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Effect of zinc supplementation on premenstrual symptoms: A systematic review and meta-analysis

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ABSTRACT

This systematic review and meta-analysis aimed to evaluate the efficacy of zinc supplementation for alleviating premenstrual symptoms (PMS) in women of reproductive age. A literature search was conducted across six electronic databases. Five randomized controlled trials were included in the qualitative synthesis and four were eligible for meta-analysis. All studies had some concerns for risk of bias. The certainty of the evidence was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation framework. Zinc supplementation reduced total PMS scores and emotional symptoms with moderate certainty of evidence, while physical symptoms were supported by low certainty of evidence. Meta-analyses revealed that zinc supplementation significantly reduced total PMS scores (Hedges's g = −0.384), emotional symptoms (g = −0.347), and physical symptoms (g = −0.512), all favoring the intervention. Sensitivity analyses confirmed the robustness of results for the total and emotional domains, but the effect sizes for physical symptoms were moderately influenced by individual studies. In conclusion, zinc supplementation shows promise as a non-pharmacological intervention for reducing PMS. However, its generalizability is limited by the small number of trials and methodological heterogeneity. Further, multicenter RCTs with standardized protocols are warranted to establish clinical utility and explore dose – response relationships.

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Dietary supplements; meta-analysis; premenstrual syndrome; reproductive-aged women; zinc

Introduction

Premenstrual symptoms (PMS) encompass various emotional issues, including depression, insomnia, irritability, and crying spells, alongside physical symptoms, such as breast tenderness, gastrointestinal disturbances, headaches, and fatigue, occurring cyclically during the luteal phase of the menstrual cycle (American College of Obstetricians and Gynecologists [ACOG] 2023). These symptoms can significantly interfere with a woman's daily functioning, negatively affecting her quality of life and academic or occupational tasks (Al-Shahrani et al. 2021; Branecka-Woźniak, Cymbaluk-Płoska, and Kurzawa 2022). Approximately 47.8 percent of women of reproductive age experience PMS (Modzelewski et al. 2024).

Pharmacological treatment for PMS includes selective serotonin reuptake inhibitors, hormonal therapies, and combined oral contraceptives (Yonkers, Ireland, and Truehart 2023). For individuals with mild symptoms or those seeking non-pharmacological options, lifestyle interventions such as dietary modifications and routine moderate exercise are commonly recommended (Carlini et al. 2022; Yurt, Mercanlıgil, and Kabaran 2020). Oral complementary medicines, including herbal remedies, vitamins, minerals, and omega-3 fatty acids, have also been used, but the literature is limited due to lack of high-quality evidence (Carlini et al. 2022; Csupor et al. 2019; Mohammadi et al. 2022).

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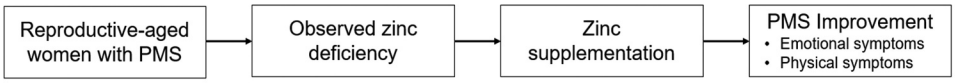


Figure 1. Structured overview of zinc supplementation and its effects on PMS. PMS = Premenstrual Symptoms

Serum zinc levels in women fluctuate significantly throughout the menstrual cycle, suggesting a potential role of zinc in reproductive physiology and cyclic symptoms (Ahmadi et al. 2023). Studies have reported that women with PMS exhibit significantly lower serum zinc levels compared to women without PMS (Fathizadeh et al. 2016; Küçükkasap Cömert et al. 2022), suggesting that zinc deficiency may contribute to the pathophysiology of PMS (Tiranini and Nappi 2022). Several randomized controlled trials (RCTs) have evaluated the effects of zinc supplementation on PMS, with inconsistent findings. Some studies have reported significant improvements in specific symptoms such as vertigo and impaired daily activities, while others found no significant effects on symptoms such as headache, nausea, or vomiting (Jafari, Amani, and Tarrahi 2020; Sangestani et al. 2015). Furthermore, small sample sizes, heterogeneity in dosage and intervention duration, and variations in symptom assessment tools across studies limit the integrated interpretation of results. Although previous reviews have examined the effects of diet and nutritional interventions on PMS (Carlini et al. 2022; Oboza et al. 2024; Robinson et al. 2025), none have specifically focused on zinc supplementation as a standalone intervention. To the best of our knowledge, no previous meta-analysis has quantitatively synthesized the effects of zinc on PMS. Figure 1 provides a structured overview of the hypothesized pathway linking zinc deficiency in women with PMS to symptom improvement through zinc supplementation.

This study aimed to systematically review existing RCTs on zinc monotherapy for relieving PMS in reproductive-aged women and to quantitatively evaluate its clinical efficacy through a domain-specific meta-analysis. By synthesizing fragmented and inconsistent evidence, it seeks to support evidence-based non-pharmacological PMS treatments.

Materials and methods

Study design

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Supplementary Table 1) and was prospectively registered with International Prospective Register of Systematic Reviews (PROSPERO) under registration number [CRD42025631801]. Methodological procedures were designed to ensure transparency and reproducibility throughout the review process.

Search strategy

A comprehensive literature search was conducted on January 8, 2025, across six electronic databases: PubMed, EMBASE, CINAHL, Web of Science, Scopus, and Cochrane Central Register of Controlled Trials (CENTRAL), using terms related to "premenstrual syndrome," "premenstrual dysphoric disorder," and "zinc." The full search strategy is shown in Supplementary Table 2. To maximize sensitivity, no restrictions were applied on language, publication date, or article type. Additionally, the reference lists of all the included studies were manually screened to potentially relevant articles missed in the initial search.

Study selection

Titles and abstracts of articles from electronic databases and manual searches were screened against predefined inclusion criteria. Full texts of potentially eligible studies were reviewed using the same

criteria. Two reviewers conducted the selection process independently to minimize bias and ensure objectivity, with interrater agreement evaluated using Cohen's kappa statistic.

Eligibility criteria

We applied the PICOS framework (Population, Intervention, Comparator, Outcome, and Study design) to define eligibility criteria. Studies were eligible if they included women of reproductive age (P); zinc supplementation as the intervention (I), regardless of dosage, formulation, or duration; and a comparator (C) group receiving no intervention, usual care, or placebo. Eligible studies had to report outcomes (O) related to premenstrual symptoms, assessed using validated instruments or self-reported scales. Only RCTs were included in the study design (S) to ensure internal validity and minimize bias, given the placebo sensitivity of PMS outcomes and the aim of synthesizing causal effects quantitatively.

Risk of bias and quality appraisal

The methodological quality of the included RCTs was independently assessed by two reviewers using the revised Cochrane Risk of Bias tool for randomized trials (RoB 2.0) (Sterne et al. 2019). This tool evaluates five domains of potential bias: (1) bias arising from the randomization process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in outcome measurement, and (5) bias in the selection of reported results. Each domain was rated as low risk, some concerns, or high risk, and the overall risk of bias was assigned accordingly. Inter-rater agreement between the two reviewers was assessed using Cohen's kappa (κ) statistic, with κ values greater than 0.6 interpreted as acceptable agreement (McHugh 2012). Statistical significance was evaluated using the p-value associated with κ. Discrepancies in judgments were resolved through discussion and consensus.

To determine the overall certainty of the evidence for each outcome, the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework was employed (Guyatt et al. 2008). Evidence quality was evaluated using the GRADEpro Guideline Development Tool (GRADEpro GDT) (Schünemann et al. 2022), considering five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Evidence certainty was rated as high, moderate, low, or very low, depending on the extent and severity of the downgrading criteria.

Data extraction and synthesis

Data extraction utilized a structured form developed by the authors, incorporating relevant variables from prior reviews. Items extracted included study design, participants, sample size, age, zinc dosage, control conditions, intervention details, PMS measurement tools, other outcomes, and findings. Since all required data were available, no contact with corresponding authors was needed.

A quantitative synthesis estimated the pooled effect size, with meta-analyses conducted using Comprehensive Meta-Analysis software (version 4.0; Biostat Inc., Englewood, NJ, USA). PMS were classified into two major domains based on the guidelines of the ACOG (2023): (1) emotional symptoms, including affective and behavioral features such as mood swings, irritability, sleep disturbances, and social withdrawal, and (2) physical symptoms, encompassing somatic complaints such as breast tenderness, abdominal bloating, headaches, and fatigue. For each study, symptom scores were extracted and reorganized into three categories: total PMS, emotional symptom, and physical symptom scores. The total PMS score was designated as the primary outcome, reflecting overall symptom burden. Emotional and physical symptom domain scores were treated as secondary outcomes. Because these measures were derived from the same sample, the standardized mean difference (SMD) was calculated using a fixed effects model. Between-study heterogeneity was evaluated using the I^2 statistic and Cochran's Q test. If I^2 exceeded 50 percent or the p-value of Q was less than 0.10, heterogeneity was

considered substantial, and a random-effects model was applied for the final analysis (Higgins et al. 2024). Hedges' g, a bias-corrected version of the SMD that adjusts for small sample sizes, was used to compute effect sizes. Statistical significance was determined based on 95 percent confidence interval (CI). Publication bias was not assessed due to fewer than ten studies, limiting the reliability of funnel plots and Egger's regression test (Sterne et al. 2011). Sensitivity analyses were performed by omitting individual studies to assess the robustness of the pooled estimates.

Results

Study selection

A total of 938 records were identified through the database search. After removing 395 duplicates and 95 non-original articles (e.g., reviews, editorials, and protocols), 448 records remained for title and abstract screening. Of these, 442 were excluded based on predefined eligibility criteria. Six full-text articles were reviewed for eligibility, and one non-RCT was excluded. Ultimately, five RCTs met all inclusion criteria and were included in the final review. The agreement between the two reviewers was 98.7 percent (Cohen's kappa = 0.91; Z = 9.92; $p < .001$) for title and abstract screening, and 100 percent (Cohen's kappa = 1.00; Z = ∞; $p < .001$) for full-text review. The study selection process is summarized in the PRISMA 2020 flow diagram (Figure 2).

Study characteristics

Supplementary Table 3 shows the characteristics of the studies included in this systematic review. A total of five studies were extracted (Ahmadi et al. 2023, Jafari, Amani, and Tarrahi 2020; Jafari et al. 2020; Sangestani et al. 2015; Siahbazi et al. 2017), with two using the same dataset (Jafari, Amani, and Tarrahi 2020; Jafari et al. 2020), yielding four unique studies. All included studies were conducted in Iran and were published between 2015 and 2023. A total of 340 participants were randomized across the four unique studies, with 322 included in the final analyses due to attrition in some studies. Participants' mean age ranged from 21.5 to 25.6 years, and all were women of reproductive age diagnosed with premenstrual syndrome (Ahmadi et al. 2023, Jafari, Amani, and Tarrahi 2020; Jafari et al. 2020; Siahbazi et al. 2017) or primary dysmenorrhea (Sangestani et al. 2015).

All interventions involved oral zinc supplementation with daily doses of 30–100 mg of elemental zinc, taken once or twice daily. The intervention durations varied, including 4 days before menstruation for two menstrual cycles (Sangestani et al. 2015), daily from day 16 to day 2 of the next cycle over three consecutive cycles (Siahbazi et al. 2017), and continuous supplementation for 12 weeks (Ahmadi et al. 2023; Jafari, Amani, and Tarrahi 2020; Jafari et al. 2020).

Premenstrual symptoms were assessed using self-report questionnaires such as the Premenstrual Symptoms Screening Tool (PSST) (Siahbazi et al. 2017) and its adolescent version (PSST-A) (Ahmadi et al. 2023), each comprising 14 items on mood, physical, and behavioral symptoms, and 5 items assessing functional impairment. Other studies employed a Diagnostic and Statistical Manual of Mental Disorders (DSM)-based PMS symptom checklist comprising 30 items covering psychological and physical symptoms (Jafari, Amani, and Tarrahi 2020; Jafari et al. 2020), or evaluated the presence or absence of PMS by assessing ten individual symptoms without severity scaling (Sangestani et al. 2015). Additional outcomes assessed included serum zinc concentrations, oxidative stress markers, quality of life, sleep quality, dysmenorrhea severity, menstrual characteristics, medication use and non-pharmacological therapies, and health-care utilization.

Quality assessment

The risk of bias was assessed using RoB 2.0, and the results are presented in Supplementary Figure 1. The most frequently noted concern was deviation from intended interventions. Four studies (Ahmadi et al.

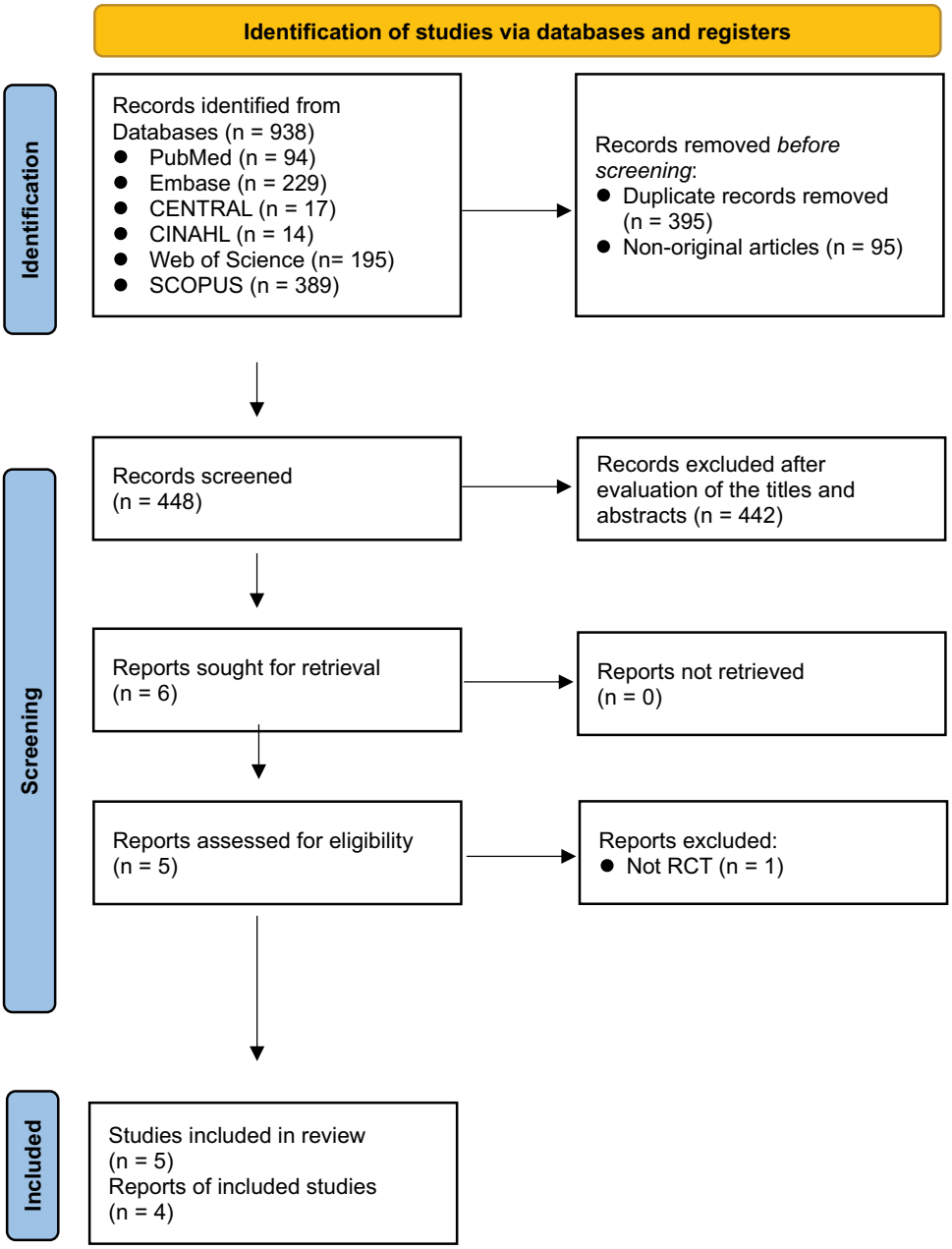


Figure 2. Preferred reporting items for Systematic Reviews and meta-analysis (PRISMA) flow diagram.

2023, Jafari, Amani, and Tarrahi 2020; Jafari et al. 2020; Siahbazi et al. 2017) employed a per-protocol analysis, which may fail to account for deviations between the intended and actual interventions and were therefore rated as having concerns in this domain. Additionally, in the randomization process domain, two studies (Sangestani et al. 2015; Siahbazi et al. 2017) were rated as having some concerns because of insufficient information regarding the generation and concealment of the allocation sequence. All other domains were assessed as low-risk. Consequently, all included studies had an overall risk of bias rated as having some concerns. The agreement between the two reviewers for risk of bias assessment was 92.0 percent, with Cohen's kappa = 0.80, Z = 6.14, $p < .001$, indicating a substantial level of inter-rater reliability.

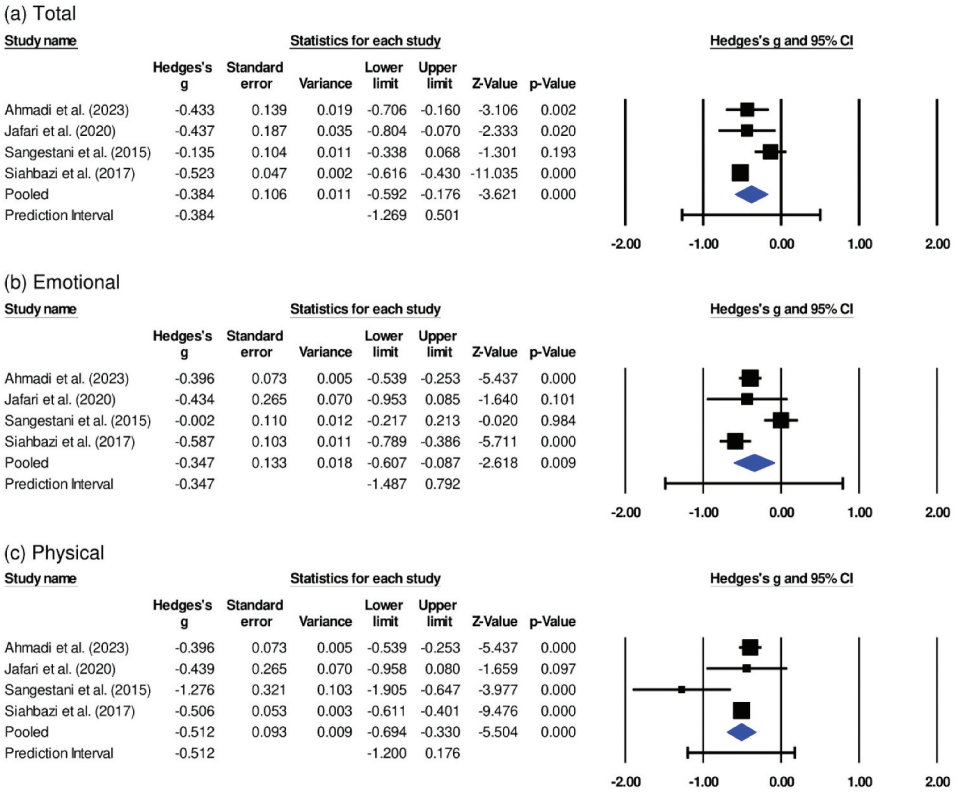


Figure 3. Forest plots of the effects of zinc supplementation on premenstrual symptoms: (a) total symptom scores, (b) emotional symptoms, and (c) physical symptoms.

Using the GRADE approach (Supplementary Table 4), the certainty of evidence for total PMS scores and emotional symptoms was rated as moderate, reflecting consistent effect direction, acceptable precision, and low risk of bias. Minor heterogeneity raised concerns about consistency. For physical symptoms, certainty was rated as low because of serious inconsistencies and imprecision, primarily attributed to the sensitivity of statistical significance in the inclusion or exclusion of certain studies during sensitivity analysis.

Results of individual studies

Of the five studies, four investigated the effects of zinc supplementation on PMS (Ahmadi et al. 2023, Jafari, Amani, and Tarrahi 2020; Sangestani et al. 2015; Siahbazi et al. 2017). The study by Jafari et al. (2020) analyzed the impact of zinc on sleep quality and quality of life in individuals with PMS, using the same dataset as Jafari, Amani, and Tarrahi (2020). The effects on PMS were presented as the results for each symptom in three studies (Ahmadi et al. 2023; Sangestani et al. 2015; Siahbazi et al. 2017), whereas one study presented the average scores for emotional and physical symptoms (Jafari, Amani, and Tarrahi 2020). In most studies, zinc supplementation reduced both psychological and physical symptoms of PMS. Additionally, zinc supplementation increased zinc levels, enhanced antioxidant capacity, and improved brain-derived neurotrophic factor (BDNF) levels (Jafari, Amani, and Tarrahi 2020). Zinc supplementation reduced dysmenorrhea severity, decreased mefenamic acid use, and positively influenced menstrual bleeding volume and local thermotherapy use (Siahbazi et al. 2017). However, while it improved physical health-related quality of life, it did not significantly affect sleep quality (Jafari et al. 2020).

Meta-analysis results

A meta-analysis was conducted on the four studies reporting PMS scores. Given the substantial heterogeneity (I^2 = 61.3–81.1 percent), a random-effects model was employed to account for variability across studies. Zinc supplementation effectively reduced the total PMS score (Hedges's g = −0.384; 95 percent CI, −0.592 to −0.176; $p < .001$; I^2 = 74.2 percent), emotional symptoms (Hedges's g = −0.347; 95 percent CI, −0.607 to −0.087; $p = .009$; I^2 = 61.3 percent), and physical symptoms (Hedges's g = −0.512; 95 percent CI, −0.694 to −0.330; $p < .001$; I^2 = 81.1 percent) (Figure 3).

Sensitivity analysis

Sensitivity analysis assessed the robustness of pooled effects on total PMS score and physical and emotional symptoms by sequentially omitting each included study (Suplementary Tables 5, 6, and 7). The direction and statistical significance of the pooled effect sizes for total PMS scores and emotional symptoms remained consistent, verifying the stability of the findings. However, in the physical symptoms domain, sensitivity analysis revealed that the pooled effect size was moderately sensitive to individual studies. Excluding either Ahmadi et al. (2023) or Siahbazi et al. (2017) led to a loss of statistical significance, although the direction of effects remained consistent. Excluding Sangestani et al. (2015) consistently reduced heterogeneity, indicating its significant contribution to between-study variance, likely because of methodological or clinical differences. Conversely, excluding the remaining studies had minimal impact on heterogeneity and effect estimates, reinforcing the reliability of results across symptom domains.

Discussion

This systematic review and meta-analysis suggests that zinc supplementation reduced total PMS score and emotional symptoms with moderate certainty of evidence compared to placebo. However, the reduction in physical symptoms occurred with low certainty of evidence. Zinc emerges as a promising non-pharmacological option, particularly for individuals seeking alternatives to conventional pharmacotherapy.

Although PMS pathophysiology remains unclear, it is hypothesized to involve oxidative stress, dysregulated inflammatory responses, serotonergic neurotransmission alteration (Fathizadeh et al. 2016; Granda, Szmidt, and Kaluza 2021; Rapkin, Korotkaya, and Taylor 2019). Zinc supplementation increases serum total antioxidant capacity, boosts BDNF levels, and enhances serotonin availability, supporting its neuroregulatory role (Jafari, Amani, and Tarrahi 2020; Jarosz et al. 2017; Siminiuc and Țurcanu 2023; Sumekar et al. 2022). Furthermore, zinc inhibits prostaglandin production, exerting anti-inflammatory effects (Ahmadi et al. 2023; Sarshin et al. 2023). These mechanisms collectively suggest a neurochemical pathway through which zinc alleviates the emotional and physical symptoms of PMS. Among the included studies, only one (Jafari, Amani, and Tarrahi 2020) incorporated biomarkers to explore zinc's neurochemical effects on PMS. To further validate these mechanistic pathways, future studies should incorporate objective biomarkers – such as inflammatory cytokines, neurotransmitter metabolites, and hormonal profiles – to elucidate the biological underpinnings of zinc's therapeutic effects. Such integrative approaches would enhance the scientific rigor of PMS research and support the development of precision-based nutritional interventions.

While the overall findings were consistent in direction, notable methodological heterogeneity was observed among the included RCTs, particularly regarding zinc dosage, intervention duration, and supplementation schedules. For instance, Ahmadi et al. (2023) administered a continuous daily dosage of 50 mg for 12 weeks, and Siahbazi et al. (2017) employed a cyclical dosage regimen of 50 mg/day during the luteal phase (day 16 to day 2 of the next cycle) for three cycles; both studies demonstrated significant improvements in total PMS scores, as well as emotional and physical symptoms. Conversely, Jafari, Amani, and Tarrahi (2020), utilizing a lower continuous dose (30 mg/day) for 12

weeks, reported limited benefits primarily in total PMS scores, with no clear improvements in emotional or physical symptoms. Sangestani et al. (2015) applied a high-dose cyclical protocol (100 mg/day for four days prior to menstruation for two cycles), yielding partial improvements limited to physical symptoms. These findings suggest that dosage and intervention duration may play a more critical role in determining treatment effectiveness than the supplementation schedule (continuous vs. cyclical). Based on current evidence, administering approximately 50 mg/day of zinc continuously for at least 12 weeks or cyclically during the luteal phase appears to be the most effective approach for improving both emotional and physical PMS symptoms. Future studies should directly compare continuous versus cyclical supplementation protocols to clarify the optimal administration strategy. Moreover, dose–response studies are warranted to identify the minimum effective and optimal safe dosages, along with investigations into the sustainability of symptom improvement and the plateau effects of zinc supplementation.

Sensitivity analysis demonstrated the robustness of results in both the emotional and total PMS score domains. However, in the physical symptoms domain, excluding certain studies (Ahmadi et al. 2023; Siahbazi et al. 2017) led to a loss of statistical significance, highlighting their substantial impact on pooled estimates. This influence may stem from clinical variations, including sample characteristics, intervention durations, or symptom assessment methods. Notably, exclusion of Sangestani et al. (2015) substantially reduced I^2, indicating it was a major source of heterogeneity. This is an unsurprising finding, as it was the only study to include participants with dysmenorrhea, administer zinc solely during a brief premenstrual period, and assess symptom presence/absence rather than severity – factors likely contributing to methodological and clinical heterogeneity.

Overall, this review offers preliminary evidence suggesting zinc supplementation as a complementary and alternative therapy for PMS, particularly for individuals seeking non-pharmacological interventions because of concerns regarding medication use. Nevertheless, the review also has some limitations. First, all included RCTs were conducted in Iran, which may limit the external validity and generalizability of the findings. For instance, the prevalence of zinc deficiency in Iran (22 percent) is higher than the global average (17 percent) (Eslami, Khoshhali, and Kelishadi 2023; Liu et al. 2018), and PMS prevalence reported in Iranian studies reaches up to 98 percent, placing it at the upper end of the global range (10–98 percent) (Direkvand-Moghadam et al. 2014; Hantsoo et al. 2022). These population-level characteristics may have amplified the observed treatment effects. However, the inclusion of studies from a single country and cultural context inherently reduced variability in lifestyle and dietary patterns, thereby increasing internal consistency across studies. Future studies involving more diverse regions and cultural contexts are warranted to enhance generalizability. Secondly, methodological heterogeneity across the included studies – in terms of zinc dosage, intervention duration, and outcome assessment tools – may have influenced the pooled estimates and likely contributed to the high I^2 values observed. This limitation reflects the current lack of standardized intervention protocols in this field. To account for such heterogeneity, a random-effects model was employed to adjust for between-study variability. Despite methodological heterogeneity, the direction of treatment effects remained consistently favorable across all symptom domains, supporting the overall utility of zinc supplementation for PMS. Third, the small number of included studies precluded a formal assessment of publication bias. Since PMS is a subjectively measured condition, we included only RCTs to minimize bias and ensure internal validity, which inherently limited the pool of eligible studies. To address this limitation, we conducted leave-one-out sensitivity analyses. While the findings for total PMS scores and emotional symptoms remained robust, the effect sizes for physical symptoms were moderately sensitive to the exclusion of individual studies. Furthermore, the certainty of evidence for the reduction of physical symptoms was rated low, and this should be explicitly considered in clinical decision-making when interpreting the applicability of zinc supplementation in practice. Future studies should include large-scale RCTs across diverse populations and regions, exploring dose – response relationships, symptom-specific efficacy, and potential synergies with other interventions. Biomarker studies are also needed to link PMS mechanisms with zinc's neurochemical effects.

Conclusion

Zinc supplementation is more effective than placebo for controlling emotional symptoms of PMS in young women, with moderate certainty of evidence. In addition, it reduces physical symptoms, but with low certainty, and this evidence, associated with other limitations, should be considered in decision-making. This review found that administering 50 mg of zinc daily – either continuously or cyclically – for at least 12 weeks yielded the most consistent symptom improvements. Based on these findings, zinc supplementation may serve as a relatively safe and practical non-pharmacological option, particularly for individuals seeking alternatives to conventional treatments. Clinical recommendations should be individualized based on the patient's zinc status, symptom profile, and treatment preferences. Despite limitations such as geographic concentration, methodological heterogeneity, and a small number of included studies, this review provides preliminary evidence supporting zinc supplementation as a complementary intervention for PMS. Future research should aim to establish standardized protocols, conduct multicenter trials across diverse populations, and explore underlying mechanisms using biomarker-based approaches.

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Disclosure statement

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Data availability statement

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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