Review

The role of vitamin D in metabolic and reproductive disturbances of polycystic ovary syndrome: A narrative mini-review

Daniela Menichini[1,2], Gianpiero Forte[3], Beatrice Orrù[3], Giuseppe Gullo[4], Vittorio Unfer[5], and Fabio Facchinetti[2]

[1] International Doctorate School in Clinical and Experimental Medicine, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Italy
[2] Unit of Obstetrics and Gynecology, Mother-Infant Department, University of Modena and Reggio Emilia, Italy
[3] Medical Affairs Department, Lo.Li. Pharma, Rome, Italy
[4] IVF Public Center, AOOR Villa Sofia Cervello, University Hospital, Palermo,Italy
[5] Department of Experimental Medicine, Sapienza University, Rome, Italy

Abstract: Vitamin D is a secosteroid hormone that plays a pivotal role in several metabolic and reproductive pathways in humans. Increasing evidence supports the role of vitamin D deficiency in metabolic disturbances and infertility in women with polycystic ovary syndrome (PCOS). Indeed, supplementation with vitamin D seems to have a beneficial role on insulin resistance (IR) and endometrial receptivity. On the other hand, exceedingly high levels of vitamin D appear to play a detrimental role on oocytes development and embryo quality. In the current review, we summarize the available evidence about the topic, aiming to suggest the best supplementation strategy in women with PCOS or, more generally, in those with metabolic disturbances and infertility. Based on the retrieved data, vitamin D seems to have a beneficial role on IR, insulin sensitivity and endometrial receptivity, but high levels and incorrect timing of administration seem to have a detrimental role on oocytes development and embryo quality. Therefore, we encourage a low dose supplementation (400–800 IU/day) particularly in vitamin D deficient women that present metabolic disturbances like PCOS. As far as the reproductive health, we advise vitamin D supplementation in selected populations, only during specific moments of the ovarian cycle, to support the luteal phase. However, ambiguities about dosage and timing of the supplementation still emerge from the clinical studies published to date and further studies are required.

Keywords: Vitamin D, PCOS, Fertility, Metabolism

Abbreviations

$1,25(OH)_2D_3$	1,25-dihydroxyvitamin D3
25OH-D 25	Hydroxy vitamin D
AMH	Antimüllerian hormone
AMHR-II	Anti-Müllerian hormone type II receptor
ART	Assisted reproductive technology
EFSA	European Food Safety Authority
FF	Follicular fluid
FSH	Follicle-stimulating hormone
hCG	Human chorionic gonadotropin
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
HOXA10	Homeobox protein Hox-A10
ICSI	Intracytoplasmic sperm injection
IR	Insulin Resistance
IVF	In vitro fertilization
mF-G score	Modified Ferriman Gallwey score
OGTT	Oral glucose tolerance test
PCOS	Polycystic ovary syndrome
SHBG	Sex hormone-binding globulin
VDD	Vitamin D deficiency
VDR	Vitamin D receptor

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorder, affecting approximately 4%–18%

of women in the reproductive age [1]. PCOS is an androgen excess disorder with different degrees of reproductive and metabolic dysfunctions including infertility, insulin resistance (IR), hyperinsulinemia and dyslipidemia [2].

Accumulating evidence suggests that vitamin D deficiency (VDD) might be a causal factor in the pathogenesis of IR and the metabolic dysfunctions in PCOS [3]. Indeed, 67%–85% of women with PCOS are vitamin D deficient [4]. Additionally, positive associations are reported between VDD and some well-known comorbidities of PCOS including type 2 diabetes, metabolic syndrome, and cardiovascular diseases [5–7].

This is supported by the fact that vitamin D modulates glucose-insulin homeostasis through the action on its own specific receptor (VDR), located also on the pancreatic beta cells and in the skeletal muscles. It directly activates the transcription of the human insulin receptor gene, activates peroxisome proliferator activator receptor-δ, stimulates the expression of insulin receptor, and enhances insulin-mediated glucose transport in vitro [8]. In addition, VDR polymorphisms seem to account for some PCOS features. Specifically, VDR variants Cdx2 and DHCR7 are associated with IR and insulin sensitivity, while Apa-I variants with altered levels of testosterone in PCOS women [9].

Plasmatic low levels of vitamin D (< 20 ng/mL) appear correlated with hirsutism, hyperandrogenism and obesity. Moreover, vitamin D plays a physiological role in reproduction by modulating follicular development through the influence on the signal of the antimüllerian hormone (AMH), on FSH sensitivity and on the production of progesterone in the ovarian granulosa cells [10] (Figure 1).

To worth noting that in the last years there have been few interventional studies about vitamin D supplementation on PCOS in which some characteristics of this syndrome substantially improved but some others have not changed. Therefore, with this review we aim to summarize the existing evidence and evaluate the effects of vitamin D supplementation on the metabolism and fertility in women with PCOS.

Methods

We conducted a literature review on the relationship between vitamin D deficiency and metabolic and reproductive disturbances, aiming to suggest the best supplementation strategy in women with PCOS or, more generally, in those with metabolic disturbances and infertility.

The review involved keyword searches in electronic databases, including PubMed, MEDLINE, ScienceDirect, the Cochrane Library, to find the available evidence published in English from inception up to August 2019.

Review search terms included "Vitamin D", "Vitamin D Deficiency", "Infertility", "Polycystic Ovary Syndrome", "Metabolism", and "Supplementation". The review included RCTs, descriptive and epidemiologic studies, systematic reviews and metanalysis, describing the processes activated in vitamin D deficiency conditions, and the supplementation/therapeutic strategies to improve metabolic and reproductive outcomes. The review was conducted in two phases: initially, abstracts were retrieved and assessed against the review criteria followed by the retrieval and assessment of full papers against review criteria. A summary of the studies included in the review and their characteristics are reported in Table 1.

Vitamin D supplementation in PCOS women

Recent studies evaluated the correlation between VDD and PCOS, with vitamin D supplementation showing promising results.

In a post-hoc analysis, Pal et al. [11] examined the relation between vitamin D status and pregnancy outcomes. They used data from a randomized prospective study performed by the Reproductive Medicine Network on 626 women and designed to look at clomiphene vs. letrozole in the treatment of PCOS patients undergoing ovulation induction. The authors found that ovulation correlated with vitamin D levels. More specifically they reported that the likelihood for live birth was reduced by 44% in women with low levels (< 30 ng/mL) of 25 hydroxyvitamin-D (25OH-D), whereas there was an improvement in the odds for live birth at the following thresholds: > 38 ng/mL, > 40 ng/mL and > 45 ng/mL. Serum 25 OH-D was significantly higher in women achieving a live birth compared to those who did not. In addition, each ng/mL increase in 25OH-D levels raised the likelihood of a livebirth by 2% [11]. These findings underline a correlation between vitamin D levels and fertility, and suggest possible beneficial effects of vitamin D supplementation in PCOS women with low serum levels of 25OH-D.

The recent meta-analysis by Łagowska et al. [12] evaluated the effect of vitamin D supplementation on insulin resistance in PCOS patients. The authors analyzed 11 studies involving 601 women diagnosed with PCOS. The results indicate that vitamin D significantly decreases both fasting glucose concentrations and the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) value. The latter significantly improved also with doses of vitamin D lower than 4000 IU/d. The authors concluded that the supplementation in PCOS patients with such low doses of vitamin D (from 200 IU/d to 4000 IU/d) may

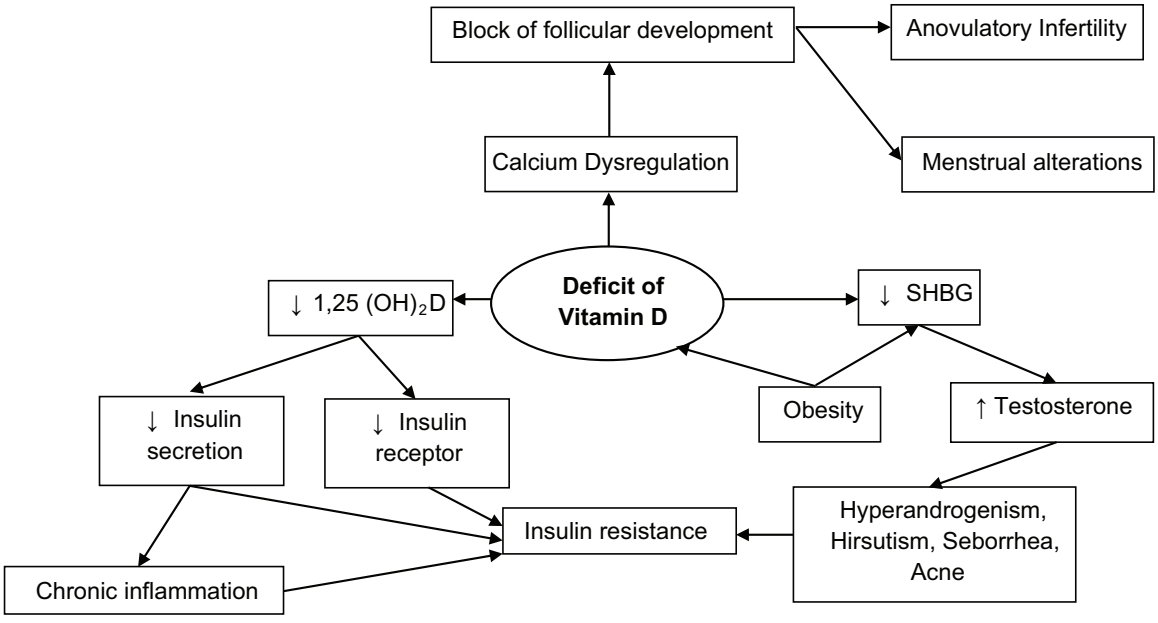

Figure 1. The role of Vitamin D deficiency on the pathogenesis of PCOS. SHBG: Sex hormone binding globulin is a protein that transports the hormones in the blood as biologically inactive forms.

improve insulin sensitivity in terms of the fasting glucose concentration (in combination with other micronutrients) and HOMA-IR (in continuous low daily doses or as co-supplement) [12].

Fertility and reproductive parameters were evaluated in another randomized double-blind, placebo-controlled trial [13]. Ninety insulin-resistant women with PCOS were assigned to three groups to take either 4000 IU of vitamin D, 1000 IU of vitamin D or placebo daily for 12 weeks. Compared with placebo, significant increases in sex hormone-binding globulin (SHBG) and in modified Ferriman Gallwey scores (mF-G scores) occur already at the lower dose of vitamin D (1000 IU).

In a double-blind, randomized placebo-controlled trial, Trummer et al. [14] enrolled 180 PCOS women and vitamin D levels < 30 ng/mL. The subjects were randomized to receive either vitamin D (20000 IU/week) or placebo for 24 weeks [14]. Supplementation with vitamin D led to a decrease in plasma glucose one-hour after the oral glucose tolerance test (OGTT), compared to the placebo.

All these studies highlighted the beneficial effects of vitamin D supplementation on different pathologic features of PCOS. However, the results should be interpreted in light of the following considerations: *a)* most of the studies presented are single center; *b)* the meta-analysis by Łagowska et al. [12] focused on studies mainly conducted in Iran. The population and ethnicity remain mostly the same, reducing the generalizability of these findings; *c)* some authors reported that the concomitant use of metformin with vitamin D or placebo may have affected results.

Diminished ovarian reserve later in life in PCOS women

PCOS is a time-evolving condition. Various authors recently reported that clinical expression and severity of PCOS decline with advancing age. Young PCOS patients suffer from the development of too many follicles at once. Over time, they face a transition from excessive to abnormally low follicle recruitment and are likely to suffer from diminished ovarian reserve, a condition in which ovaries no longer produce a good number of high-quality eggs.

A longitudinal study [15], which focused on the ovarian reserve parameters, was conducted on women with documented PCOS, as per Rotterdam criteria [16]. According to Ahmad et al. [15], AMH and antral follicle count declined more abruptly in the PCOS population, as compared to controls with normal menstrual cycle.

The role of vitamin D in ovarian reserve

In 1978, it was demonstrated that both the decidua and the placenta produce active vitamin D metabolites [17]. In addition, the presence of 1-α-hydroxylase and VDR receptors was demonstrated in the ovary (particularly in granulosa cells) [18], the endometrium [19], the pituitary gland [20] and the placenta [21], suggesting that vitamin D

Table 1. Summary of the major studies on the effects of vitamin D on PCOS

Study	Study type	N	Intervention and doses	Main findings
Pal et al. [11]	Retrospective cohort study	626 (18–39 yrs)	Measurement of serum 25OHD levels	Vitamin D levels correlated with ovulation. The likelihood for live birth was reduced by 44% in women with low levels (< 30 ng/mL) of 25OH-D, whereas there was an improvement in the odds for live birth at the following thresholds: > 38 ng/mL, > 40 ng/mL and > 45 ng/mL
Łagowska et al. [12]	Systematic review and meta-analysis of RCTs	601 (18–40 yrs)	Vitamin D supplementation (doses from 200 IU/d to 4000 IU/d)	Supplementation in PCOS patients with low doses of vitamin D improved insulin sensitivity in terms of the fasting glucose concentration (in combination with other micronutrients, p = 0.01) and HOMA-IR (in continuous low daily doses or as co-supplement) (p = 0.02)
Jamilian et al. [13]	RCT	90 (18–40 yrs)	4000 IU of vitamin D, 1000 IU of vitamin D or placebo daily for 12 weeks	Significant increases in SHBG and in mF-G scores occurred already at the lower dose of vitamin D (1000 IU) (Vit D: +4.5 ± 11.0 vs Placebo: +0.7 ± 10.4 nmol/L, p < 0.001)
Trummer et al. [14]	RCT	180 (≥ 18 yrs)	vitamin D (20000 IU/ week) or placebo for 24 weeks	Vitamin D decreased plasma glucose one-hour after the oral glucose tolerance test, compared to the placebo (mean treatment effect − 10.2 mg/dL; 95% CI 20.2 to −0.3; p = 0.045)
Ahmad et al. [15]	Prospective longitudinal study	85 (18–50 yrs)	Ovarian reserve controls	AMH and antral follicle count declined more abruptly in the PCOS population, as compared to controls with normal menstrual cycle (p < 0.01)
Irani et al. [10]	Systematic Review	93 (18–38 yrs)	50,000 IU/w Vit D	Vitamin D correlates with AMH signaling and FSH sensitivity in human granulosa cells. It influences the production and release of progesterone
Merhi et al. [25]	Prospective cohort study	33 Infertile (≥ 18 yrs)	Supplementation with 50 or 100 nM of vit D3	Vitamin D supplementation increased progesterone production in the presence of the precursor substrate pregnenolone (p < 0.05)
Ciepiela et al. [28]	Prospective cohort study	198 Infertile (18–38 yrs)	Measurement of 25OHD levels in the follicular fluid	Vitamin D levels in the FF of successfully fertilized oocytes (following ICSI) were significantly lower compared with those of unfertilized ones (28.4 vs. 34.0 ng/ml, p = 0.001). Top quality embryos developed from oocytes collected from follicles containing significantly lower vitamin D levels

orchestrates several regulatory pathways in human reproduction [22]. VDD has been related with primary ovarian insufficiency [23] and with impaired embryo implantation in humans. On the other hand, the role of vitamin D in ovarian reserve is much less clear, and existing literature provides controversial reports on vitamin D and AMH [24].

A systematic review by Irani et al. [10] investigated the role of vitamin D in ovarian physiology with a focus on the genes involved in steroidogenesis, follicular development, and ovarian reserve. In particular, the review took into account the ovulatory dysfunction associated with PCOS, and the ovarian response to assisted reproductive technology (ART). The authors reported that vitamin D affects both AMH signaling and FSH sensitivity in human granulosa cells. It influences also the production and release of progesterone, suggesting its involvement in ovarian follicular development and luteinization. The authors found a positive correlation between serum vitamin D and AMH, which is a clinical marker of ovarian reserve, and concluded that the supplementation with vitamin D helps preventing the seasonal changes in serum AMH. Although one of the best markers of ovarian reserve, AMH expression and serum levels are altered by factors as vitamin D deficiency and obesity [25], typical features in PCOS women. Vitamin D supplementation to PCOS patients, reduced the abnormally elevated serum AMH levels, possibly indicating a positive effect of vitamin D on folliculogenesis [10]. Hence, the possibility to include the assessment of vitamin D status

in the routine evaluation of infertility, considering that appropriate supplementation may translate into more reliable ovarian reserve markers and into better ovarian follicular dynamics.

Merhi et al. [25] evaluated the role of 1,25-dihydroxyvitamin D3 [$1,25(OH)_2D_3$] in ovarian follicular development and steroidogenesis, using a human granulosa cell (GC) model. Upon treatment with $1,25(OH)_2D_3$, they reported increased progesterone production in the presence of the precursor substrate pregnenolone. Similarly, Parikh et al. [18] proved that vitamin D increased the production of progesterone, estrogen, estrone, and insulin-like growth factor–binding protein 1 in human ovarian cells. Interestingly, $1,25(OH)_2D_3$ inhibits the Anti-Müllerian hormone type II receptor (AMHR-II) expression and signaling, thus potentially counteracting the repressive effect of AMH on granulosa cell differentiation. The lesser AMH sensitivity allows follicles to reach terminal maturation and ovulation [26]. Moreover, $1,25(OH)_2D_3$ stimulated estrogen and progesterone production in human placenta [27].

Understanding the mechanistic actions of vitamin D in ovarian physiology is fundamental to strategically target the right population, timing and dosage of supplementation. In particular, there is still a lack of good data pertaining to the impact of vitamin D supplementation on pregnancy rates following *in vitro* fertilization (IVF). Since most of the studies in this regard are observational, a randomized trial is required to elucidate the impact of supplementation on controlled ovarian hyperstimulation/IVF outcome and ovulatory dysfunction associated with PCOS.

Vitamin D, follicular fluid and embryo quality

A recent prospective cohort study conducted in Poland by Ciepiela et al., [28] investigated the relationship between vitamin D level in follicles and oocyte developmental competence. The study included one hundred ninety-eight infertile women scheduled for intracytoplasmic sperm injection (ICSI) and a single embryo transfer. Serum samples and follicular fluid (FF) were collected from single follicles on the day of oocyte retrieval. The authors reported that vitamin D levels in the FF of successfully fertilized oocytes (following ICSI) were significantly lower compared with those of unfertilized ones. They also found that top quality embryos (on day 3 after fertilization) developed from oocytes collected from follicles containing significantly lower vitamin D levels. Moreover, embryos from oocytes that developed in FF with lower vitamin D concentrations showed better results in terms of: positive human chorionic gonadotropin (hCG), clinical pregnancy, and live birth rates. Serum levels of vitamin D < 20 ng/mL resulted in a higher fertilization rate and clinical pregnancy rate. Interestingly they also reported a higher miscarriage rate compared with those with levels $\geq$ 20 ng/ml.

Thus, vitamin D levels in FF seem to negatively correlate with the fertilization ability of oocytes and the following embryo development, before implantation. Oocytes matured in low FF vitamin D concentrations also correlate with better embryo quality and with higher pregnancy and delivery rates. Low vitamin D concentrations in the serum, on the other hand, positively correlate with miscarriage rates [28].

In order to explain these findings we have to consider that vitamin D has been shown to regulate hCG expression and secretion in cultured syncytiotrophoblast, and to stimulate estradiol and progesterone secretion from trophoblasts in a dose-dependent manner [29]. Moreover, vitamin D can induce the transcription of Homeobox protein Hox-A10 (HOXA10) [30] in the endometrium, decidua and placenta. Indeed, HOXA10 plays a pivotal role in orchestrating embryo implantation [31] and the development of female tract organogenesis [32].

The effect of vitamin D on progesterone has been investigated in an animal study conducted on porcine granulosa cells [33]. The results showed that $1,25(OH)_2D_3$ significantly alters the transcription and the translation of the genes encoding for progesterone biosynthesis. They further indicate that progesterone concentrations decrease in response to $1,25(OH)_2D_3$. Progesterone modulates the immune response at the maternal-fetal interface, preventing spontaneous miscarriage and preterm labor. In this perspective, it is possible to hypothesize that excess vitamin D causes a reduction of progesterone concentration, playing a detrimental role during early pregnancy [34].

The proposed biological role of vitamin D in the implantation process led research groups to investigate the effect of vitamin D status in patients undergoing ART. Some studies report that replete vitamin D levels correlate with increased clinical pregnancy and live birth rates [35–38]. Ozkan et al. found positive correlation between vitamin D levels in the serum and in the FF in a group of 84 patients, and a positive tendency to achieve clinical pregnancy following IVF. High vitamin D levels were also significantly associated with improved parameters of the controlled ovarian hyperstimulation [35, 38]. Interestingly, Rudick et al. observed that the status of vitamin D (both in the serum and FF) and the achievement of clinical pregnancy depend on the patient's ethnicity ($p < 0.01$). Indeed, vitamin D deficiency is associated with lower pregnancy rates in non-Hispanic whites, but not in Asians [37].

Anifandis et al. showed a negative effect of vitamin D on the quality of embryos ($r = -0.27$, $p = 0.027$). They reported a lower quality of embryos and a lower likelihood to achieve

clinical pregnancy in women with FF 25(OH)D > 30 ng/ml, in comparison with women with FF 25(OH)D in the range 20.1–30 ng/ml or with FF 25(OH)D < 20 ng/ml [39].

Summary on the role of vitamin D in PCOS

Vitamin D appears to be negatively correlated with follicular quality and fertilization rate. Indeed, top quality embryos derive from oocytes collected from follicles containing significantly lower 25(OH)D levels [28]. On the other hand, low levels of vitamin D are also associated with high rates of miscarriage.

Vitamin D exerts positive effects during the early stages of pregnancy through several mechanisms. It binds to its receptor (VDR) in the endometrium, regulating target genes such as calbindin and osteopontin, both essential for embryonic implantation and placental development. Vitamin D also interferes with the production of pro-inflammatory cytokines, as demonstrated with endometrial cells isolated from women with a history of recurrent miscarriage [40].

Thus, we speculate that vitamin D at physiologic levels has a beneficial role on endometrial receptivity, whereas an excess plays a detrimental role on oocyte development and embryo quality. Based on these conclusions, dietary supplementation of vitamin D is preferable to administration of heavier pharmacological doses. Furthermore, the European Food Safety Authority (EFSA) guidelines state that vitamin D supplementation up to 4000 IU/day is safe even for prolonged use [41], without occurrence of hypercalcemia or hypercalciuria. Accordingly, vitamin D supplementation should be tailored on selected populations and on specific moments of the ovarian cycle, in order to support specifically the luteal phase.

Genetic/ethnic aspects play a fundamental role, considering that the pregnancy rate among Asian women is not negatively influenced by vitamin D deficiency, unlike non-Hispanic whites [37]. The controversial findings reported might be also due to the clinical and geographical heterogeneity of the studies analyzed. Several individual cohort studies were, indeed, conducted in different geographical locations, with variability in population characteristics and ART protocols used [42].

The rate of VDD is very high in PCOS women, but whether it contributes to the pathogenesis of the syndrome (independently from the elevated body mass index) is still uncertain. Most PCOS women are either overweight or obese, and obesity causes a decrease in circulating 25 (OH)D, which remained confined in the adipose tissue. Arguably, vitamin D supplementation holds a promise of becoming a potential therapeutic adjunct for the ovulatory dysfunction and metabolic alterations observed in women with PCOS. The available data need to be validated with well-designed randomized controlled trials aimed to specifically evaluate the direct effect of oral vitamin D supplementation on long-term ovarian physiology and metabolic alterations in PCOS women with VDD [10].

Conclusion

Considering the described effects, a favorable clinical indication for the use of vitamin D in ART could be reasonable also in PCOS women. However, ambiguities about dosage and timing of the supplementation still emerge from the clinical studies published to date.

Future perspectives on this concern could be represented by a universal evaluation of vitamin D status, performed in order to early discover the vitamin D-deficient population and intervene with an adequate supplementation, thus reducing the possible onset of health issues related to the deficiency of this important secosteroid hormone involved in several physiologic pathways.

Vitamin D seems to have a beneficial role on IR, insulin sensitivity and endometrial receptivity, but high levels and incorrect timing of administration may have a detrimental role on oocytes development and embryo quality.

Based on the retrieved data, we encourage a daily supplementation of 400–800 IU, or 10–20 micrograms of vitamin D in deficient women presenting metabolic disturbances, like PCOS. As far as the reproductive health is concerned, we recommend supplementation specifically to support the luteal phase of the ovarian cycle. On the other hand, based on the data on embryo quality, we advise against supplementation during the follicular phase.

References

1. Sirmans S, Pate K. Epidemiology, diagnosis, and management of polycystic ovary syndrome. Clin Epidemiol. 2013;6:1–13.
2. Teede H, Deeks A, Moran L. Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. BMC Med. 2010;8:41.
3. Wehr E, Pilz S, Schweighofer N, Giuliani A, Kopera D, Pieber T, et al. Association of hypovitaminosis D with metabolic disturbances in polycystic ovary syndrome. Eur J Endocrinol. 2009;161:575–82.
4. Thomson R, Spedding S, Buckley J. Vitamin D in the aetiology and management of polycystic ovary syndrome. Clin Endocrinol. 2012;77:343–50.
5. Khan H, Kunutsor S, Franco O, Chowdhury R, Vitamin D. Type 2 diabetes and other metabolic outcomes: A systematic review and meta-analysis of prospective studies. Proc Nutr Soc. 2013;72:89–97.

6. Song Y, Wang L, Pittas A, Del Gobbo L, Zhang C, Manson J, et al. Blood 25-hydroxy vitamin D levels and incident type 2 diabetes: A meta-analysis of prospective studies. Diabetes Care. 2013;36:1422–8.
7. Krul-Poel Y, Snackey C, Louwers Y, Lips P, Lambalk C, Laven J, et al. The role of vitamin D in metabolic disturbances in polycystic ovary syndrome: A systematic review. Eur J Endocrinol. 2013;169:853–65.
8. Alvarez J, Ashraf A. Role of vitamin D in insulin secretion and insulin sensitivity for glucose homeostasis. Int J Endocrinol. 2010;2010:351–85.
9. Wehr E, Trummer O, Giuliani A, Gruber H, Pieber T, Obermayer-Pietsch B. Vitamin D-associated polymorphisms are related to insulin resistance and vitamin D deficiency in polycystic ovary syndrome. Eur J Endocrinol. 2011;164(5):741–9.
10. Irani M, Merhi Z. Role of vitamin D in ovarian physiology and its implication in reproduction: a systematic review. Fertil Steril. 2014;102(2):460–468.e3.
11. Pal L, Zhang H, Williams J, Santoro N, Diamond M, Schlaff W, et al. Reproductive Medicine Network. Vitamin D status relates to reproductive outcome in women with polycystic ovary syndrome: Secondary analysis of a multicenter randomized controlled trial. J Clin Endocrinol Metab. 2016;101:3027–35.
12. Łagowska K, Bajerska J, Jamka M. The role of vitamin D oral supplementation in insulin resistance in women with polycystic ovary syndrome: A systematic review and meta-analysis of randomized controlled trials. Nutrients. 2018;10:1637.
13. Jamilian M, Foroozanfard F, Rahmani E, Talebi M, Bahmani F, Asemi Z. Effect of two different doses of vitamin D supplementation on metabolic profiles of insulin-resistant patients with polycystic ovary syndrome. Nutrients. 2017;12(9):E1280.
14. Trummer C, Schwetz V, Kollmann M, Wölfler M, Münzker J, Pieber T, et al. Effects of vitamin D supplementation on metabolic and endocrine parameters in PCOS: a randomized-controlled trial. Eur J Nutr. 2018;58(5):2019–28.
15. Ahmad A, Kao C, Quinn M, Lenhqrt N, Rosen M, Cedars M. Differential rate in decline in ovarian reserve markers in polycysctic ovary syndrome compared to controls: Results of a longitudinal study. Fertil Steril. 2018;109:526–31.
16. The Rotterdam ESHRE/ASRM Sponsored PCOS Consensus Workshop Group.. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Human Reproduction. 2004;81(1):19–25.
17. Weisman Y, Harell A, Edelstein S, David M, Spirer Z, Golander A. 1 alpha, 25-Dihydroxyvitamin D3 and 24,25-dihydroxyvitamin D3 in vitro synthesis by human decidua and placenta. Nature. 1979;281:317–9.
18. Parikh G, Varadinova M, Suwandhi P, Araki T, Rosenwaks Z, Poretsky L, 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;42:754–7.
19. Viganò P, Lattuada D, Mangioni S, Ermellino L, Vignali M, Caporizzo E, et al. Cycling and early pregnant endometrium as a site of regulated expression of the vitamin D system. J Mol Endocrinol. 2006;36:415–24.
20. Pérez-Fernandez R, Alonso M, Segura C, Muñoz I, García-Caballero T, Diguez C. Vitamin D receptor gene expression in human pituitary gland. Life Sci. 1997;60:35–42.
21. Evans K, Nguyen L, Chan J, Innes B, Bulmer J, Kilby M, et al. Effects of 25-hydroxyvitamin D3 and 1,25-dihydroxyvitamin D3 on cytokine production by human decidual cells. Biol Reprod. 2006;75:816–22.
22. Luk J, Torrealday S, Neal Perry G, Pal L. Relevance of vitamin D in reproduction. Hum Reprod. 2012;27:3015–27.
23. Kebapcilar A, Kulaksizoglu M, Kebapcilar L, Gonen M, Unlü A, Topcu A, et al. Is there a link between premature ovarian failure and serum concentrations of vitamin D, zinc, and copper? Menopause 2013;20:94–9.
24. Hornstein M. Vitamin D and Infertility: The Evidence. Fertil Reprod. 2019;1(1):31–3.
25. Merhi Z, Doswell A, Krebs K, Cipolla M. Vitamin D alters genes involved in follicular development and steroidogenesis in human cumulus granulosa cells. J Clin Endocrinol Metab. 2014;99(6):E1137–45.
26. Visser J, de Jong F, Laven J, Themmen A. Anti-Müllerian hormone: a new marker for ovarian function. Reproduction. 2006;13(1):1–9.
27. Barrera D, Avila E, Hernandez G, Halhali A, Biruete B, Larrea F. Estradioland progesterone synthesis in human placenta is stimulated by calcitriol. J Steroid Biochem Mol Biol. 2007;103:529–32.
28. Ciepiela P, Duleôba A, Kowaleczko E, Cheõõlstowski K, Kurzawa R. Vitamin D as a follicular marker of human oocyte quality and a serum marker of in vitro fertilization outcome. J Assist Reprod Genet. 2018;35(7):1265–76.
29. Barrera D, Avila E, Hernández G, Méndez I, González L, Halhali A, et al. Calcitriol affects hCG gene transcription in cultured human syncytiotrophoblasts. Reprod Biol Endocrinol. 2008;6:3.
30. Du H, Daftary G, Lalwani S, Taylor H. Direct regulation of HOXA10 by 1,25-(OH)2D3 in human myelomonocytic cells and human endometrial stromal cells. Mol Endocrinol. 2005; 19:2222–33.
31. Bagot C, Troy P, Taylor H. Alteration of maternal Hoxa10 expression by in vivo gene transfection affects implantation. Gene Ther. 2000;7:1378–84.
32. Taylor H, Vanden Heuvel GB, Igarashi P. A conserved Hox axis in the mouse and human female reproductive system: late establishment and persistent adult expression of the Hoxa cluster genes. Biol Reprod. 1997;57:1338–45.
33. Hong S, Lee J, Kim H, Jung Y, Hwang D, Lee J, et al. Effect of vitamin D3 on production of progesterone in porcine granulosa cells by regulation of steroidogenic enzymes. J Biomed Res. 2016;30:203–8.
34. Laganà A, Vitale S, Ban Frangež H, Vrtačnik-Bokal E, D'Anna R. Vitamin D in human reproduction: the more, the better? An evidence-based critical appraisal. Eur Rev Med Pharmacol Sci. 2017;21(18):4243–51.
35. Ozkan S, Jindal S, Greenseid K, Shu J, Zeitlian G, Hickmon C, et al. Replete vitamin D stores predict reproductive success following in vitro fertilization. Fertil Steril. 2010;94:1314–9.
36. Paffoni A, Ferrari S, Viganò P, Pagliardini L, Papaleo E, Candiani M, et al. Vitamin D deficiency and infertility: Insights from in vitro fertilization cycles. J Clin Endocrinol Metab. 2014;99:E2372–6.
37. Rudick B, Ingles S, Chung K, Stanczyk F, Paulson R, Bendikson K. Influence of vitamin D levels on in vitro fertilization outcomes in donorrecipient cycles. Fertil Steril. 2014; 101:447–52.
38. Garbedian K, Boggild M, Moody J, Liu K. Effect of vitamin D status on clinical pregnancy rates following in vitro fertilization. C Open. 2013;1:E77–82.
39. Anifandis G, Dafopoulos K, Messini C, Chalvatzas N, Liakos N, Pournaras S, et al. Prognostic value of follicular fluid 25-OH vitamin D and glucose levels in the IVF outcome. Reprod Biol Endocrinol RB&E. 2010;8:91.
40. Viganò P, Lattuada D, Mangioni S, Ermellino L, Vignali M, Caporizzo E, et al. Cycling and early pregnant endometrium as a site of regulated expression of the vitamin D system. J Mol Endocrinol. 2006;36(3):415–24.

41. EFSA Panel on Dietetic Products Nutrition and Allergies (NDA). Scientific opinion on dietary reference values for iodine. EFSA J. 2014;12(5):3660.
42. Chu J, Gallos I, Tobias A, Tan B, Eapen A, Coomarasamy A. Vitamin D and assisted reproductive treatment outcome: a systematic review and meta-analysis. Hum Reprod. 2018;33(1): 65–80.

History
Received February 6, 2020
Accepted November 11, 2020
Published online December 7, 2020

Conflicts of interest
The other authors declare that they have no conflict of interest and have received no payment in preparation of their manuscript.

Authorship
G.F, B.O. and V.U. are employee at LO.LI. Pharma, Rome, Italy.

Daniela Menichini, MSN, PhD student
Via del Pozzo 71
41124 Modena, Italy
daniela.menichini91@gmail.com