Vitamin D deficiency in gynaecological diseases

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VITAMIN D
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The role of vitamin D (VitD) as a significant element in the pathophysiology of gynaecological diseases has been growing in recent years, with laboratory data intersecting with clinical data in indicating the role, or possible roles, that this vitamin may play in the field of gynaecology.

The production and metabolism of VitD originates from the stimulus exerted by ultraviolet rays on the skin, with the transformation of 7-dehydrocholesterol into cholecalciferol, which, in turn, is metabolised in the liver by a 25-hydroxylase. 25(OH)D is converted at the level of the kidneys by 1-alpha-hydroxylase into $1,25(OH)_2D$ or calcitriol, the active metabolite. Again in the kidney, $1,24,25(OH)_3D$, which is a biologically inactive compound, is formed by 24-hydroxylase (Fig. 1).

VitD, which should more properly be referred to as D-hormone, through its specific receptor (Vitamin D Receptor, VDR), is able to modulate the activity of approximately 3,000 genes located in different areas of the human body, including the tissues of the female reproductive tract (ovary, uterus, vagina). Genetic polymorphisms of VDR have been associated with different levels of luteinising hormone (LH), Sex Hormone Binding Globulin (SHBG), testosterone and insulin [1].

In particular, as far as the reproductive tract is concerned, VitD may exert control over ovarian follicle development and the luteal phase through an interaction with anti-Müllerian hormone (AMH) signalling and follicle-stimulating hormone (FSH) [2] sensitivity pathways.

Furthermore, and interestingly, the addition of VitD to human granulosa cells in a culture medium has also been shown to increase the production of certain hormones, which are critical for ovarian activity, compared to the non-addition of VitD, such as progesterone (to the extent of 13%; $p < 0.001$), oestradiol (to the extent of 9%; $p < 0.02$), estrone (to the extent of 21%; $p < 0.002$), again due to the presence of VDR in these cells, where it mediates such VitD-stimulating activity on ovarian activity [3].

In a 2018 study [4], which assessed the relationship between VitD status and the menstrual cycle in women who did not have a diagnosis of Polycystic Ovary Syndrome (PCOS), where there were 60 women with low VitD levels (< 30 ng/mL) and 17 with normal VitD levels (> 30 ng/mL ≤ 80 ng/mL), it was shown that in the group with low VitD levels there were 40% of subjects with irregular cycles, 27% with oligomenorrhea and 13% with amenorrhoea. Instead, in the group with normal VitD levels, only 12% of the women had menstrual cycle disorders, 6% had oligomenorrhea and 6% had amenorrhoea. Furthermore, belonging to the group with low VitD increased the likelihood of having an irregular menstrual cycle by a factor of 5 compared with those women in the group with normal VitD levels [OR = 5; (CI 95%: 1.047-23.87), p = 0.04]. Thus, even in women without hormonal disorders, VitD can contribute to the

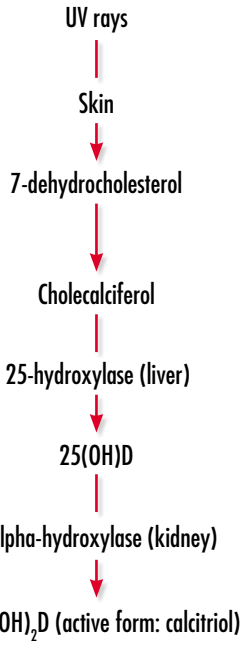

FIGURE 1.
Vitamin D: synthesis and metabolism

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Conflict of interest
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regularity of the menstrual cycle rhythm by modulating ovarian activity. Furthermore, it is worth mentioning how VDR is present at the level of the endometrium [5] and how, also at the endometrial level, enzymatic activities are present, such as 1-alpha-hydroxylase, which are fundamental for VitD metabolism and the production of its active metabolite, $1,25(OH)_2D$ or calcitriol [6].

VITAMIN D AND POLYCYSTIC OVARY SYNDROME

PCOS is the most frequent hormonal disorder among females. It occurs in approximately the following percentages in association with different conditions: 20% of fertile healthy women, 75% of women with ovulatory infertility, 80% of women with oligomenorrhea, 80% of women with hypertrichosis and regular menstrual cycle, 30% of women with secondary amenorrhoea, 80% of women with severe acne [7].

Wanting to consider the implications of VitD in certain pathophysiological conditions of gynaecology, one cannot but consider PCOS, which is the most frequent hormonal disorder in women and whose diagnosis is based on the finding of two of the following three parameters: oligo-anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic morphology of the ovary on ultrasound examination. In addition to this, the role of hyperinsulinemia as a factor that dysregulates ovarian activity and the production and action of androgenic hormones [8] must be mentioned from a pathophysiological point of view. Clinically, aside from menstrual cycle disorders, the dermatological manifestations associated with PCOS are frequently the reason for affected patients seeking medical advice. Specifically, PCOS can be associated with seborrhoea (oily skin), acne, hirsutism, and androgenetic alopecia. Besides this, hyperinsulinemia, which is frequently associated with PCOS, can cause a characteristic skin manifestation such as acanthosis nigricans, which is a condition that causes areas of dark, thick velvety skin to form in body folds and creases.

VitD deficiency can affect fertility among women with PCOS. As pointed out above, VDRs are present at various levels, such as in granulosa cells of ovarian follicles, in the pituitary gland and in the endometrium. The AMH promoter gene also contains VitD response elements [9].

As far as the association between VitD and PCOS is concerned, it is important to recall how lower VitD levels are often found in patients with PCOS and that an association between low VitD levels and insulin resistance (resulting in hyperinsulinemia) has been described in PCOS. Finally, low VitD levels are frequently found in obese PCOS patients [10,11].

Indeed, several studies have shown low levels of VitD in the PCOS population, with average 25(OH)D levels ranging from 11 to 31 ng/mL, although the majority of patients have levels <20 ng/mL (67-85%) [10].

A particularly interesting aspect is the relationship between VitD and glucose homoeostasis, which appears to be based on the presence of VDR in the beta cells of the pancreas and skeletal muscle, cells where the 1-alpha-hydroxylase enzyme is found, which catalyses the conversion of 25(OH)D to $1,25(OH)_2D$. Furthermore, there are response elements for VitD in the human insulin gene promoter [12]. First of all, it should be recalled that elevated calcium levels at the intracellular level may alter the post-receptor effects of insulin binding to its receptor, such as glycogen synthase dephosphorylation and Glucose Transporter-4 (GLUT-4) activation. Therefore, VitD deficiency could lead to a secondary increase in parathormone levels (secondary hyperparathyroidism), with increased intracellular calcium levels, thus reducing the response of target cells to insulin action (glucose transport). The prevalence of VitD deficiency in PCOS patients is approximately 67-85%, with serum levels of 25(OH)D < 20 ng/mL [13]. As such, the endocrine-metabolic consequences of VitD deficiency may be important in the pathogenesis of PCOS, as well as in its clinical expressivity (Fig. 2). With regard to the relationship between VitD levels and metabolic profiles in PCOS, reduced VitD levels are associated with insulin resistance, regardless of body mass index (BMI) or waist-to-hip ratio (WHR) in women with PCOS. Interestingly, there is an increase in insulin levels in women without PCOS but who are VitD deficient, whilst HDL cholesterol (high density lipoprotein) correlates positively with VitD levels regardless of BMI or WHR [14].

A cross-sectional study explored the association between VitD status and the diagnosis of ovulatory disorder/PCOS in a population of 67 infertile women in good general health. As a result, reduced VitD values (normalised for other confounding factors) were found in women with ovulation disorder and PCOS when compared to women with infertility from other causes. However, each unit increase in VitD levels (normalised for BMI) reduced the probability of being diagnosed with PCOS by 96% ($p = 0.015$), whilst none of the patients with both ovulation disorder and PCOS had normal VitD levels, with 39% of women with ovulation disorder and 38% of women with PCOS had serum levels <15 ng/mL indicating a vitamin Deficiency [15].

From the standpoint of metabolic impact, VitD status correlates with insulin resistance markers in PCOS (correlation between VitD deficiency and HOMA-IR with $p = 0.0001$ and with fasting blood glucose $p = 0.047$) [16].

A Chinese cross-sectional study[17], conducted on 169 women with PCOS and 114 controls, found lower VitD levels in PCOS patients compared to the controls (11.6 ± 7.2 *vs* 18.9 ± 8.4 ng/mL; $p < 0.05$) and lower VitD levels in PCOS patients with obesity or insulin resistance compared to women without obesity or insulin resistance (8.9 ± 3.7 *vs* 13.6 ± 5.3 ng/mL, $p < 0.05$; 7.2 ± 2.9 *vs* 15.8 ± 4.9 ng/mL, $p < 0.01$). Other metabolic and inflammatory parameters also correlated significantly with baseline VitD levels (Tab. I).

The first study, which evaluated the effect of VitD supplementation in the management of PCOS, was carried out by Thys-Jacobs et al. in 1999. In this study, 13 women with PCOS were treated with 50,000 IU ergocalciferol weekly or every 2 weeks to achieve a serum VitD level of 75-100 nmol/L. An improvement in menstrual regularity was reported within two months [18].

In a 2012 study [19], 12 women with PCOS, who were both overweight and VitD-deficient, received VitD supplements for 3 months (daily dose of 3,533 units, increased to 8,533 units after the first 5 participants) along with 530 mg calcium. After 3 months there was a reduction in total testosterone ($p = 0.036$) and androstenedione levels (although this reduction was not significant). A randomised, placebo-controlled trial [20] conducted on 70 women with PCOS and VitD deficiency (< 20 ng/mL) (aged between 18 and 40 years), studied two groups of patients. One group was treated with 50,000 units of VitD every 2 weeks for 3 months and the other with placebo. The results showed a statistically significant difference in fasting blood glucose levels (-3.1 ± 7.3 *vs* + 0.5 ± 6.3 mg/dL,

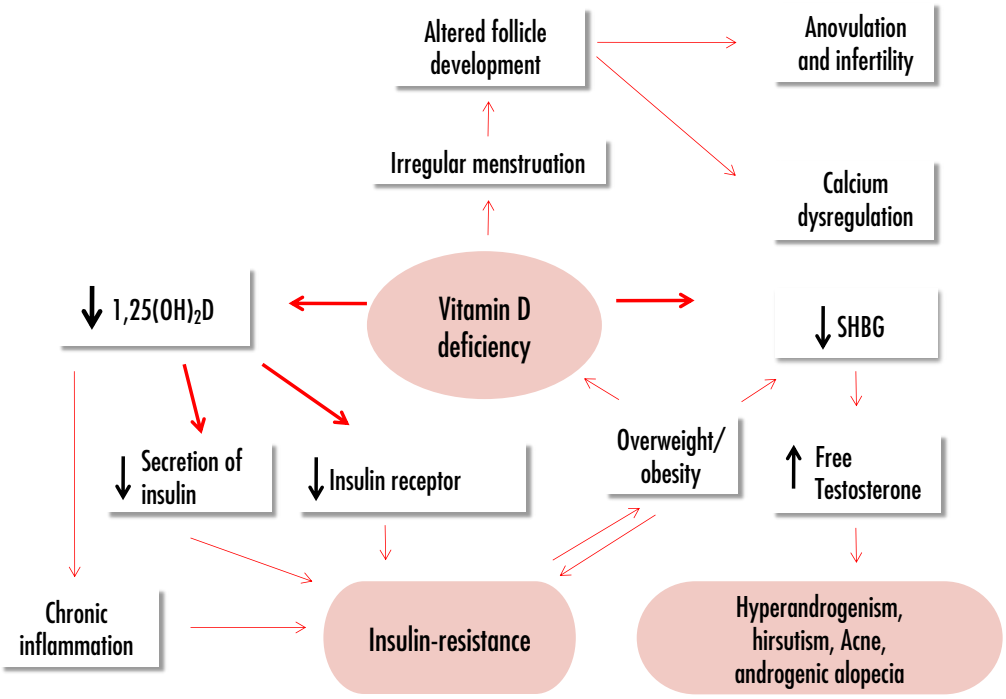

FIGURE 2.
Possible role of vitamin D in the pathogenesis of PCOS (from Thomson et al., 2012, mod.) [13].

p = 0.02), in baseline insulin levels (-1.4 ± 3.6 *vs* +2.6 ± 7.0 µIU/mL, p = 0.004) and in HOMA-IR levels (-0.3 ± 0.8 *vs* + 0.6 ± 1.6, p = 0.003).
Furthermore, hs-CRP levels were also found to be significantly lower (-0.7 ± 1.4 *vs* + 0.5 ± 2.1 µg/mL; p = 0.009), as were malondialdehyde levels (-0.1 ± 0.5 *vs* + 0.9 ± 2.1 µmol/L, p = 0.01).
A 2020 meta-analysis, published by Miao et al.[21], looked at 11 studies (= 483 subjects): of the 11 studies considered, 7 reported PCOS diagnosis and VitD deficiency as inclusion criteria. This meta-analysis showed VitD supplementation to be associated with a reduction in total testosterone (mean difference: -0.10; CI 95%: -0.18, -0.02; p = 0.02), reduction in HOMA-IR (mean difference: -0.44, CI 95%: -0.86, -0.03, p = 0.04), reduction in total cholesterol levels (mean difference:-11.90, CI 95%: -15.67, 8.13, p < 0.01), reduction in LDL-cholesterol levels (mean difference: -4.54, CI 95%: -7.29, -1.80, p = 0.001).
In another meta-analysis published in 2021, conducted considering 18 randomised, placebo-controlled trials (= 1,060 subjects, all with mean VitD values at baseline < 30 ng/mL), Zhao et al. [22] showed that VitD supplementation had a positive impact on the hormonal, oxidative and inflammatory profile in PCOS. Indeed, there was a reduction in total testosterone levels (CI 95%: -0.40, -0.07; p = 0.006), reduced levels of high-sensitivity C-reactive protein (hs CRP) (CI 95%: -0.73, -0.38; p < 0.00001), reduction in malondialdehyde levels (CI 95%: -0.90, -0.54; p < 0.0001), increased levels of total antioxidant capacity (CI 95%: 0.01, 0.83; p = 0.04). Again, in this meta-analysis, it was shown that the most appropriate supplementation scheme to achieve these results is daily supplementation with doses ≤ 1,000 U/day, which appeared to be better than weekly administration, with a suitable duration appearing to be at least 12 weeks.
A recent systematic review with methanolysis 23, was conducted considering 9 RCTs (randomised controlled trials) (n = 1677)

TABLE I
Vitamin D status and metabolic factors in PCOS (Wang et al., 2020, mod.).[17]

	25(OH)D < 20 ng/mL (deficiency)	25(OH)D ≥20 ≤30 ng/mL (deficiency)	25(OH)D >30 ng/mL (normal level)	p*
BMI	27.3 ± 9.2	25.4 ± 8.1	23.5 ± 9.3	0.029
WHR	1.0 ± 0.4	0.9 ± 0.5	0.8 ± 0.3	0.036
Insulin (mIU/L)	39.6 ± 10.7	33.5 ± 9.9	26.8 ± 8.5	0.012
HOMA-IR	8.9 ± 3.7	7.3 ± 2.8	5.7 ± 2.1	0.009
Total Cholesterol(mmol/L)	6.1 ± 1.7	5.5 ± 1.6	4.2 ± 1.4	0.03
hs-CRP (mg/L)	2.4 ± 0.9	1.9 ± 0.6	1.4 ± 0.3	0.017
HDL(mmol/L)	1.3 ± 0.6	1.4 ± 0.7	1.8 ± 0.6	0.03

* Analysis of variance. BMI: Body mass index; WHR: Waist/Hip Ratio; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; hs-CRP: high sensitivity C-reactive protein; HDL: high density lipoprotein.

and 3 cohort studies (n = 675), on infertile patients with VitD deficiency, that evaluated the influence of VitD supplementation on reproductive outcome, starting from the fact that a low VitD level is associated with an increased risk of infertility. So, VitD treatment significantly increased the clinical pregnancy rate compared to the control group (OR: 1.70, CI 95%: 1.24-2.34; p = 0.001). The improvement in the pregnancy rate was influenced by the patients' VitD level, the type of preparation administered, the total dosage administered, the duration of treatment, the frequency of administration, and the daily administration of VitD supplementation. Infertile women (with VitD levels <30 ng/mL) treated with multicomponent preparations with VitD or with 1,000-10,000 units of VitD per day for 30-60 days could have had a better pregnancy outcome.

CONCLUSIONS

VitD plays a physiological role in female reproductive function. Specifically, it is important to maintain an adequate vitamin D status, both under normal physiological conditions and in women with gynaecological conditions (e.g., PCOS). Assessment of vitamin D status in women's health and, if necessary, supplementation can be very important for clinical practice.

References

1. Lerchbaum E,Obermayer-Pietsch B. Vitamin D and fertility: a systematic review. J Endocrinol 2012;166:765-778. https://doi.org/10.1530/EJE-11-0984
2. Irani M, Merhi Z. Role of vitamin D in ovarian physiology and its implication in reproduction: a systematic review. Fertil Steril 2014;102:460-468.e3. https://doi.org/10.1016/j.fertnstert.2014.04.046
3. Parikh G, Varadinova M, Suwandhi P, et al. Vitamin D regulates steroidogenesis and insulin-like growth factor binding protein-1 (IGFBP-1) production in human ovarian cells. Horm Metab Res 2010;42:754-757. https://doi.org/10.1055/s-0030-1262837
4. Lagowska K. The Relationship between Vitamin D status and the menstrual cycle in young women: a preliminary study. Nutrients 2018;10:1729. https://doi.org/10.3390/nu10111729
5. Vienonen A, Miettinen S, Bläuer, et al. Expression of nuclear receptors and cofactors in human endometrium and myometrium. J Soc Gynecol Investig 2004;11:104-112. https://doi.org/10.1016/j.jsgi.2003.09.003
6. Becker S, Cordes T, Diesing, D, et al. Expression of 25 hydroxyvitamin D3 -1α-hydroxylase in human endometrial tissue. J Steroid Biochem Mol Biol 2007;103:771-775. https://doi.org/10.1016/j.jsbmb.2006.12.075
7. Homburg R. Polycystic Ovary Syndrome. Best Pract Res Clin Obstet Gynaecol 2008;22:261-274. https://doi.org/10.1016/j.bpobgyn.2007.07.009
8. Rotterdam ESHRE/ASRM-sponsored PCOS Consensus Workshop 2003.
9. Colonese F, Laganà AS, Colonese E, et al. The pleiotropic effects of vitamin D in gynaecological and obstetric diseases: an overview on a hot topic. Biomed Res Int 2015:986281. https://doi.org/10.1155/2015/986281
10. Wehr E, Pilz S, Schweighofer N, et al. Association of hypovitaminosis D with metabolic disturbances in polycystic ovary syndrome. European J Endocrinol 2009;161:575-582. https://doi.org/10.1530/EJE-09-0432
11. Krul Poel YHM, Snackey C, Louwers Y, et al. The role of vitamin D in metabolic disturbances in polycystic ovary syndrome: a systematic review. Eur J Endocrinol 2013;169:853-865. https://doi.org/10.1530/EJE-13-0617
12. Alvarez JA, Ashraf A. Role of vitamin D in insulin secretion and insulin sensitivity for glucose homeostasis. Int J Endocrinol 2010:351385. https://doi.org/10.1155/2010/351385
13. Thomson RL, Spedding S, Buckley JD. Vitamin D in the aetiology and management of polycystic ovary syndrome. Clin Endocrinol (Oxf) 2012;77:343-350. https://doi.org/10.1111/j.1365-2265.2012.04434.x
14. Li HWR, Brereton RE, Anderson RA, et al. Vitamin D deficiency is common and associated with metabolic risk factors in patients with polycystic ovary syndrome. Metab Clin EXP 2011;60:1475-1481. https://doi.org/10.1016/j.metabol.2011.03.002
15. Pal L, Shu J, Zeitlan G, et al. Vitamin D insufficiency in reproductive years may be contributory to ovulatory infertility and PCOS. Fertil Steril 2008;90(S14). https://doi.org/10.1016/j.fertnstert.2008.07.382
16. Patra SK, Nasrat H, Goswami B, et al. Vitamin D as a predictor of insulin resistance in Polycystic Ovarian Syndrome. Diabetes Metab Syndr 2012;6:146-9. https://doi.org/10.1016/j.dsx.2012.09.006
17. Wang L, Lv S, Yu X, et al. Vitamin D deficiency is associated with metabolic risk factors in women with Polycystic Ovary Syndrome: a cross-sectional study in Shaanxi China. Front Endocrinol (Lausanne) 2020;11:171. https://doi.org/10.3389/fendo.2020.00171
18. Thys-Jacobs S, Donovan D, Papadopoulos A, et al. Vitamin D and calcium dysregulation in the polycystic ovarian syndrome. Steroids 1999:64:430-435. https://doi.org/10.1016/s0039-128x(99)00012-4
19. Pal L, Berry A, Coraluzzi L, et al. Therapeutic implications of vitamin D and calcium in overweight women with Polycystic Ovary Syndrome. Gynecol Endocrinol 2012;28:965-968. https://doi.org/10.3109/09513590.2012.696753
20. Maktabi M, Chamani M, Asemi Z. The effects of vitamin D supplementation on metabolic status of patients with Polycystic Ovary Syndrome: a randomized, double-blind, placebo-controlled trial. Horm Metab Res 2017;49:493-498. https://doi.org/10.1055/s-0043-107242
21. Miao C-Y, Fang X-J, Chen Y, et al. Effect of vitamin D supplementation on polycystic ovary syndrome: a metaanalysis. Exp Ther Med 2020;19:2641-2649. https://doi.org/10.3892/etm.2020.8525
22. Zhao J-F, Li B-X, Zhang Q. Vitamin D improves levels of hormonal, oxidative stress and inflammatory parameters in polycystic ovary syndrome: a meta-analysis study. Ann Palliat Med 2021;10:169-183. https://doi.org/10.21037/apm-20-2201
23. Meng X, Zhang J, Wan Q, et al. Infuence of Vitamin D supplementation on reproductive outcomes of infertile patients: a systematic review and meta-analysis. Reprod Biol Endocrinol 2023;21:17. https://doi.org/10.1186/s12958-023-01068-8