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REVIEW ARTICLE

Vitamin D Supplementation and Longer-Term Endometriosis-Associated Pain Outcomes: A Systematic Review

Anushree Ashokkumar[1, ID*], Ruchi Bhikaji Gawde[1, ID], Sohana Parvin[1, ID], Tanisha Fernandes[1, ID], Ayushi Sawant[1, ID]
[1] Faculty of Medicine, SEU Georgian National University, Tbilisi, Georgia

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ABSTRACT

Endometriosis is a chronic inflammatory condition that is known to be associated with severe pelvic pain and dysmenorrhea. Vitamin D has potential anti-inflammatory and immunomodulatory effects that may influence these outcomes. This review aimed to assess the effects of vitamin D supplementation on longer-term endometriosis-associated outcomes, defined as pain assessed at six months or longer from baseline or beginning of treatment. The methodology involved searching databases such as PubMed and Scopus from October 2025 through January 2026, identifying 604 records, of which three met the inclusion criteria. Studies including women with diagnostically confirmed endometriosis, vitamin D supplementation, and reporting pain outcomes like dysmenorrhea and pelvic pain, with a follow-up of at least six months, were considered. We excluded case reports, editorials, reviews, animal studies, and in vitro studies, as well as studies involving women without diagnostically confirmed endometriosis.

Additionally, the risk of bias assessment indicates that both RCTs show some overall concerns of bias. The non-randomized study was rated as having a serious risk of bias, mainly due to participant selection, intervention classification, deviation from intended interventions, and outcome measurement. The results mainly include three studies that met the inclusion criteria, one non-RCT and two RCTs. It was observed that vitamin D showed slight improvement in pelvic pain and dysmenorrhea. The current studies are insufficient to confirm whether vitamin D can effectively improve endometriosis-associated pain outcomes. Findings across studies remain inconsistent, with substantial improvement also observed in placebo and no statistically significant between-group differences, undermining definitive conclusions. Additionally, the longer-term outcomes remain under-explored. These limitations highlight the need for well-designed trials with standardized outcome measures and a follow-up of six months or more.

Keywords. Adjunct therapy; Dysmenorrhea; Endometriosis-associated pain; Long-term effects; Pelvic pain; Vitamin D supplementation.

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INTRODUCTION

Endometriosis is a chronic inflammatory condition in which endometrium-like tissue grows outside the uterus. It affects approximately 10% (190 million) of reproductive-age women globally.[1] There were approximately 22.28 million cases of endometriosis reported globally, with women in the age group 25 to 29 years being the most widely affected group.[2] According to the Global Burden of Disease Study 2023, endometriosis represents a significant health burden globally. However, its true magnitude is likely underestimated because of diagnostic delays and varying healthcare access across regions. According to the 2023 GBD data, endometriosis accounted for approximately 1.9 million DALYs globally among females, with a rate of 47.48 per 100,000 females, reflecting the substantial long-term disability burden.[3] Additionally, the prevalence of endometriosis varies considerably depending on the clinical presentation. It is identified in 48–80% of patients presenting with lower abdominal pain and in 20–48% of those experiencing infertility. Notably, in younger populations and adolescents with chronic lower abdominal pain refractory to conventional analgesic therapy, prevalence can reach 70%. Despite this, endometriosis often remains absent from clinical consideration until late in the diagnostic process.[4]

Endometriosis is characterized by symptoms like chronic pelvic pain, dysmenorrhoea, and dyspareunia,[5] causing major deviation in the quality of life and a very high economic burden. Due to the wide heterogeneity of symptoms, the diagnosis of endometriosis can be difficult. Evidence suggests diagnostic delays of 6.7 to 11.7 years between symptom onset and confirmed diagnosis. This diagnostic delay could lead to suboptimal care that results in worse quality of life for women ultimately diagnosed with the disease, as well as significant healthcare costs.[6]

Given its association with anti-inflammatory, immunomodulatory, and anti-proliferative processes, Vitamin D has been emphasized as a potential supplement for treating endometriosis and improving symptoms, as it may enhance cellular apoptosis and reduce inflammation;[7] however, clinically supporting evidence remains limited.

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As per the ESHRE guidelines, the current management of endometriosis-associated pain includes NSAIDs or other analgesics, either alone or combined with hormonal treatments; combined hormonal contraceptives, progestogens, GnRH agonists, and GnRH antagonists constitute the hormonal options. Shared decision-making and an individualized approach are recommended when selecting an option based on patient preferences, side-effect profile, efficacy, cost, and availability.[8] Additionally, chronic use of GnRH may result in side effects that may arise because of a fall in estrogen levels, causing patients to experience symptoms like hot flashes, bone loss, and vaginal dryness.[9] Furthermore, the hormonal therapies are considered to have contraceptive outcomes; pain and lesions tend to reappear after treatment is stopped.[10] This may limit the patient's adherence to the already existing hormonal therapies. Surgical methods like hysterectomy may help reduce the symptoms. However, they may not be preferred by patients, as they impede fertility.[11] Additionally, the probability for endometriosis-related pain to recur after surgical interventions is projected to be around 40-50% within 5 years.[12]

Inflammatory and immune pathways contribute to endometriosis pathophysiology and provide a biological rationale for investigating immunomodulatory interventions.[12] The endometrial lesions contain immune cells which possess vitamin D receptors (VDR), with the capacity to convert vitamin D into its metabolically active form locally. Thus, vitamin D can bind to these receptors at the disease site.[13] This may provide a physiological relevance for investigating vitamin D intervention during the course of disease treatment; however, the clinically supporting evidence remains limited.

Kalaitzopoulos (2022)[14] and Zheng (2023)[15] have focused primarily on vitamin D as a standalone treatment and suggest that its clinical significance may be limited. However, these reviews did not comprehensively assess vitamin D's potential role as an adjuvant therapy alongside standard hormone therapies, highlighting an important gap in the literature.

Because endometriosis-associated pain is chronic, we considered a minimum follow-up of six months from baseline pain or treatment initiation necessary to assess any long-term sustained effects of vitamin D supplementation, as short-term evaluations may fail to capture clinically relevant changes in symptom progression. This systematic review aims to assess the potential effects of longer-term outcomes following vitamin D supplementation on the symptoms, including pelvic pain and dysmenorrhea, in women with endometriosis, with its specific role as an adjunctive therapy alongside standard hormonal therapies and as a standalone intervention, which appears to be under addressed in the existing literature.

REVIEW

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines and is registered under PROSPERO ID: CRD420251147450. The aim was to understand the effects of vitamin D supplementation on longer-term endometriosis-associated symptoms like pelvic pain and dysmenorrhea, with pain outcomes assessed at six months or longer.

We searched databases from October 2025 to January 2026, and database-level filters restricted studies to English-language papers published between 2012 and 2025 that included human participants. The inclusion criteria also focused on RCTs, prospective cohort studies, and non-randomized interventions. We restricted the search to studies published between 2012 and 2025 to capture emerging evidence on vitamin D supplementation and reflect recent shifts in clinical interest in endometriosis management. We excluded earlier studies, which may have omitted relevant evidence; we acknowledge this limitation. At title and abstract screening, we excluded case reports, reviews, and editorials. At full-text review, we excluded animal and in vitro studies, as well as studies not confined to women of reproductive age with laparoscopically or surgically confirmed endometriosis.

We studied vitamin D supplementation in any form (oral or parenteral). We compared it with placebo or standard-treatment controls to assess primary outcomes, including pain at six months or longer from baseline or treatment initiation, and secondary outcomes such as pain frequency and quality of life; the original protocol planned to review three databases: PubMed, Scopus, and Cochrane. However, due to limited institutional access, the final search included only PubMed and Scopus, which deviates from the registered protocol. Limited access to Cochrane may have reduced the number of studies included, as certain RCTs or systematic reviews uniquely indexed in the Cochrane Library may not have been captured, potentially limiting the search's comprehensiveness. While PubMed and Scopus index a vast number of MEDLINE journals, they do not replace a direct search of CENTRAL or other clinical

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trial registries, and the search may be less comprehensive than originally planned.

Additionally, we searched ClinicalTrials.gov using the same key terms; however, we identified no additional trials meeting the inclusion criteria beyond those captured through PubMed and Scopus. We also manually screened the reference lists of the included studies for additional eligible studies; however, we identified no further studies meeting the strict inclusion criteria. We did not search Embase and Web of Science because we lacked institutional access. The PubMed and Scopus searches were conducted using the following MeSH: PubMed: "Endometriosis" [MeSH] OR "Endometriosis" [tiab]) AND ("Vitamin D supplementation" "[tiab] OR "Cholecalciferol" "[MeSH] OR "Ergocalciferol" "[MeSH] OR "cholecalciferol" "[tiab] OR "ergocalciferol" "[tiab]) AND ("pelvic pain" "[MeSH] OR "dysmenorrhea" "[MeSH] OR "chronic pelvic pain" "[tiab] OR "dyspareunia" "[tiab]; Scopus-(TITLE-ABS-KEY (endometriosis)) AND (TITLE-ABS-KEY ("vitamin D" OR cholecalciferol OR ergocalciferol OR "vitamin D supplementation"). We ran an updated search before resubmission and found no new studies.

We added spelling variants of key terms, such as cholecalciferol/cholecalciferol, to account for differences in terminology across the literature. The PubMed strategy included outcome-specific terms like pelvic pain, dysmenorrhea, and dyspareunia as required search components. The Scopus search strategy, however, did not restrict results to outcome terms. Scopus searched more broadly for endometriosis and vitamin D-related studies, so PubMed may have excluded studies that reported relevant outcomes (e.g., QoL measures or unlabeled pain scores). This explains the asymmetry in search sensitivity across databases. We acknowledge this inconsistency as a limitation of the search strategy.

Two authors independently screened titles and abstracts, then full texts, and resolved disagreements through discussion. Two reviewers extracted the data, with each collecting data from a pre-assigned subset of included studies. We used a prespecified extraction template in the form of an Excel sheet to capture the study design, sample size, participant demographics, intervention and comparator details, treatment duration, follow-up duration, pain scale, outcome time points, and effect estimates. The authors did not prespecify an outcome hierarchy distinguishing primary and secondary outcomes; they included pelvic pain and dysmenorrhea as co-primary outcomes because they are relevant to the review question. The number of studies identified and screened is structured in the PRISMA 2020 flow diagram.

We present key data from the included studies in a standardized data extraction **TABLE 1**.

TABLE 1. Summary of the data extraction of the included studies

Author	Year	Study design	Total number of patients	Mean age	Endometriosis stage	Diagnostic method	Baseline 25(OH)D	Final 25(OH)D
Yarmolinskaya[16]	2021	Comparative	217 (cholecalciferol +HMT) vs 200 (HMT), total 440 women with genital endometriosis reproductive age	Not reported	I-IV-degree GE	Laparoscopic, confirmed morphological lay (surgical + histological)	Peripheral blood: 22.1ng/mL (GE group) vs 36.0 ng/mL (control). Not reported separately for the two treatment-comparison groups	Not reported
Almassinokiani[7]	2016	Double blind RCT	39	29.89±5.30	Not quantified by stage	Laparoscopic confirmation	Not measured	Baseline levels not assessed (trial authors note that there is High prevalence of vitamin D deficiency in Iran where the study was conducted
Nodler[18]	2020	Double blind RCT	69 (Placebo= 22, vit D= 27, fish oil = 20)	12-25 years (mean/median not reported)	Majorly stage I and II	Surgical confirmation	Measured but only as an exclusion filter (>=100 ng/mL excluded)	Measured at 6 months to verify patient compliance only

The risk of bias assessment was conducted using the Cochrane Risk of Bias tool for the RCTs and ROBINS-I for the non-RCTs by two independent reviewers.[19,20]

Study selection

Following the strict inclusion criteria, the search identified 604 records from all databases (PubMed, n=552; Scopus, n=52). After removing duplicates, we 6

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articles. We screened the titles and abstracts of these 598 studies and excluded 568 at this stage because they were not related to either Vitamin D or Endometriosis (n=560), were non-English publications (n=1), were systematic reviews/meta-analyses/case reports (n=4), or had no abstract available (n=3). We assessed the remaining 30 articles in full text. We excluded 6 at this stage because only abstracts were available, despite multiple attempts to retrieve the full text through institutional and publicly accessible sources. We did not contact the authors to request full-text access, so we cannot determine whether including them would have altered the findings of this review. After the full-text screening of the remaining 24 articles, 21 were excluded because of inappropriate intervention (n=10), inappropriate study design, including cross-sectional, in vitro, and animal studies (n=1), no laparoscopically confirmed diagnosis (n=2), follow-up less than 24 weeks (n=3), and no vitamin D supplementation of any kind (n=5). Three articles met the inclusion criteria and were included. The detailed study selection process will be presented in the PRISMA flow diagram.

Study characteristics

The included studies ranged from 2016 to 2021 and were assessed to understand patterns in the effects of vitamin D supplementation in women with a confirmed diagnosis of endometriosis. The included studies comprised two double-blind RCTs and one non-RCT.[16-18]

A non-randomized comparative trial included 217 women of reproductive age with laparoscopically diagnosed and morphologically confirmed genital endometriosis (GE I-IV) who received cholecalciferol combined with standard hormone-modulating therapy, compared with 200 women who received only hormone-modulating therapy, drawn from a cohort of 440 women assessed for vitamin D levels. After a six-month follow-up, the combined therapy reduced pain more than HMT alone, as measured by the percentage of patients reporting symptom relief. The data extraction table summarizes the key findings. (**TAB.1**).

This study did not assess or report adverse events. A major strength of this study is its six-month follow-up and its adjunct-therapy design, with reasonably sized comparison groups (217 vs 200) compared with other included studies. However, the lack of reported statistical significance values, along with baseline pain and a serious risk of bias, limits the ability to confirm the positive outcomes.

Almassinokiani[17] conducted a double-blind RCT randomly assigning 39 women with laparoscopically confirmed endometriosis, with a mean age of 29.89±5.30 years, to the vitamin D group (n=19) and the placebo group (n=20). Participant demographics have been detailed in **TABLE 2**. The vitamin D group received 50,000 IU oral vitamin D3 weekly for 12 weeks, while the placebo group received identical placebo capsules. After 24 weeks of follow-up, symptoms decreased from baseline in both groups (vitamin D Δ=-3.21; placebo Δ=-4.14), with no statistically significant between-group differences ($p > 0.05$). Detailed pain and dysmenorrhea scores are presented in **TABLE 1.** This trial reported no adverse events. The study's robustness is enhanced by its double-blind design, inclusion of patients with laparoscopically confirmed endometriosis, and an overall risk-of-bias judgment with some concerns. However, the study included a small sample size, did not specify the stage of endometriosis, and the vitamin D intervention lasted only 12 weeks, despite a 24-week follow-up.

Nodler[18] conducted a double blind, multi-arm RCT, randomly assigning 69 women into a placebo group (n=22), vitamin D group (n=27), and fish oil (n=20), with an age range of 12-25 years. Participants received vitamin D3 (2000 IU) or fish oil (1000 mg) orally daily, or an identical placebo capsule, for six months. Vitamin D, placebo, and fish oil reduced pain. The trial concluded that neither vitamin D nor fish oil differed significantly from placebo, although the within-group reductions with vitamin D reached statistical significance. **TABLE 1** presents the pain score details. This trial reported no adverse events. The multi-arm design, active comparator, and six-month follow-up strengthen the study's credibility. However, unequal group sizes and no statistically significant between-group differences may limit evidence for vitamin D superiority over placebo.

We assessed risk of bias for the RCTs using the Cochrane RoB 2 tool and found concerns in both studies due to deviations from the intended intervention. For the non-RCT, we used the ROBINS-I tool and found a serious risk of bias due to participant selection, which may limit generalizability; individualized dosing, poor adherence, and unblinded outcome measurement may have inflated the reported benefit. Thus, the 92.3% vs 77.7% pain relief finding should be interpreted cautiously.

TABLES 2 and **3** present the risk-of-bias assessment for the three included studies.

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TABLE 2. Randomized controlled trials (The Cochrane risk-of-bias tool for randomized trials, RoB 2)

Study	Bias due to randomization	Bias due to deviations	Bias due to missing outcome data	Bias in measurement of the outcome	Bias due to reporting of the result	Overall bias
Almassinokiani (2016)[17]	Low	Low	Some concerns	Low	Low	Some concerns
Nodler (2020)[18]	Low	Low	Some concerns	Low	Low	Some concerns

TABLE 3. Non-randomized controlled trials (ROBINS-I stands for Risk of Bias in Non-randomized Studies - of Interventions)

Study	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of outcomes	Bias in selection of reported result	Overall bias
Yarmolinskaya (2021)[16]	Serious	Serious	Serious	Serious	Serious	Serious	Low	Serious

We assessed evidence certainty using GRADE's 5 downgrading domains because we could not perform a meta-analysis. For pelvic pain, the RoB for both RCTs raises concerns, and the non-RCT shows a serious RoB. Yarmolinskaya[16] suggests benefit, while Almassinokiani[17] and Nodler[18] show no benefit over placebo, indicating directional inconsistency. Different dosing regimens, different populations (adolescents in Nodler vs. adults elsewhere), and different comparators (placebo vs. hormone therapy might give rise to indirectness. Very small sample sizes (n=39, n=69 for RCTs) and wide/uncertain CIs where reported might have led to imprecision. Publication bias could not be assessed with only three studies included. Thus, starting from high (RCTs)/Low (non-RCTs) with multiple downgrades across the board, the certainty could be very low. For dysmenorrhea, RoB indicates some concerns in Almassinokiani's dtudy.[17] Inconsistency could not be assessed (single study). The trial was small and had a narrow population so that indirectness may have developed; the very small sample size (n=39) and wide uncertainty may also have led to imprecision. Thus, the certainty appears very low. Quality of life was a prespecified secondary outcome. However, it was not reported in Almassinokiani's[17] or Yarmolinskaya's[16] studies and was only indirectly addressed in Nodler's study[18] (physical/mental QoL, catastrophizing), but not as a primary outcome. Thus, we could not grade certainty because insufficient data were reported. Adverse events were not systematically assessed; therefore, we could not grade certainty. **TABLE 4** summarizes the certainty assessment.

TABLE 4. Certainty assessment

Outcome	Number of studies	Certainty	Reason for downgrading
Pelvic pain	3	Very low	RoB, inconsistency, indirectness, imprecision
Dysmenorrhea	1	Very low	RoB, indirectness, imprecision
Quality of life	0 studies with usable data	No usable evidence	Outcome not tradable due to absence of usable data
Adverse events	0 studies with usable data	No usable evidence	Outcome not tradable due to absence of usable data

Effects of vitamin D on pelvic pain

To assess the effects of vitamin D intervention on pelvic pain, we reviewed three studies. The evidence originates from two double-blind RCTs and one non-randomized comparative study. Pelvic pain improved slightly across all intervention arms, including placebo. However, vitamin D did not consistently outperform the placebo.

Both RCTs[17,18] observed symptom improvements, including pelvic pain, in both the vitamin D intervention and placebo arms, but there were no significant between-group differences. Yarmolinskaya[16] however, suggested using vitamin D as an adjunct therapy; nonetheless, it reported no statistically significant differences. Nodler[18] observed reductions in pain across all the arms (vitamin D 7.0→5.5, Δ=-1.5; placebo 6.0→4.4, Δ=-1.6; fish oil 5.9→5.2, Δ=-0.7). The trial concluded that vitamin D was not significantly different from placebo, as placebo's absolute reduction was numerically larger than vitamin D's. Thus, the trial did not establish vitamin D superiority over placebo. Evidence on dysmenorrhea outcomes was limited, with only one small double-blind RCT reporting effects. Almassinokiani[17] observed that dysmenorrhea improved in both vitamin D and placebo groups (vitamin D 7.37→2.10, Δ=-5.27; placebo 6.42→2.73, Δ=-3.69). Vitamin D showed a greater decline, though

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the differences did not reach statistical significance (p=0.45).

The included studies did not report other endometriosis-related symptoms, including dyspareunia or quality of life.

Comparison with existing evidence

The review focuses on synthesizing the long-term pain outcomes assessed at six months or longer following vitamin D supplementation on endometriosis-associated pain symptoms like dysmenorrhea and pelvic pain. After applying the strict inclusion criteria, we included only three studies because evidence of longer-term follow-up is limited. Although the studies with short-term follow-up periods are large in number, they may fail to assess the chronic nature of endometriosis-associated pain adequately. We could not conduct a meta-analysis for several reasons. Of the three included studies, only two were RCTs (Almassinokiani,[17] Nodler[18]); pooling data from just two studies may yield imprecise estimates.

Additionally, the third study[16] reported outcomes as categorical percentages rather than continuous VAS scores, which excluded direct quantitative synthesis with the two RCTs. Furthermore, clinical heterogeneity arose from differences in dosing regimens, treatment duration, and comparator design, which may have complicated interpretation of any pooled data. Thus, we used a structured narrative synthesis. Additionally, substantial improvement in placebo arms across all included studies complicates interpretation and must be considered when concluding.

Systematic reviews show overall pain reduction in both intervention and control groups, with some studies showing greater improvement in placebo arms than vitamin D, while others report symptom-specific improvements. Findings from a non-RCT suggest an additional benefit of vitamin D for pelvic pain reduction. While Yarmolinskaya16 reported a strong association between peritoneal fluid levels and disease morbidity (p=0.004), the study did not provide a significance test for the clinical outcome difference between the two arms. This highlights a need for more rigorous, well-structured RCTs in the future. Consequently, one small RCT reported improved endometriosis-associated dysmenorrhea. Across all three included studies, both intervention and control groups showed an overall reduction in pain. However, vitamin D did not consistently outperform placebo in either pelvic pain or dysmenorrhea outcomes. Almassinokiani[17] reported comparable reductions in both groups (vitamin D Δ=-3.21; placebo Δ=-4.14) but no statistically significant between-group differences (p=0.513). Nodler[18] observed reductions in pain across all the arms (vitamin D 7.0→5.5, Δ=-1.5; placebo 6.0→4.4, Δ=-1.6; fish oil 5.9→5.2, Δ=-0.7), with placebo's absolute reduction exceeding that of vitamin D. The trial concluded that neither vitamin D nor fish oil differed significantly from placebo, which limits conclusions about the superiority of vitamin D over placebo. Yarmolinskaya16, the only non-RCT, suggests an additional benefit of vitamin D with respect to pelvic pain reduction by combining vitamin D and hormone therapy group compared to hormone therapy alone. However, the study did not test whether the clinical outcome difference between the two arms was statistically significant. Given the serious risk of bias associated with this non-RCT, interpret its findings with considerable caution.

The improvement observed in placebo/control arms across the included studies may reflect natural postoperative recovery, other non-specific therapies, the placebo itself, regression to the mean, or a true placebo response. This complicates the findings and may mask the true treatment effects. Therefore, any conclusion about vitamin D's efficacy must be made with caution.

Previous studies have focused on vitamin D as monotherapy, with little support for adding it to standard treatment. Evidence from a recent systematic review examining the effects of vitamin supplementation on endometriosis-associated pain found that vitamin D monotherapy was insufficient in reducing significant pelvic pain and dysmenorrhea.[21]

This supports the basis of the present review, in which one of the three included studies examined vitamin D as an adjunct to the standard hormone therapy. In contrast, the remaining two studies evaluated it as a standalone intervention. This highlights a gap in the literature: adjunctive evidence has not been comprehensively explored.

The effect of vitamin D supplementation on endometriosis has been examined in several recent systematic reviews. Zhou[22] in a review of seven RCTs, reported that two RCTs found significantly lower pain severity and primary dysmenorrhea in people prescribed vitamin D than in those receiving placebo. However, these studies had small sample sizes and short follow-up periods of about two months, limiting the applicability of their findings to chronic pain management in endometriosis-associated pain. Similarly, Zheng[15] in a review of thirteen RCTs, found that one RCT used a six-month dosing protocol and observed pain reduction in the vitamin D group;

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however, this reduction was not significantly greater than in the placebo group. Both reviews were further limited by considerable heterogeneity across included studies. Furthermore, previous studies have examined vitamin D only as a standalone monotherapy, without evaluating its role as an adjunct to standard hormone therapy. The 2022 ESHRE guidelines also note a similar pattern in the evidence for nutritional and dietary approaches including vitamin D, thus highlighting its insufficiency to support a specific clinical recommendation.[8] The present review addresses this gap, highlighting that only limited evidence currently evaluates vitamin D's potential ability to act as an adjunct to standard treatment in real-world practice.

Study limitations

This review has limitations because it includes few eligible studies, vitamin D dosing varies, and database access is limited. Furthermore, limited institutional access to the Cochrane Library may reduce the review's comprehensiveness. Specifically, for Yarmolinskaya,[16] the serious risk of bias identified across multiple domains, including participant selection, intervention classification, deviations from the intended intervention, and outcome measurement, suggests that the reported pain-relief difference (92.3% vs 77.7%) should be interpreted with caution. Additionally, unblinded outcome measurement along with inconsistent vitamin D administration may have amplified the observed benefits. No minimally clinically important difference (MCID) has been established for VAS pain specifically in endometriosis-associated pain populations, which may limit the ability to determine whether observed changes in pain scores across studies represent clinically meaningful improvement independent of statistical significance. These limitations may restrict interpretation, but they highlight important gaps and underscore the need for well-structured long-term trials.

Despite the substantial improvement observed in control arms, vitamin D's potential ability to modify the inflammatory effects suggests a strong need for long-term studies. Future clinical trials should assess vitamin D as an adjunct to standard treatments for pain outcomes, with a minimum six-month follow-up, while cautiously accounting for the substantial improvement also observed in control arms.

CONCLUSIONS

This systematic review focused on the effects of vitamin D supplementation on the longer-term endometriosis-associated pain outcomes. With only three studies meeting the inclusion criteria, and small sample sizes across all included studies, the current evidence is insufficient to establish a clinically meaningful benefit of vitamin D for endometriosis-associated pain. In both included RCTs, placebo responses matched or exceeded the vitamin D group, suggesting the observed improvements cannot be attributed to vitamin D alone. Evidence also suggests that vitamin D as a monotherapy may be insufficient, highlighting the need for further evidence for its role as an adjunct to standard hormone therapy, an area addressed by only one of the three included studies. Because the studies show substantial improvement in placebo/control arms, conclusions about the efficacy of vitamin D must be drawn with considerable caution. This review calls for future well-designed, adequately powered, long-term randomized controlled trials that evaluate vitamin D as both an adjunct to standard hormone therapy and a standalone intervention, categorized by baseline vitamin D status, and that address the imbalance between the chronic nature of endometriosis and the short follow-up periods in the literature.

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