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Review Article

Biochemistry Section

Effect of Vitamin D and Calcium Supplementation on Menstrual Abnormalities, Follicular Response and Metabolic Status in Polycystic Ovary Syndrome: A Systematic Review

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ABSTRACT

Introduction: Polycystic Ovary Syndrome (PCOS) is a prevalent hormonal disorder affecting women. It presents with irregular periods, high levels of male hormones and multiple cysts on the ovaries. Metabolic disruptions related to PCOS consist of insulin resistance, obesity and dyslipidaemia. Recent studies show that supplementing with vitamin D and calcium could benefit metabolic health, menstrual cycle regularity and follicular growth in women with PCOS.

Aim: To analyse the effectiveness of Vitamin D and Calcium on metabolic parameters, menstrual cycles and follicular response in patients with PCOS.

Materials and Methods: The studies were reviewed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A thorough literature search was conducted in databases including PubMed, Pub Med Central, Web of Science, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), Evidence-based Medicine Reviews (EBMR), and Google Scholar. The quality of the studies was evaluated using the Joanna Briggs Institute (JBI) checklist for systematic reviews and research syntheses and the data were analysed using a narrative approach.

Results: The systematic review of 12 experimental studies showed mixed results on the effects of vitamin D and calcium supplementation in women with PCOS. Some studies reported improved insulin sensitivity, lipid profiles and menstrual cycle regularity, while others found inconsistent outcomes in follicular development and ovarian morphology, with some showing improvement and others finding no significant changes compared to controls.

Conclusion: The present systematic review suggests that vitamin D and calcium supplementation can potentially improve metabolic status in women with PCOS, but the effects on menstrual cycle abnormalities and follicular response are inconsistent. The variability in study outcomes highlights the need for personalised supplementation strategies and further research to determine the optimal treatment approach for improving both metabolic and reproductive health in women with PCOS.

Keywords: Calcium supplementation, Menstrual cycle abnormalities, Reproductive health

INTRODUCTION

The PCOS, a prevalent endocrine disorder, impacts women in their reproductive years. It is identified by irregular periods, excess male hormones and ovaries with multiple cysts. PCOS has important clinical consequences, such as reproductive, metabolic and psychological issues [1]. The occurrence of PCOS in India shows significant variability, with rates ranging from 3.7 to 22.5% based on the specific diagnostic criteria utilised [1]. The overall prevalence according to Rotterdam's criteria is approximately 10% [2]. This strong prevalence highlights the significance of early detection and treatment in reducing long-term health dangers [3]. Most evidence indicates that insulin resistance exacerbates excess androgen production in adolescent and adult PCOS patients. It has been repeatedly suggested that addressing insulin resistance improves reproductive and metabolic abnormalities, potentially reducing the future risk of diabetes and cardiovascular disease in PCOS women [4]. Vitamin D deficiency has been proposed as a potential link between insulin resistance and PCOS [5].

Vitamin D, a fat-soluble vitamin, is synthesised endogenously through sunlight-induced conversion of cholesterol to 7-dehydrocholesterol in the skin or obtained from the diet. Vitamin D undergoes two hydroxylations: first, in the liver by 25-hydroxylase to form 25-hydroxyvitamin D (25(OH)D) and second, in the kidney by 1 alpha-hydroxylase to form 1,25-dihydroxyvitamin D (1,25(OH)2D), the active metabolite. Circulating 1,25(OH)2D binds to Vitamin D Receptors (VDR) to exert its effects. Serum 25(OH)D, the major circulating form of vitamin D, is the primary indicator of vitamin D status with a half-life of 2-3 weeks, compared to 4-6 hours for 1,25(OH)2D [6].

For many years, vitamin D's role has been suggested beyond calcium and bone homeostasis due to the presence of VDR and 1 alpha-hydroxylase in various tissues, including pancreatic beta-cells, immune cells and reproductive organs in both genders [4]. This assumption is supported by the discovery that the active vitamin D-VDR complex regulates over 300 genes, including those crucial for glucose and lipid metabolism and gonadal function [7].

The biological actions of vitamin D are mediated through VDR, a member of the steroid/thyroid nuclear hormone receptor superfamily [8]. VDR is found in calcium-regulating tissues like intestines, skeleton and parathyroid glands, as well as reproductive organs such as the ovary (particularly granulosa cells), uterus, placenta, testis, hypothalamus and pituitary [9,10]. This widespread expression of VDR suggests a potential role for vitamin D in female reproductive physiology [9]. Parikh G et al., demonstrated that vitamin D increased the production of progesterone, oestrogen, oestrone and insulin-like growth factor-binding protein 1 in human ovarian cells [11].

Overall, this systematic review aimed to address the significant challenges posed by PCOS by systematically evaluating the impacts of vitamin D and calcium supplementation along with metformin or alone on metabolic status, menstrual cycle irregularities and follicular

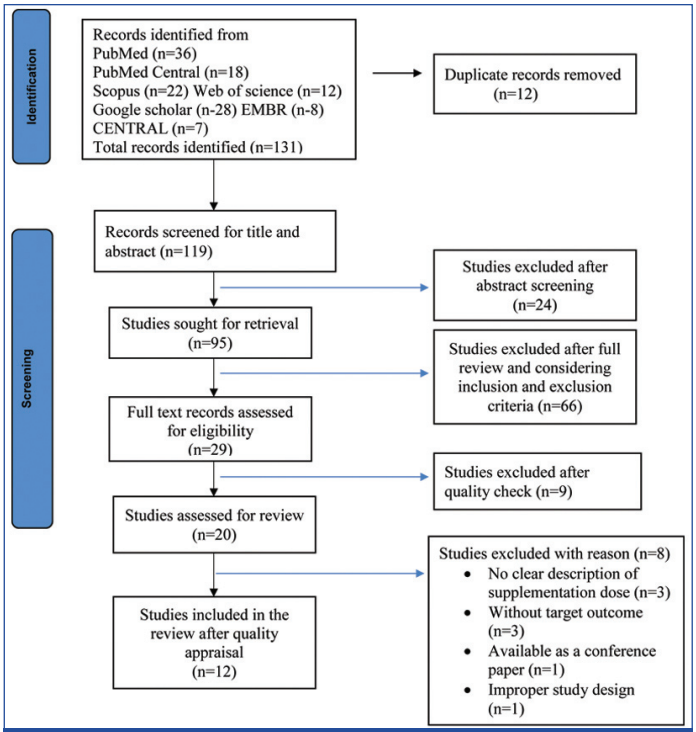
response. By synthesising existing evidence, this study seeks to inform clinical decision-making, enhance understanding of PCOS pathogenesis, and lay the groundwork for more personalised and effective supportive interventions, ultimately improving the health and well-being of women with PCOS.

Research question: What are the effects of vitamin D and calcium supplementation on metabolic status, menstrual cycle abnormalities, and follicular response in women with PCOS.

Method: This systematic review followed the guidelines of the PRISMA.

MATERIALS AND METHODS

A literature search strategy involved finding relevant studies from different electronic databases, such as PubMed, PubMed Central, Web of Science, Scopus, CENTRAL, EBMR, and Google Scholar between January 2010 and April 2024. Keywords covered include polycystic ovarian syndrome, vitamin D, calcium compounds, calcitriol and the combination thereof. Furthermore, cited references of retrieved trials and systematic reviews were manually screened to identify any additional relevant trials that were not found by the electronic search [Table/Fig-1].



[Table/Fig-1]: Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flow diagram.

Screening: To determine eligibility for inclusion, all selected articles were initially screened based on their title and abstract. The identified citations were then imported into Zotero, where duplicate articles were eliminated. Articles were then evaluated by two independent reviewers under the selection criteria. A third mediator helped to settle any disputes. Full-text versions of studies that met the inclusion criteria were obtained. Once duplicate entries were eliminated, a final evaluation of the articles was carried out using the predetermined criteria for inclusion and exclusion.

Inclusion criteria:

- **Study design:** The study included both observational studies (such as cohort, case-control and cross-sectional studies) and Randomised Controlled Trials (RCTs) to examine the effects of vitamin D and calcium supplementation on PCOS.
- **Participants:** Women diagnosed with PCOS according to recognised diagnostic criteria, regardless of age or ethnicity, were included. Diagnosis of PCOS required the presence of at least two out of three criteria: hyperandrogenism (clinical and/or biochemical), oligo-ovulation or anovulation and polycystic ovaries on ultrasound examination [12].
- **Intervention:** The focus was on the effects of vitamin D and calcium supplementation, either alone or in combination, on metabolic status, menstrual irregularities and follicular response in women with PCOS.
- **Outcome measures:** Studies reporting significant clinical outcomes related to metabolic parameters (e.g., insulin sensitivity, lipid profile), menstrual regularity and follicular response (e.g., ovarian morphology, follicular development) were included.

Exclusion criteria:

- Studies involving individuals with other underlying endocrine disorders or significant co-morbidities unrelated to PCOS, to ensure the homogeneity of the study participants.
- Studies lacking significant outcome measures, to avoid insufficient data for evaluation.
- Non-human studies, reviews, opinions, editorials, and conference abstracts.

Quality assessment: The evaluation of the studies' quality was carried out with the JBI checklist for systematic reviews [13]. The checklist consisted of 11 criteria. Two evaluators individually assessed each attribute on the list, indicating whether the answers were "yes" or "no." A score of one was given for each "yes" response, and zero for each "no", leading to a maximum score of 11. Quality was specifically evaluated in the methodology and results sections of the studies. The review included studies with a score of six or above [Table/Fig-2].

S. No.	Checklist	Yes (number of articles)	No (number of articles)
1.	Is the review question clearly and explicitly stated?	12	0
2.	Were the inclusion criteria appropriate for the review question?	9	3
3.	Was the search strategy comprehensive	10	2
4.	Were the sources and resources used for searching adequate?	8	4
5.	Were the criteria for appraising studies appropriate?	10	2
6.	Was critical appraisal conducted by two or more reviewers independently?	12	0
7.	Were practice recommendations supported by the reported data?	8	4
8.	Were specific directives for new research appropriate and identified?	9	3
9.	Was the impact of heterogeneity (differences between studies) assessed?	12	0
10.	Were the conclusions drawn from the findings justified?	10	2
11.	Were study limitations identified and addressed?	9	3

[Table/Fig-2]: Joanna Briggs Institute (JBI) checklist for systematic review.

RESULTS

A comprehensive review was conducted to assess the impact of vitamin D and calcium supplementation on metabolic status, menstrual irregularities and follicular response in women with PCOS. A total of 12 studies met the inclusion criteria, including 10 RCTs, seven of which were double-blind placebo-controlled, two were single-arm open-label trials, and one was an RCT pilot trial. Additionally, one case-control and one comparative observational study was included [Table/Fig-3] [14-25].

Figurová J et al., compared alfacalcidol (vitamin D), metformin, and their combination in 39 women with PCOS [14]. The study found

S. No.	Author, publication year, reference	Country	Study design	Sample size and population	Type of intervention	Duration of intervention	Key findings
1	Figurová J al., 2017 [14]	Slovakia	Randomised Controlled Trial (RCT)	Total sample=39 Group-1 (n=13) Group-2 (n=13) Group-3 (n=13)	Randomly allocated into three groups. Group-1: 1 µg of Alfacalcidol/day plus 700-2550 mg of metformin daily Group-2: 1 µg of Alfacalcidiol per day Group-3: 700-2550 mg of metformin daily	6 months	Vitamin D supplementation has no significant effect on anthropometric and metabolic parameters in PCOS women. Metformin has been still the most effective modality for the treatment of metabolic changes in PCOS.
2	Firouzabadi Rd et al., 2012 [15]	Iran	Case-control	Total sample=100 Group-1=50 Group-2=50	Randomly allocated into two groups. Group-1: Metformin 1500 mg/day+Calcium 1000 mg/day+Vitamin D 50000 IU/week Group-2: Metformin 1500 mg/day	6 months	This study showed the positive effects of calcium and vitamin D supplementation on weight loss, follicle maturation, menstrual regularity and improvement of hyperandrogenism, in infertile women with PCOS.
3	Pal L et al., 2012 [16]	Atlanta, USA	RCT- single-arm open-label trial	Total sample=12	Vitamin D 50000 IU/week calcium 530 mg/day	3 months	Androgen and Blood Pressure (BP) profiles improved following three-month interventions, suggesting therapeutic implications of vitamin D and Ca in overweight and vitamin D deficient women with PCOS.
4	Raja-Khan N et al., 2014 [17]	Pennsylvania, USA	RCT- pilot trial	Total sample=28 Group-1=13 Group-2=15	Randomly allocated into two groups. Group-1: Vitamin D 12000 IU/day Group-2: Placebo for vitamin D/day	12 weeks	In women with PCOS, insulin sensitivity was unchanged with high-dose vitamin D but there was a trend towards decreased 2-hour insulin and a protective effect on blood pressure.
5	Maktabi M et al., 2017 [18]	Iran	RCT- double-blinded, placebo-controlled trial	Total sample=70 Group-1=35 Group-2=35	Randomly allocated into two groups. Group-1: Vitamin D 12000 IU/day Group-2: Placebo for vitamin D/day	12 weeks	Vitamin D supplementation for 12 weeks in vitamin D-deficient women with phenotype B-PCOS had beneficial effects on glucose homeostasis parameters, hs-CRP, and Malondialdehyde (MDA).
6	Seyyed Abootorabi M et al., 2018 [19]	Iran	RCT- double-blinded, placebo-controlled trial	Total sample=44 Group-1=19 Group-2=17	Group-1: Vitamin D3 50,000 IU/week Group-2: Placebo for vitamin D/week	8 weeks	Vitamin D supplementation for 8 weeks among vitamin D deficient women with PCOS significantly decreased fasting blood glucose and increased HOMA-B, Adiponectin and serum 25OHD levels.
7	Jamilian M et al., 2017 [20]	Iran	RCT- double-blinded, placebo-controlled trial	Total sample=90 Group-1=30 Group-2=30	Group-1: Vitamin D 4000 IU/day Group-2: Vitamin D 1000 IU/day Group-3: Placebo for vitamin D	12 weeks	Overall, high-dose vitamin D supplementation (4000 IU/day) for 12 weeks to insulin-resistant women with PCOS had beneficial effects in total testosterone, Sex Hormone Binding Globulin (SHBG), FAI, hs-CRP and TAC values compared with low-dose vitamin D (1000 IU/day) and placebo groups, but unchanged DHEAS, NO, GSH and MDA values.
8	Kadoura S et al., 2019 [21]	Syria	RCT- single-blinded, placebo-controlled trial	Total sample=34 Group-1=18 Group-2=16	Group-1: Vitamin D 6000 IU/day plus Calcium carbonate 1000 mg/day plus metformin 500 mg/day first week Vitamin D 6000 IU plus Calcium 1000 mg plus metformin 1000 mg/day second week Vitamin D 6000 IU plus Calcium 1000 mg plus metformin 1500 mg/day third week onwards Group-2: Metformin plus placebo	8 weeks	Calcium and vitamin D supplements can support the metformin effect on the regulation of menstrual cycle irregularity in vitamin D-deficient/insufficient PCOS patients, but this effect is not associated with any significant changes in gonadotropins or the IGF-1 system. These results suggest a possible role of calcium and vitamin D supplements in managing PCOS. However, further studies are needed to identify the underlying mechanisms.
9	Al-Bayyari N et al., 2021 [22]	Jordan	RCT- double-blinded, placebo-controlled trial	Total sample=60 Group-1=30 Group-2=30	Group-1: Vitamin D 50,000 IU/week Group-2: Placebo for Vitamin D	12 weeks	It can be concluded that vitamin D3 in a treatment dose of 50,000 IU per week for 12 weeks improved serum 25(OH)D concentrations and reduced the PTH, hirsutism score, and FAI, as well as increased the SHBG level of overweight women suffering from PCOS. These positive improvements in androgen levels and hirsutism score helped improve ovarian ultrasonography and regulate the menstrual cycle, which will reflect better fertility and reproductive life for overweight women with PCOS.
10	Garg S and Makhija N 2022 [23]	Delhi, India	Prospective cohort comparative observational study	Total=96 Group-1=48 Group-2=48	Group-1: Vitamin D 60,000 IU/week plus metformin 1000 mg/day Group-2: Metformin 1000 mg/day	24 weeks	Remarkable improvement was seen in clinical, hormonal, metabolic and sonographic parameters in the experimental group and a noteworthy reduction in The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), BP and triglyceride values was also seen. Hence, supplementation of vitamin D is highly effective in improving PCOS and preventing future consequences as well.

11	Azemi Z et al., 2014 [24]	Iran	RCT-double blind, placebo-controlled trial	Total=104 Group-1=26 Group-2=26 Group-3=26 Group-4=26	Group-1: Vitamin D 50,000 IU/week plus 1000 mg/day calcium Group-2: Vitamin D 50,000 plus calcium placebo Group-3: Calcium 1000 mg/day plus vitamin D placebo. Group-4: Vitamin D placebo plus calcium placebo	8 weeks	Calcium plus vitamin D supplementation for eight weeks among vitamin D-deficient women with PCOS had beneficial effects on serum insulin levels, HOMA-IR, QUICKI, serum triglycerides and VLDL-cholesterol levels, but it did not affect FPG and other lipid profiles.
12	Trummer C et al., 2019 [25]	Austria	RCT-double blind, placebo-controlled trial	Total=180 Group-1=119 Group-2=61	Group-1: Vitamin D 20000 IU/ weekly Group-2: Placebo for vitamin D	24 weeks	No significant effects of vitamin D supplementation on either metabolic or endocrine parameters in the cohort of PCOS women with insufficient baseline 25(OH)D concentrations, except for a decrease in plasma glucose after 60 min during OGTT. These results need to be confirmed in other cohorts with comparable or even larger population sizes.

[Table/Fig-3]: Characteristics of the included studies and study populations [14-25].

significant reductions in body weight, Body Mass Index (BMI), waist circumference, total body fat and serum glucose levels in the metformin group compared to the alfacalcidol group (p-value <0.05).

Firouzabadi Rd et al., studied 100 infertile women with PCOS, where one group received metformin and the other received metformin with calcium and vitamin D supplements [15]. The combination group showed improved menstrual regularity, follicle maturation and weight loss. The study also corrected vitamin D deficiency in most participants, suggesting a beneficial effect of calcium and vitamin D on PCOS symptoms.

Pal L et al., evaluated 12 overweight women with PCOS and vitamin D deficiency [16]. After three months of vitamin D and calcium supplementation, improvements were seen in serum 25OHD levels, blood pressure and androgen levels, though glucose homeostasis and insulin resistance remained unchanged.

Raja-Khan N et al., conducted a 12-week study on 28 women with PCOS, finding that vitamin D supplementation significantly increased 25OHD levels and reduced 2-hour insulin levels, with no major impact on other insulin sensitivity markers [17]. The study highlighted an improvement in diastolic blood pressure.

Maktabi M et al., performed a 12-week trial on 70 women with PCOS [18]. Vitamin D supplementation significantly reduced fasting plasma glucose, insulin, The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), and improved inflammatory markers like hs-CRP and plasma Malondialdehyde (MDA) levels. However, no significant effects were observed on hormonal or lipid profiles.

Seyyed Abootorabi M et al., conducted an 8-week study on 44 participants, reporting significant decreases in fasting plasma glucose and HOMA-B improvements in the vitamin D group [19]. Vitamin D supplementation also significantly increased adiponectin and serum vitamin D levels.

Jamilian M et al., studied 95 women with PCOS, where vitamin D supplementation (4000 IU) led to significant improvements in fasting plasma glucose, insulin, HOMA-IR, testosterone levels, and Hirsutism [20]. Sex Hormone Binding Globulin (SHBG) levels increased significantly, showing the beneficial effects of vitamin D in combination with metformin.

Kadoura S et al., evaluated 40 women, finding that calcium and vitamin D supplementation improved menstrual cycle regularity and increased 25-OH-vitamin D levels [21]. However, weight, BMI, and waist-to-hip ratios decreased in both groups without significant differences.

Al-Bayyari N et al., demonstrated that 50,000 IU of vitamin D3 weekly improved serum 25(OH)D levels, reduced hirsutism scores, and improved androgen and reproductive health markers in overweight women with PCOS [22].

Garg S and Makhija N, studied 96 women, concluding that vitamin D supplementation significantly improved clinical, hormonal, metabolic, and sonographic parameters, particularly in reducing HOMA-IR and improving oligomenorrhoea and hirsutism [23].

Azemi Z et al., showed that calcium and vitamin D co-supplementation significantly improved insulin sensitivity and certain lipid parameters in overweight PCOS patients [24].

Trummer C et al., found that vitamin D supplementation in 180 women led to increased 25(OH)D levels but had limited impact on metabolic and endocrine parameters, except for reduced glucose during an OGTT [25].

Metabolic and endocrine status: The systematic review revealed mixed findings regarding the effects of vitamin D and calcium supplementation on metabolic parameters in women with PCOS. Some studies reported improvements in insulin sensitivity and lipid profiles following supplementation [15,18,19,23,24], while few other studies found no significant changes compared to placebo or control groups [14,17,25]. Variability in supplementation protocols, including dosage, duration, and participant characteristics, may have contributed to the inconsistencies in metabolic outcomes across studies.

Menstrual cycle abnormalities: Studies investigating the effect of vitamin D and calcium supplementation on menstrual consistency in women with PCOS showed promising results. Supplementation was associated with improvements in monthly cycle regularity and a reduction in menstrual irregularities in several RCTs [21-23]. These findings suggest that vitamin D and calcium may play a role in managing PCOS in women, though further research is needed to understand the underlying mechanisms.

Follicular response: Evidence on the effects of vitamin D and calcium supplementation on follicular response in women with PCOS was limited and inconclusive. Few studies reported improvements in follicular development and ovarian function with supplementation [15,16,20,22] while some others found no significant changes compared to control groups [14,17,25]. Variability in study designs and methodologies may have contributed to discrepancies in follicular response outcome.

DISCUSSION

The findings from this review suggest that vitamin D supplementation, either alone or in combination with calcium, may lead to improvements in insulin resistance, as measured by the HOMA-IR, and lipid profiles in women with PCOS. For instance, Study by Irani M and Merhi Z, reported that vitamin D supplementation led to improvements in menstrual cycle regularity and follicular development [26]. These improvements are hypothesised to be mediated by the role of vitamin D in ovarian folliculogenesis and the modulation of Anti-Müllerian Hormone (AMH) levels, a marker of ovarian reserve that is often elevated in women with PCOS.

Conversely, Rashidi B et al., found no significant changes in menstrual cycle regularity or follicular response following supplementation

[27]. The discrepancies in findings may be attributed to variations in study design, dosage and duration of supplementation, as well as differences in the baseline vitamin D status of participants. It is also possible that vitamin D and calcium supplementation alone may not be sufficient to induce significant changes in reproductive outcomes, suggesting the need for adjunctive therapies or lifestyle interventions.

Implications for Practice

The findings of this systematic review have several implications for clinical practice in managing PCOS. Healthcare providers should consider integrating vitamin D and calcium supplementation as adjunctive therapies for women with PCOS, especially those with metabolic disturbances or menstrual irregularities. Regular monitoring of metabolic parameters and menstrual cycle regularity can help assess treatment response and adjust supplementation regimens accordingly. Additionally, healthcare professionals should address modifiable risk factors such as obesity, physical inactivity, and socio-economic status to optimise treatment outcomes and improve overall health in women with PCOS.

Future Recommendations

Despite the promising findings, further research is needed to better understand the role of vitamin D and calcium supplementation in managing PCOS. Future studies should focus on the mechanisms underlying the observed effects of supplementation, including potential interactions with hormonal and metabolic pathways. Long-term, RCTs with larger sample sizes are needed to establish the efficacy and safety of supplementation and determine optimal dosing regimens. Additionally, research on the impact of supplementation on fertility and pregnancy outcomes in women with PCOS would provide valuable insights into the broader effects on reproductive health.

Limitation(s)

While this systematic review provides important insights into the effects of vitamin D and calcium supplementation in women with PCOS, several limitations should be acknowledged. The heterogeneity in study designs, participant characteristics, and outcome measures across included studies may limit the comparability and generalisability of the findings. Additionally, the potential for publication bias and selective reporting cannot be completely ruled out, which may affect the strength of the evidence base. Furthermore, the review may be subject to inherent biases in the selection and interpretation of studies, despite efforts to minimise bias through systematic methodology and careful quality assessment. These limitations underscore the need for a cautious interpretation of the findings and highlight the importance of continued research to address remaining gaps in knowledge regarding supplementation strategies for PCOS.

CONCLUSION(S)

In conclusion, while there is evidence to suggest that vitamin D and calcium supplementation may improve metabolic status in women with PCOS, the effects on menstrual cycle regularity and follicular response remain inconclusive. Given the heterogeneity of PCOS and the variability in study findings, a personalised approach to supplementation, considering baseline vitamin D status and individual metabolic and reproductive profiles, may be warranted. Further research is needed to elucidate the optimal dosage, duration, and combination of supplements for improving both metabolic and reproductive outcomes in women with PCOS.

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