic complications and long term morbidities [23]. Phenotype A presents with hirsutism/hyperandrogenism (HA), ovulatory dysfunction and polycystic ovaries; phenotype B presents hirsutism/HA and ovulatory dysfunction; phenotype C presents

hirsutism/HA and polycystic ovaries; and Phenotype D presents ovulatory dysfunction and polycystic ovaries.

Despite its precise physiopathology being unknown, there are a number of theories, some of which are described below.

In a prospective study carried out by Irani et al in 2017, an increase in the circulating serum and follicular fluid levels of Vascular Endothelial Growth Factor (VEGF), an angiogenic growth factor, was observed in women with PCOS when compared with normal women. They proposed that the increase in VEGF would be responsible for the increased ovarian mass due characteristic of these patients due to an excessive neovascularization in stroma and theca of PCOS ovaries. Moreover, this could increase the risk of ovarian hyperstimulation syndrome. [24]

Irani et al. carried out another prospective study in 2015 where they observed an increase in serum Transformation Growth Factor TGF- β 1 (TGF- β 1), which stimulates angiogenesis and fibrosis. Furthermore, there was a decrease in serum endoglin (sENG) in women with PCOS. Serum endoglin decreases TGF- β 1's bioavailability by binding to it, thus improving fibrosis. They also observed that this imbalance was corrected when supplementation with vitamin D was given. [25]

Another theory which is being studied is that of Advanced Glycation End products (AGEs). They are products of the non-enzymatic modification of proteins, lipids and nucleic acids by glucose. They are proinflammatory molecules which, when binded to their cell receptor, may be involved in abnormal follicle development. On the other hand, its soluble receptor (sRAGE) binds to AGEs, avoiding follicle damage. In 2014, Irani et al. observed an increase in AGEs levels in PCOS patientes. Moreover, by treating PCOS patients and VDD with vitamin D during 16 weeks, the increase in 25-(OH)-D serum concentration was associated with a significant increase in sRAGE levels ($p=0,03$) (and therefore a decrease in the inflammatory response, and a decrease in abnormally high levels of anti-Müllerian hormone present in these patients ($p<0,001$)). [26]

Vitamin D and Pcos

A higher prevalence of vitamin D deficiency (67-85%) has been observed in women with PCOS. [27] According to a series of meta-analysis, these women have a higher risk of insulin resistance and cardiovascular disease. [28]. Moreover, it has been suggested that VDD predicts more severe metabolic disturbances in these patients. [29]

Patients with VDD have been shown to have a greater prevalence of insulin resistance, obesity, inflammation and dyslipidemia. Therefore, it is postulated that, given that

women with PCOS also suffer from the above, VDD is implicated in PCOS's physiopathology. However, there is a high prevalence of obesity in women with PCOS, which makes it difficult to decide whether VDD contributes to PCOS regardless of increased body mass index (BMI), or if the latter acts as a confusing factor. [30]

Regarding PCOS's genetics, polymorphisms of the vitamin D receptor, especially single nucleotide polymorphisms (SNP), have not been associated with an increase in the risk of PCOS but there is a correlation with the severity of the pathology. [31]

A relationship between vitamin D levels and metabolic and hormonal dysfunction has been confirmed in PCOS women. [32] Even though its mechanism remains unknown, it has been suggested that it may be because of loss in apoptotic mechanisms present in ovarian follicles. Moreover, due to the immunomodulatory role played by vitamin D, VDD may trigger the inflammatory responses that lead to insulin resistance.

Vitamin D and Ovarian Reserve Markers

Anti-müllerian hormone (AMH) is a glycoprotein produced by granulosa cells in antral follicles, where it modifies follicle response to follicle stimulating hormone (FSH). It is, alongside antral follicle count (AFC), the most studied ovarian reserve marker.

AMH prevents oocyte loss by inhibiting antral follicle recruitment and slowing down their growth. It is a serum protein with a peak during puberty and slowly decreases with age. A wide range of literature has been published suggesting a possible relationship between vitamin D and AMH levels.

In a prospective study carried out by Drakopoulos in 2017, there was no positive correlation between 25-(OH)-D and AMH levels (Spearman's $r = 0,02$, P value = 0,7) nor with follicle antral count (AFC) ((Spearman's $r = -0,02$, P value = 0,7). [33]

However, confusion remains in literature regarding whether or not vitamin D has the capacity to influence AMH production. In **Table 1** there is a summary of some

of the latest studies regarding the latter. Authors agree that more prospective studies are required in order to establish the relationship between vitamin D and ovarian reserve markers.

Vitamin D Supplementation

It is much discussed whether or not women with VDD and PCOS should be treated with dietary supplements.

Wehr et al conducted a study in 57 PCOS women which received 20 000 IU of colecalciferol weekly during 24 weeks. They observed that treatment with vitamin D might improve glucose metabolism and menstrual frequency in these women. [34,35] Menstrual frequency was improved in 30% of these women after 12 weeks of treatment, and in 50% after 24 weeks. Moreover, 25% of women seeking pregnancy at baseline conceived during the study. [36]

Regarding metabolic disturbance, after treatment with 150 000 IU of vitamin D every 20 days during 2 years, there was a decrease in triglyceride serum levels, total cholesterol and very low density lipoproteins (VLDL). However, no changes were observed in high density lipoproteins (HDL), low density lipoproteins (LDL), apolipoprotein A1 nor high-sensitivity C-reactive protein (hs-CRP). [36]

Pal et al conducted a study where obese PCOS women with VDD were treated with a combination of vitamin D and calcium. A decrease in testosterone and androstenedione serum levels was observed. [37]

Given its beneficial effects on menstrual frequency and metabolic parameters (hence the decrease in cardiovascular risk), the Endocrine Society's recommendations are to supplement women aged 18-70 with a daily dose of 1500-2000 IU of vitamin D in order to achieve adequate levels (>30 ng/dL). [16]

Conclusion

Even though further studies are required, there is scientific evidence supporting the beneficial effects of vitamin D supplementation of women with PCOS and VDD. The aim of this treatment would be to improve both metabolic health and reproductive outcomes in these women.

Table 1: Correlation between vitamin D and PCOS and vitamin D and AMH according to recent studies.

	VITAMIN D - PCOS	VD - AMH	Type of study
Pearce et al (2011)	No	No	Retrospective
Dennis et al (2012)	Not conclusive data	Yes, positive correlation	Prospective
Irani et al (2014)	No	No	Prospective
Lata et al (2017)	No	No	Prospective
Muscoguirri et al (2017)	Not conclusive data	Yes, positive	Systematic review
Drakopoulos et al. (2017)	Not conclusive data	No	Prospective
Irani et al. (2017)	Not conclusive data	Si	Prospective

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Financial or other Competing Interests: None.