The effect of Vitamin D supplementation on hormonal and glycaemic profile of patients with PCOS: A meta-analysis of randomised trials

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Summary

Background: Vitamin D deficiency is frequently manifested in women with polycystic ovarian syndrome (PCOS). To date, supplementation of deficient patients has not been correlated with the hormonal and metabolic status of these patients.

Purpose: We aimed to investigate the impact of vitamin D supplementation on the hormonal and metabolic profile of PCOS women.

Materials and Methods: We searched Medline, Scopus, ClinicalTrials.gov and Cochrane Central Register databases for published randomised controlled trials. The meta-analysis was performed with the RevMan 5.3.5 software.

Results: Nine studies were included in the present meta-analysis which investigated the impact of vitamin D supplementation in 647 patients. According to our meta-analysis neither serum testosterone (MD 0.04 ng/mL, 95% CI −0.09 to 0.17) nor serum LH (MD −0.48 IU/mL, 95% CI −1.97 to 1.00) were significantly affected by vitamin D supplementation in any of the subgroup comparisons. On the contrary, serum DHEAS was significantly affected by vitamin D (MD −32.24 μg/dL, 95% CI −32.24 to −14.01) an effect which was mainly affected by the vitamin D vs placebo comparison. Vitamin D supplementation did not have an impact on fasting glucose (MD 0.42 mg/dL, 95% CI −2.75 to 3.60) or fasting insulin (MD 1.27 μU/mL, 95% CI −1.42 to 3.97) levels. HOMA-IR was, however, increased among patients that received placebo compared to vitamin D (MD 0.52, 95% CI 0.39–0.65).

Conclusion: There is no evidence to support that vitamin D supplementation significantly benefits PCOS patients. However, given the relatively small number of enrolled patients further studies are needed to elucidate this field.

1 | INTRODUCTION

Polycystic ovarian syndrome affects approximately 5%-10% of women of reproductive age and is considered to be one of the most frequent endocrine disorders.1 As a disorder, it seems to be a quite heterogeneous and complicated disorder, whose pathophysiological pathway has not yet been completely clarified.2 Insulin resistance seems to be a predominant feature of PCOS along with the disruption of the hypothalamic-pituitary axis which results in hormonal alterations including increased LH/FSH ratio and circulating androgens.2 The most common clinical manifestations of this syndrome include menstrual disturbances, such as amenorrhea and oligomenorrhea, hirsutism, resistant acne, hyperhidrosis, dysfunctional uterine bleeding and development of the metabolic syndrome.3–5

A recent meta-analysis by He et al. underlined the existence of a significant correlation between PCOS and vitamin D deficiency.6 According to their findings it seems that 67%-85% of women with PCOS have also significant vitamin D deficiency.6 Vitamin D intake is
based on daily consumption from various foods and on skin production from 7-dehydrocholesterol with the aid of ultraviolet irradiation.\textsuperscript{7} Current knowledge supports that vitamin D and its active metabolite \(1,25(\text{OH})_2\text{D}_3\) are not only involved in bone homeostasis but may also enhance glucose metabolism by elevating insulin production and the expression of insulin receptors.\textsuperscript{6} As a consequence, insulin resistance, which is a predominant feature of PCOS as already described might actually be reduced through vitamin D supplementation.\textsuperscript{6} To date, firm consensus is lacking in the field, although several studies have addressed this question. Taking this information into account, we designed a meta-analysis of randomised trials to accumulate current knowledge in the field and to reach firm conclusions regarding the effect of vitamin D on hormonal and glycaemic profile of patients with PCOS.

2 | METHODS

2.1 | Study design

This study was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.\textsuperscript{8} Eligibility criteria were predetermined. Specifically, we chose to avoid language or date restrictions during the literature search. The studies were selected in three consecutive stages. The titles and/or abstracts of all electronic articles were screened to assess their eligibility. All the articles that met or were presumed to meet the criteria were retrieved as full texts. In the final stage, after carefully reading the full text, we selected all randomised controlled trials that reported the impact of vitamin D supplementation on the metabolic and hormonal profile of PCOS patients. References of full text articles were also screened to determine if they were eligible for inclusion in the present meta-analysis. Retrospective and prospective non-randomised trials were excluded from the present meta-analysis. Similarly, case reports and review articles were also withdrawn from tabulation and analysis of results. Vasilios Pergialiotis and Nikoleta Karampetsou tabulated the selected indices in structured forms. Any discrepancies in the methodology, retrieval of articles, and statistical analysis were resolved by consensus.

2.2 | Literature search and data collection

We used the Medline (1966-2016), Scopus (2004-2016), Popline (1974-2016), ClinicalTrials.gov (2008-2016) and Cochrane Central

![FIGURE 1] Search strategy plot

Review Criteria

The present systematic review included randomised trials that evaluated the impact of vitamin D supplementation on the metabolic and hormonal profile of PCOS patients.

Message for the clinic

To date, there is not enough evidence to support vitamin D supplementation as a beneficial factor that influences the metabolism of these women.
Register of Controlled Trials CENTRAL (1999-2016) databases in our primary search along with the reference lists of electronically retrieved full-text papers. Our strategy was restricted to a minimum number of keywords to assess an eligible number of papers that could be hand-searched and together minimise the potential loss of articles. Search strategies and results are shown in Figure 1.

Our search strategy included the MeSH terms ["vitamin d"[MeSH Terms] OR "vitamin d"[All Fields] OR "ergocalciferols"[MeSH Terms] OR "ergocalciferols"[All Fields]] AND pcos[All Fields]]. The date of last search was on September 30, 2016. The PRISMA flow diagram schematically present our strategy (Figure 1).

2.3 | Quality assessment

The methodological quality of included randomised trials was evaluated with the modified Jadad scale using the following criteria: description of the studies as randomised along with details of randomisation, description of the studies as double blind, details of double blinding procedure, information on withdrawals and allocation concealment (Figure 2).9

2.4 | Statistical analysis

Statistical meta-analysis was performed with the Review Manager (RevMan) 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). We calculated the pooled mean differences (MD) and 95% confidence intervals (CI) using the DerSimonian-Laird random effect model due to the significant heterogeneity in the methodological characteristics of included studies (Table 1).10 The methodological heterogeneity of included studies and their small number rendered impossible the evaluation of publication bias.11

2.5 | Definitions

We investigated the alterations of metabolic and hormonal parameters in patients with PCOS that received vitamin D, metformin, their combination or placebo. Studies that co-administrated calcium with vitamin D were also included but substratification of patients was not undertaken as there are no evidence to support the beneficial effect of calcium on the metabolic or hormonal characteristics of PCOS patients. Glycaemic parameters included fasting glucose and fasting serum insulin. The investigated hormonal parameters were serum luteinizing hormone (LH), follicle stimulating hormone (FSH), dehydroepiandrosterone sulfate (DHEAS) and sex hormone-binding globulin (SHBG).

3 | RESULTS

3.1 | Excluded studies

Five studies were excluded from the present meta-analysis. Four of them were either not randomised, did not investigate the outcomes of interest12-14 or did not include a control group.15,16 The fifth study, although randomised, did not investigate the outcomes of interest.17

3.2 | Ongoing studies

Three studies are ongoing in this field. Neither of those has published preliminary data. The first one had a study completion date on November 2016, however, its status is still ongoing in clinicaltrials.gov.18 The remaining two studies are still recruiting participants.19,20

3.3 | Included studies

Nine studies were included in the present meta-analysis which investigated the impact of vitamin D supplementation in 647 patients.21-29 The actual number of patients that were randomised in the various treatment groups is available in Table 1. The glycaemic profile of patients, serum cholesterol level and hormonal profile of patients are presented in Tables 2 and 3.

According to our meta-analysis neither serum testosterone (MD 0.04 ng/mL, 95% CI −0.09 to 0.17) nor serum LH (MD −0.48 IU/mL, 95% CI −1.97 to 1.00) were significantly affected by vitamin D supplementation in any of the subgroup comparisons. On the contrary,

<table>
<thead>
<tr>
<th>Study</th>
<th>2005; Rashid</th>
<th>2012; Bonodar</th>
<th>2012; Acobblil</th>
<th>2014; Tehrani</th>
<th>2014; Raja Khan</th>
<th>2015; Gang</th>
<th>2015; Irani</th>
<th>2016; Razavi</th>
<th>2016; Drouweka</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomisation</td>
<td>✦</td>
<td>✦</td>
<td>✦</td>
<td>✦</td>
<td>✦</td>
<td>✦</td>
<td>✦</td>
<td>✦</td>
<td>✦</td>
</tr>
<tr>
<td>Randomisation scheme</td>
<td>✦</td>
<td>✦</td>
<td>✦</td>
<td>✦</td>
<td>✦</td>
<td>✦</td>
<td>✦</td>
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<td>Double-blind</td>
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<td>✦</td>
<td>✦</td>
<td>✦</td>
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</tr>
<tr>
<td>Double-blind method</td>
<td>✦</td>
<td>✦</td>
<td>✦</td>
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<td>✦</td>
<td>✦</td>
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</tr>
<tr>
<td>Dropouts and withdrawals</td>
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<td>✦</td>
<td>✦</td>
<td>✦</td>
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<td>✦</td>
<td>✦</td>
<td>✦</td>
<td>✦</td>
</tr>
</tbody>
</table>

FIGURE 2 Jadad score
serum DHEAS was significantly affected by vitamin D (MD -32.24 μg/dL, 95% CI -32.24 to -14.01) an effect which was mainly affected by the vitamin D vs placebo comparison (Figure 3).

Neither fasting glucose (MD 0.42 mg/dL, 95% CI -2.75 to 3.60) nor fasting insulin (MD 1.27 μU/mL, 95% CI -1.42 to 3.97) were significantly affected by vitamin D supplementation. Increased levels of HOMA-IR were observed among cases that were not offered vitamin D (MD 0.50, 95% CI 0.37-0.63). This effect was mainly affected by the vitamin D vs placebo subgroup analysis (MD 0.52, 95% CI 0.39-0.65). No significant differences were observed in the case of the QUICKI index (MD -0.01, 95% CI -0.04 to 0.01), however, this index was reported by two studies only.23,25

The total cholesterol of patients was not affected when we analysed all patients without taking into account the potential

<p>| TABLE 1 | Patient groups and baseline characteristics |</p>
<table>
<thead>
<tr>
<th>Date; author</th>
<th>Patient Number</th>
<th>Studied Groups</th>
<th>Age</th>
<th>BMI</th>
<th>Baseline Vitamin D</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009; Rashidi</td>
<td>20 vs 20 vs 20</td>
<td>Ca+vD vs Ca+vD+Met vs Met</td>
<td>24.95±3.56 vs 25.805±4.61 vs 26.95±4.44</td>
<td>25.75±3.94 vs 27.81±3.78 vs 25.162±3.860</td>
<td>N/A</td>
</tr>
<tr>
<td>2012; Bonakdaran</td>
<td>17 vs 15 vs 16</td>
<td>Met vs vD vs placebo</td>
<td>25.9±4.5 vs 24.7±3.3 vs 25.2±7.9</td>
<td>95% CI -32.24 to -14.01</td>
<td>N/A</td>
</tr>
<tr>
<td>2012; Ardabili</td>
<td>24 vs 26</td>
<td>Vitamin D vs placebo</td>
<td>26.8±4.7 vs 27.0±3.7</td>
<td>29.0±4.69 vs 28.18±3.45</td>
<td>6.9±2.8 vs N/A</td>
</tr>
<tr>
<td>2014; Tehran</td>
<td>20 vs 20 vs 20 vs 20</td>
<td>Met vs Met+Ca+vD vs Ca+vD vs placebo</td>
<td>27.4±2.2 vs 28.7±4.5 vs 31.3±4.6 vs 27.2±6.5</td>
<td>95% CI 20.1±3.2 vs 18.71±2.69 vs 19.53±3.25 vs 20.03±2.91</td>
<td>N/A</td>
</tr>
<tr>
<td>2014; Raja Khan</td>
<td>13 vs 15</td>
<td>vD3 vs placebo</td>
<td>28.2±5.2 vs 28.7±5.6</td>
<td>37.85±4.50 vs 37.62±10.0</td>
<td>19.95±9.47 vs 22.20±6.86</td>
</tr>
<tr>
<td>2015; Carg</td>
<td>15 vs 17</td>
<td>vD+Met vs placebo</td>
<td>22.0±4.61 vs 22.8±4.56</td>
<td>25.4±5.65 vs 25.9±6.05</td>
<td>7.7±6.05 vs 6.8±2.46</td>
</tr>
<tr>
<td>2015; Irani</td>
<td>35 vs 18</td>
<td>vD vs placebo</td>
<td>30.5±1 vs 29.6±1.7</td>
<td>N/A</td>
<td>16.3±0.9 vs 17±1.9</td>
</tr>
<tr>
<td>2016; Razavi</td>
<td>27 vs 27</td>
<td>vD+vK+ Ca vs placebo</td>
<td>18-40</td>
<td>N/A</td>
<td>14.4±2.9 vs 14±5.5</td>
</tr>
<tr>
<td>2016; Dravecka</td>
<td>9 vs 11 vs 12</td>
<td>vD vs vD+Met vs Met</td>
<td>29.33±4.89 vs 29.2±5.42 vs 27.6±4.96</td>
<td>N/A</td>
<td>24.1±8.0 vs 22.0±8.4 vs 24.3±6.8</td>
</tr>
</tbody>
</table>

<p>| TABLE 2 | Glycaemic and lipidemic profile |</p>
<table>
<thead>
<tr>
<th>Date; author</th>
<th>Glucose</th>
<th>Insulin</th>
<th>HOMA-IR</th>
<th>QUICKI</th>
<th>Total cholesterol</th>
<th>LDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009; Rashidi et al.</td>
<td>N.A</td>
<td>N.A</td>
<td>N.A</td>
<td>N.A</td>
<td>N.A</td>
<td>N.A</td>
</tr>
<tr>
<td>2012; Bonakdaran et al.</td>
<td>102.0±25.5 vs 89.0±12.3 vs 87.3±5.3</td>
<td>14.2±15.1 vs 13.1±14.8 vs 8.6±5.0</td>
<td>4.2±6.9 vs 2.7±3.1 vs 1.9±1.0</td>
<td>N.A</td>
<td>N.A</td>
<td>N.A</td>
</tr>
<tr>
<td>2012; Ardabili et al.</td>
<td>96.6±9.87 vs 98.77±14.62</td>
<td>13.4±9.66 vs 9.98±4.09</td>
<td>3.21±2.59 vs 2.6±1.14</td>
<td>0.337±0.046 vs 0.343±0.034</td>
<td>N.A</td>
<td>N.A</td>
</tr>
<tr>
<td>2014; Tehran et al.</td>
<td>N.A</td>
<td>N.A</td>
<td>N.A</td>
<td>N.A</td>
<td>N.A</td>
<td>N.A</td>
</tr>
<tr>
<td>2014; Raja Khan et al.</td>
<td>83.8±8.02 vs 77.6±14.6</td>
<td>38.0±7.30 vs 28.7±14.64</td>
<td>7.79±7.37 vs 5.69±2.97</td>
<td>0.296±0.022 vs 0.309±0.039</td>
<td>177.18±37.17 vs 181.09±40.10</td>
<td>105.91±27.69 vs 116.55±32.69</td>
</tr>
<tr>
<td>2015; Carg et al.</td>
<td>90±7 vs 89±8</td>
<td>10.3±5.92 vs 12.2±6.67</td>
<td>2.3±1.32 vs 2.6±1.32</td>
<td>N.A</td>
<td>158±20 vs 154±27</td>
<td>102±13 vs 102±27</td>
</tr>
<tr>
<td>2015; Irani et al.</td>
<td>N.A</td>
<td>2.03±0.22 vs 1.52±0.24</td>
<td>N.A</td>
<td>166±11 vs 177±6.3</td>
<td>101±5.1 vs 100±4.1</td>
<td></td>
</tr>
<tr>
<td>2016; Razavi et al.</td>
<td>N.A</td>
<td>N.A</td>
<td>N.A</td>
<td>N.A</td>
<td>N.A</td>
<td>N.A</td>
</tr>
<tr>
<td>2016; Dravecka et al.</td>
<td>N.A</td>
<td>N.A</td>
<td>N.A</td>
<td>N.A</td>
<td>N.A</td>
<td>N.A</td>
</tr>
</tbody>
</table>

Glucose levels in mg/dL, Insulin in μIU/mL, total Cholesterol and LDL in mg/dL.
co-administration of other regimens (MD = −6.63 mg/dL, 95% CI −16.43 to 3.18). However, a significant decrease among patients that received vitamin D compared to a placebo group was evident (MD = −10.82 mg/dL, 95% CI −15.42 to −6.22). This effect was not significant in the case of serum LDL (MD 0.99 mg/dl, 95% CI −1.38 to 3.35).

Only two studies investigated the impact of vitamin D on acne and hirsutism with conflicting evidence.\textsuperscript{27,28} Evidence regarding its action on menstrual cycle regularity remain also inconclusive.\textsuperscript{14,28}

### 4 | DISCUSSION

Polycystic ovarian syndrome affects a significant number of women of reproductive age.\textsuperscript{30} The underlying pathophysiology has not been completely elucidated. However, several factors have been implicated in its pathogenesis and vitamin D deficiency seems to have a higher prevalence in PCOS women.\textsuperscript{6} Given this information, we designed the present meta-analysis to gather all the available evidence regarding the effectiveness of vitamin D supplementation in women with PCOS. According to the findings of our study, vitamin D does not seem to affect glucose and insulin levels. Similarly, it does not influence the hormonal profile of these women. On the other hand, a mild effect of vitamin D compared to placebo treatment on HOMA-IR was detected. A potential effect of vitamin D supplementation on DHEAS levels is evident, however, this effect is the result of two studies that compare vitamin D supplementation to placebo.\textsuperscript{12,29} Similarly, total serum cholesterol might be also affected, although mildly, when vitamin D supplementation is compared with placebo treatment.

In a meta-analysis that was just published Xue et al. observed that vitamin D significantly improved the serum triglyceride levels.\textsuperscript{31} In this paper, the authors evaluated the impact of vitamin D supplementation by comparing the pre- treatment with the post-treatment values. However, they incorporated studies with different arms of treatment; hence it is impossible to understand whether this effect comes from vitamin D or from other treatment regimens (such as metformin). In our meta-analysis, we investigated only the post-treatment serum levels of these parameters after incorporating subgroup analysis according to the treatment groups. Given the fact that pretreatment levels did not significantly differ among the investigated groups, every significant difference could be taken in favour or against vitamin D supplementation. The contradictory findings of our meta-analysis compared to those by Xue et al., regarding the importance of vitamin D on serum triglyceride levels could be also explained by the fact that the differences observed in the latter study were mild and of no particular clinical importance (MD 0.32, 95% CI 0.03–0.60 mg/dL).\textsuperscript{31}

The concept of a potential correlation of vitamin D deficiency with metabolic disorders has been investigated thoroughly the last decade. More specifically, in 2010 Takiishi et al. demonstrated that reduced amounts of vitamin D which are accompanied by simultaneous increase in parathyroid hormone (PTH) lead to increased production of intracellular calcium levels in adipocytes.\textsuperscript{32} The direct consequence of this effect is a triggering effect which enhances lipogenesis, weight gain, insulin resistance and a marked increase in serum triglycerides.\textsuperscript{32,33} The latter increase in free fatty acid has been previously correlated with a reduction in insulin secretion caused by accumulation of lipotoxic triglycerides in β-cells.\textsuperscript{34}

### TABLE 3 Hormonal profile

<table>
<thead>
<tr>
<th>Date; author</th>
<th>DHEA-S</th>
<th>SHBG</th>
<th>Testosterone</th>
<th>LH</th>
<th>FSH</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009; Rashidi</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>9.90±3.58 vs 10.24±3.68 vs 8.81±4.51</td>
<td>5.20±1.98 vs 4.95±1.66 vs 5.67±1.70</td>
</tr>
<tr>
<td>2012; Bonakdaran</td>
<td>281.62±168.41 vs 264.50±107.12 vs 333.58±154.65</td>
<td>N/A</td>
<td>1.07±0.62 vs 1.06±0.31 vs 1.22±0.65</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>2012; Ardabili</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>2014; Tehran</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>2014; Raja Khan</td>
<td>N/A</td>
<td>N/A</td>
<td>0.55±37 vs 0.50±0.29</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>2015; Carg</td>
<td>238.3±126 vs 305±98.36</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>2015; Irani</td>
<td>121±13 vs 143±18</td>
<td>33.9±3.6 vs 43±9.4</td>
<td>0.38±0.04 vs 0.36±0.04</td>
<td>8.3±1.2 vs 9.2±1.6</td>
<td>4.5±0.5 vs 5.2±0.6</td>
</tr>
<tr>
<td>2016; Razavi</td>
<td>110±140 vs 170±80</td>
<td>N/A</td>
<td>N/A</td>
<td>7.7±4.8 vs 12±7.1</td>
<td>7.6±3.9 vs 8.3±2.3</td>
</tr>
<tr>
<td>2016; Dravecka</td>
<td>431.22±207.92 vs 322.42±184.13 vs 406.50±209.23</td>
<td>44.33±28 vs 28.4±14.5 vs 56.3±49.7</td>
<td>1.22±0.30 vs 1.03±0.046 vs 0.97±0.033</td>
<td>8.33±6.42 vs 5.87±2.90 vs 11.9±20.41</td>
<td>N/A</td>
</tr>
</tbody>
</table>

DHEA-S in μg/dL, SHBG in nmol/L, Testosterone in ng/mL, LH and FSH in IU/mL.
However, despite the proposed pathophysiological mechanisms, vitamin D supplementation does not seem to exert a direct effect in the lipidemic or glycaemic profile of patients with PCOS. A potential explanation for this observation might be the type of population that was used in the primary randomisation. Participants in studies included in the present meta-analysis had variable degree of vitamin D deficiency according to the dietary reference intakes for vitamin D from the Institute of Medicine, Food and Nutrition. A potential effect of vitamin D supplementation could be, therefore, predominant in patients with levels lower than 12 ng/mL, while in patients with mild deficiency (12-20 ng/mL) this could be minimal.

### 4.1 Implications for current clinical practice and future research

Vitamin D supplementation is not justified in PCOS patients, according to the results of our meta-analysis. However, we strongly believe that future research is required in this field, because several data were lacking from the studies included. Firstly, the analysis should be specifically based on the severity of vitamin deficiency as previously stated in the present article. Furthermore, the additive effect of vitamin D supplementation on the hormonal and metabolic profile of patients treated with metformin deserves further investigation as current data are based only in two studies. Moreover, the investigation of the phenotypic alterations of PCOS such as acne and hirsutism with a thorough evaluation based on the Ferriman-Gallwey classification is required as current data in the field remain very limited. The changes of these parameters may depict the influence of vitamin D supplementation in hormonal factors, such as testosterone, androstenedione and DHEAS which were also underreported in studies included in the present meta-analysis. Finally, to date, the impact of vitamin D supplementation on the lipidemic status of PCOS patients has not been adequately investigated; hence, the potential benefit of this treatment on the prevention of cardiovascular diseases remains unknown. Future studies should specifically mention the alterations in serum LDL, HDL and triglyceride levels.

### 4.2 Strengths and weaknesses of our study

The present meta-analysis is based on meticulous review of the literature and is, to our knowledge, the first to accumulate current evidence from randomised controlled trials. Patient randomisation prevents selection bias and permits accurate interpretation of findings.
5 | CONCLUSION

Current data do not support the use of vitamin D supplementation in PCOS patients for the improvement of their hormonal and metabolic status. However, given the promising pathophysiological pathways that seem to correlate vitamin D with the glycaemic and lipidemic profile further research is needed in the field. To reach firm conclusions, future studies should include a power-analysis; hence, permitting accurate interpretation of their findings and also investigate in depth all the parameters which were discussed in our study.

DISCLOSURES

None

AUTHOR CONTRIBUTION

Vasilios Pergialiotis and Nikolaos Papantoniou conceived the idea; Vasilios Pergialiotis and Nikoleta Karampetsou performed the electronic search; Vasilios Pergialiotis and Periklis Panagopoulos performed the statistical analysis; Nikoleta Karampetsou, Periklis Panagopoulos and Nikolaos Papantoniou wrote the manuscript.

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