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Review Article

Effects of Zinc Supplementation on Premenstrual Syndrome: A Systematic Review of Observational and Randomized Clinical Trials

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ABSTRACT

Background and Objectives: Premenstrual syndrome is a common problem in young females, characterized by a variety of physical, psychological, emotional and behavioral symptoms. Studies on the effectiveness of zinc supplementation in decreasing premenstrual syndrome symptoms have shown contradictory results. Therefore, the purpose of this systematic review was to summarize the available data, address discrepancies and pinpoint patterns in premenstrual syndrome zinc supplementation research.

Materials and Methods: Data within PubMed, Scopus and ISI Web of Science databases until December 2023 were searched to collect data on the associations between zinc and premenstrual syndrome. This systematic review included keywords such as "premenstrual syndrome," "premenstrual dysphoric disorder," "premenstrual tension," "zinc," "zinc sulfate," and "zinc acetate". Inclusion criteria were original articles, human studies and articles published in English that assessed the association between zinc and premenstrual syndrome. Randomized controlled trials and observational studies were included.

Results: Out of 103 studies, 11 studies met the inclusion criteria. Observational studies included moderate quality, while randomized controlled trials included high quality. Due to data heterogeneity, no significant relationship was detected between zinc supplementation and premenstrual syndrome symptom decrease, preventing a meta-analysis. However, zinc levels were generally lesser in individuals with premenstrual syndrome and randomized controlled trials indicated that zinc supplementation could significantly decrease certain physical and psychological symptoms.

Conclusions: Nutrients, including zinc, are vital for women's health. Based on the available evidence, zinc supplementation may help alleviate some symptoms of premenstrual syndrome. However, further clinical trials with larger sample sizes and longer durations are needed to assess the effect of zinc on premenstrual syndrome further reliably.

Keywords: Zinc, Premenstrual syndrome, Women's health, Systematic review

Introduction

Premenstrual syndrome (PMS) is one of the most common female disorders in women of childbearing age and affects millions of women worldwide (1). This includes a set of physical, psychological, emotional and behavioral symptoms that occur in the luteal phase of the menstrual cycle (2). The prevalence of this syndrome in women worldwide is generally 48% (3). Almost 80% of women experience one or more of these symptoms every month; however, only 2-5% of them experience these symptoms as very annoying symptoms, which cause disruption in daily activities (4). Moreover, PMS not only affects quality of life in women but can also include a negative effect on personal activities, social relationships, sexual function and job performance (5).

Premenstrual syndrome leads to family disruption and social or work activities, known as premenstrual dysphoric disorder (PMDD), that is observed in approximately 3-5% of women (6). The underlying

mechanisms of this syndrome are complex and not fully understood (7). The diagnosis of PMS is determined by valid and reliable questionnaires. Premenstrual

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symptoms screening tool (PSST) is a common tool for assessing PMS in women. The PSST contains two sections. The first part includes 14 questions about psychological, physical and behavioral symptoms and the second part assesses these symptoms in personal life (8).

A study by Modzelewski and colleagues linked development of PMS to changes in neurosteroid levels, particularly allopregnanolone and GABA conductance. The study emphasized the importance of customized treatment diets that included non-pharmacological and pharmaceutical interventions to improve the lives of affected women (9). Another study by Yi and colleague. (2023) assessed the factors affecting PMS in female students. The research detected significant links between PMS severity and factors such as depression, stress, sleep disorders and eating habits problems. The study suggested that interventions targeting these factors could help improve PMS symptoms (10).

Nutritional factors and various nutrients play a crucial role in the prevention and management of chronic disease symptoms (11). Vitamin and mineral deficiencies such as those of vitamin A, vitamin E, thiamin, magnesium and pyridoxine (B6) have been reported in women with PMS (12).

Previous studies have suggested a decrease in zinc concentration during the luteal phase; however, the role of this mineral has not fully been investigated (13). Zinc is a crucial trace mineral with numerous roles in biological processes. Zinc deficiency may cause disturbances in body functions; for example, decreased zinc concentration in the hippocampus and irregular production of glucocorticoids, which lead to the development of neuropsychiatric symptoms such as emotional instability, isolation, irritability and depression (14,15). Brain-derived neurotrophic factor (BDNF) is an important factor that contributes to neurogenesis and neuronal plasticity and plays a role in regulating sex hormones in women. Zinc might be involved in antidepressant activities through increasing BDNF gene expression. Moreover, zinc includes anti-inflammatory effects by improving inflammatory factors such as high-sensitivity C-reactive protein (hs-CRP) (16). A systematic review by Robinson and colleague detected that treatment with vitamin B6, calcium and zinc consistently included significant positive effects on the psychological symptoms of PMS. However, no enough evidence was available to support the effects of other vitamins and dietary interventions (17). Regarding the clinical importance of addressing PMS through zinc supplementation, this study aimed to investigate the relationship between the zinc supplementation and decreases in PMS symptoms. Previous studies included limitations such as methodological weaknesses and lack of diversity in study populations. This systematic review aimed to fill these gaps by providing a comprehensive analysis of the current evidence on zinc supplementation for PMS.

Materials and Methods

This systematic review was carried out based on the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement (18) and registered in the PROSPERO database (CRD42022343818). PubMed, Scopus and ISI Web of Science databases were searched up to December 2023. To increase the precision of the study, two researchers checked the search strategy (Table 1). The keywords of "premenstrual syndrome," "premenstrual dysphoric disorder," "premenstrual tension," "zinc," "zinc sulfate," and "zinc acetate" were used. The search was filtered to include only original articles, human studies and articles published in English.

The inclusion criteria for this review were original articles, human studies and articles published in English that assessed the association between zinc and PMS. Randomized controlled trials (RCTs) and observational studies were included. Exclusion criteria comprised non-peer-reviewed articles, studies with incomplete data, review articles and studies focusing on zinc intake through dietary questionnaires. The articles, including the author's name, publication year, country, sample size, dose of supplement, type of assessing PMS symptoms and method of analyzing data, were assessed and screened by two independent reviewers. Debates on choosing a study were resolved by a third reviewer.

To assess the quality of the studies, the Newcastle-Ottawa quality assessment scale was used for observational studies. Based on this scale, the highest score was 10, with three levels of quality of high-quality (7-10 points), moderate (3-6 points) and low (0-3 points) (19). Another scale was used to assess randomized clinical trials (RCTs), including the Jadad scale. Based on the parameters of this scale, articles with scores of three or more points are considered as high quality articles (20).

The study extracted and tabulated data from the included studies. The Results section described the study outcomes. A limited interventional studies focusing on the effect of zinc on PMS symptoms were available.

Additionally, observational studies have not been able to integrate data and variables effectively and the outcomes reported in these studies varied. Due to the wide dispersion of publication years of these studies, it was not possible to carry out a meta-analysis.

Table 1. Search strategy of the current review

Database	Keywords			results
PubMed	((((("premenstrual syndrome") OR ("Premenstrual Syndrome"[Mesh])) OR ("premenstrual dysphoric disorder")) OR ("Premenstrual Dysphoric Disorder"[Mesh])) OR ("premenstrual tension")	and	(((((("zinc") OR ("Zinc"[Mesh])) OR ("zinc sulfate")) OR ("Zinc Sulfate"[Mesh])) OR ("zinc acetate")) OR ("Zinc Acetate"[Mesh])	21
Scopus	(TITLE-ABS-KEY ("premenstrual syndrome") OR TITLE-ABS-KEY ("premenstrual dysphoric disorder") OR TITLE-ABS-KEY ("premenstrual tension"))	and	(TITLE-ABS-KEY ("zinc") OR TITLE-ABS-KEY ("zinc sulfate") OR TITLE-ABS-KEY ("zinc acetate"))	63
Web of science	"premenstrual syndrome" (All Fields) or "premenstrual dysphoric disorder" (All Fields) or "premenstrual tension" (All Fields)	and	"zinc" (All Fields) or "zinc sulfate" (All Fields) or "zinc acetate" (All Fields)	19

Results

A comprehensive search across selected databases yielded 103 articles (21 from PubMed, 63 from Scopus and 19 from ISI Web of Science). After removing 31 duplicates, two reviewers screened the titles and abstracts of the rest of articles, excluding 34 that were not relevant. The full texts of 27 studies were reviewed and 11 articles met the inclusion criteria for this systematic review.

The PRISMA flow diagram (Figure 1) summarized the study selection process. Out of the 16 articles excluded at the full-text review stage, two articles were irrelevant to the study focus, seven articles were review studies, four articles assessed zinc intake through dietary questionnaires and three articles were not available in full-text format.

The included studies varied in design, with case-control, cross-sectional and experimental studies in Turkey, USA, Iran, Australia and Indonesia. Sample sizes and follow-up times varied and not consistently reported. The relationship between zinc supplementation and PMS showed mixed results, with studies reporting beneficial effects and others finding no significant relationships.

The findings suggested that while evidence were available supporting zinc supplementation for managing PMS symptoms, the results were inconclusive. The variability in study designs, sample sizes and methodologies highlighted needs of further standardized research.

Most studies were region-specific, limiting generalizability. A significant variation was seen in zinc formulations and doses. Several studies lacked long-term follow-up data. Further studies should be carried out as well-designed randomized controlled trials with standardized methodologies, diverse populations and long-term follow-up to provide further definitive evidence on the efficacy of zinc supplementation for PMS.

Overview of the included studies

In this systematic review, 11 articles, including four interventional (16, 21-23) and seven observational studies (24-30) with 1196 participants, were included. The included articles were published between 1988 and 2023. From the included observational studies, five case–control (25-27, 29, 30) and one cross-sectional studies were recorded (24). Moreover, the interventional studies included four RCT (16, 21-23) and one experimental design studies (28). In the eligible studies, seven studies were from Iran (16, 21-24, 26, 27), one from Turkey (30), one from Australia (29), one from Indonesia (28) and one from the United States (25). The characteristics of the included studies are shown in Tables 2 and 3.

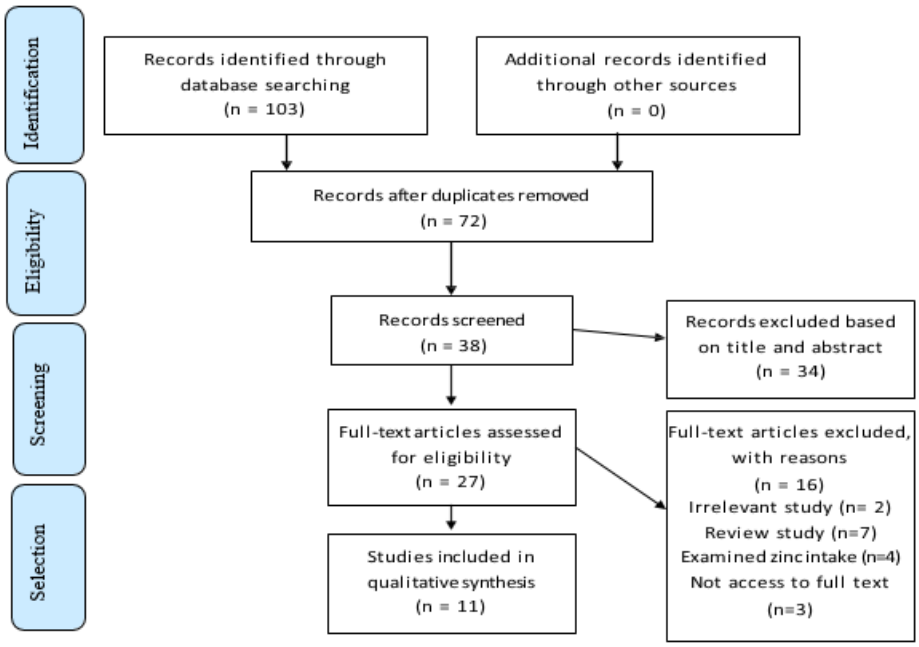

Figure 1. The PRISMA flow diagram for the selection of studies

Quality of the included studies

The quality of the observational studies was assessed using Newcastle-Ottawa scale, while the quality of the interventional studies was assessed using Jadad scale. Based on these scales, the observational studies received a moderate score and RCTs were considered as high quality studies.

Effects of zinc supplementation on premenstrual syndrome in randomized clinical trials

Two RCTs were carried out to investigate the effect of zinc sulfate on PMS. One of the studies revealed a significant decrease in the prevalence of PMS in the intervention group with an improvement in the PSST questionnaire scores (23). Another study showed a significant effect in decreasing physical symptoms and psychological distress in women with PMS (21).

A later study that investigated the effect of zinc gluconate reported a significant decrease in PMS physical and psychological scores (16); however, this supplement did not significantly affect quality of life or sleep quality of the patients (22).

The results of RCTs have shown that zinc supplementation is associated with a significant decrease in physical and psychological symptoms. In Table 4, the authors briefly discuss the effect of zinc supplementation on quality of life, PMS symptoms, prevalence, sleep quality and biochemical factors.

Associations between zinc and premenstrual syndrome in case controls

In three studies, the level of serum zinc in the PMS group was significantly lesser than that in the control group and this decrease was observed mostly during the luteal phase (16, 26, 29). However, the other articles did not detect significant differences in the serum zinc level between the case and control groups (22, 24, 25, 28).

A significant decrease in zinc levels in people with PMS was generally observed in the luteal phase. However, a number of other studies did not show a significant difference in the level of this micronutrient between patients and healthy individuals. The serum zinc level, zinc:copper ratio and prevalence of PMS in the menstrual stages in case-control studies are summarized in Table 5.

Discussion

The present systematic review was the first one to comprehensively review the effect of zinc on PMS. The results showed that low zinc levels were associated with manifestations of PMS. The serum zinc concentration was separately assessed during the follicular and luteal phases in some studies. In other studies, this was reported in total. Low zinc levels are linked to mental and physical symptoms and interventions involving zinc supplements could improve these symptoms.

Table 2. Characteristics of the included randomized controlled trials

Autho r	Count ry	Stud y desig n	Age (mea n or range)	Sample size	Outcome	interventi on	place bo	adjustm ent	Questionna ire	rateof complia nce
Shiva Siahba ziet al. (23)	Iran	RCT parall el	20-35	142 (ZS group: 65 control: 65)	mean PSST component scores improved inZS group, "decreased interest in social Activitie" item improved in placebo group	ZS220-mg capsules (containin g 50mg elemental zinc)	placeb o	Mean age, and ageat menarche	PSST	
Jafari etal. (16)	Iran	RCT	18-30	60 (ZG: 30 Control: 30)	Increased TACand BDNF, decreased physical and psychologi cal symptoms, CRP unchanged inZG group	ZG (containin g 30-mg elemental zinc)	placeb o		30-item checklist Beck's depression and anxiety inventory (BDI) questionnai re consisted of30 symptoms ofPMS based on DSM-VI FFQ	90%
Jafari etal. (22)	Iran	RCT	18-30	60 (ZG: 30 Control: 30)	Increased serum zinc leveland increased physical aspectof quality of life	ZG (containin g 30-mg elemental zinc)	placeb o		Pittsburgh sleep quality questionnai re (PSQI) WHOQOL-BREF American Psychiatry Association	90%
Ahma diet al. (21)	Iran	RCT	18-35	69 (Zinc group:33 , control:3 6)	anxiety and tension ,anger and irritability was significantl y differed, relationshi p improved inZS group	220mg zinc sulfate capsules (containin g 50 mg zinc)	placeb o		PSST	

BDNF: brain-derived neurotrophic factor, RCT: randomized clinical trial, TAC: total antioxidant capacity, ZG: zinc gluconate, ZS: zinc sulfate

Table 3. Characteristics of the included observational studies

Author	Country	Study design	Age (mean or rang)	Sample size	Outcome	Compari son	Adjustm ent	Question naire
Posaci et al. (30)	Turkey	Case–control	20-45	60 (case: 40 Control:2 0)	Znand Zn/Cu ratio significan tly lower inluteal phase	PMS group vs Normal group Case: premenstr ual score above 95and postmenst rual scores below 80 Control: premenstr ual scores below 94 and postmenst rual score below 80.		Meiistrual s Distress Questionn aire
Chuong et al. (25)	Texas	Case–control	24-39	23 (case: 13 Control:1 0)	Znand Zn/Cu ratio significan tly lower inluteal phase	PMS group vs Normal group. Case: scores on the Menstrual Distress Questionn aire<80 on day 7 or >95 on day 25 ofthe menstrual cycle		Menstrual Distress Questionn aire 24food recall
Bahrami et al. (24)	Iran	cross-sectional	12-18	448	No significan t difference s between the mean values for serum and dietary intake of Zn among four groups (PMS,PD, PMS and PD, Normal)		age, BMI and anthropo metric measurem ents	
Fathizadeh et al. (27)	Iran	Case–control	21-31	48 (case:23	serum levelof Zn lower inPMS	PMSvs healthy groups Control:	Age, BMR	PMS questionn aire (Rossigno
				Control:25)	group	people who had not experienc ed any of premenstr ual symptoms)		land Bonnland er scores)
Fatemi et al. (26)	Iran	Case–control	19-21	278	Serum level of Zn not significan tly less thanthe control group	PMSvs healthy groups		premenstr ual symptoms screening tool (PSST)
Mira et al. (29)	Australia	Case–control	20-45	61 (Case: 38 Control:23)	Not significan t difference in plasma concentra tion of Zn between case and control	PMSvs healthy group (who reported minimal omo change in symptoms)		
Juber et al. (28)	Indonesia	Experime ntal	18-24	7	No different in serum Znlevel between groups	Comparis onof PMSvs healthy group		

PD: primary dysmenorrhea, PMS: premenstrual syndrome, Zn: zinc, Cu: copper

Table 4. Effects of zinc supplementation on premenstrual syndrome symptoms

		Siahbazi et al. (23)	Jafari et al. (22)	Jafari et al. (16)	Ahmadi et al. (21)
Quality of Life	Psychological	+	-	NI	NI
	Physical	+	+	NI	NI
PMS symptoms		+	NI	+	+
PMS prevalence		↓	NI	NI	NI
Sleep quality		NI	-	NI	NI
Biochemical factors		NI	NI	↑TAC, BDNF	NI

(+): improvement, (-): no change, (↑): increase, (↓): decrease, (NI): no information, TAC: total antioxidant capacity, BDNF: brain-derived neurotrophic factor

Table 5. The level of serum zinc in premenstrual syndrome patients against controls

Author	Fatemi et al. (26)			Fathizadeh et al. (27)			Posaci et al. (30)			Chung et al. (25)			Bahramiet al. (24)			Mira et al. (29)			Juber et al. (28)		
Group	PMS		Control	PMS		Control	PMS		Control	PMS		Control	PMS		Control	PMS		Control	PMS		Control
Menstrual phases	luteal	Follicular		Luteal	Follicular		Luteal	Follicular		Luteal	Follicular		Luteal	Follicular		Luteal	Follicular		Luteal	Follicular	
Zinc level	-			↓			↓	-		↓	-		-			-			-		
Zinc: Copper ratio	NI			NI			↓	-		↓	-		-			NI			NI		
PMS prevalenc e	NI			NI			NI	NI		N I	NI		NI			NI			NI		

(-): No change, (↓): Decrease, (NI): No Information

Interventional studies

In the first study, which was carried out by Siahbazi et al., the effect of zinc sulfate (ZS) on PMS and health-related quality of life was assessed. One hundred forty-two young women (20-35 years old) participated in this study. The participants were divided into two groups of the intervention group (treated with 220 mg d^{-1} of ZS capsules containing 50 mg of elemental zinc) and the control group. The duration of intervention ranged from the Day 16 of the menstrual cycle to Day 2 of the next cycle for 3 m. The prevalence of PMS in the intervention group decreased significantly from 9.5 to 2.6% at the end of the study (p = 0.001). Furthermore, the ZS supplement improved the PSST component

scores (p = 0.001) and the mean scores of the QoL questionnaire in the mental and physical sections (23). Overall, breast tenderness and bloating during PMS can hurt function and quality of life and the results of their study showed that ZS improved health-related quality of life outcomes and potentially decreased complications from the disorder. A clinical trial by Jafari et al. (2020) investigated the effect of daily consumption of one zinc gluconate tablet (containing 30 mg of elemental zinc) for 3 m on quality of life and sleep quality among women with PMS. Although no significant changes were observed in the psychological aspects of quality of life or sleep quality (p=0.07) in the intervention group, zinc supplementation was associated with improvements in physical aspects of quality of life (p<0.001) (22). Zinc may regulate sleep by inhibiting the stimulation of glycinergic neurons that maintain wakefulness, regulating dopamine function and increasing the synthesis of melatonin and serotonin (31). However, the short study time and low dose of zinc contributed to the lack of positive outcomes in the study.

Zinc exerts its antidepressant-like effects by increasing the synthesis of BDNF in the hippocampus and other parts of the brain (32). The BDNF is a protein that helps survival and differentiation of serotonin neurons (33). Serotonin is a neurotransmitter that plays a crucial role in regulating mood, sleep, learning, memory and sexual behavior (34); therefore, studies have suggested that serotonin may be involved in the development of PMS. In

another study, Jafari et al. showed that a daily intake of 30 mg of zinc

gluconate (ZG) for 12 w was associated with a significant decrease in physical ($p = 0.03$) and psychological ($p = 0.006$) scores in women with PMS. However, BDNF (0.01) and total antioxidant capacity (TAC) ($p = 0.001$) increased (21).

Zinc is concentrated in the brain and involved in neuropsychological functions. Chronic zinc deficiency decreases zinc in the hippocampus, causing neuropsychological symptoms such as depression (16). Gamma-aminobutyric acid (GABA) is an amino acid involved in the transmission of signals and regulation of neurological functions (35). Modulating GABA is a key strategy in pharmacological treatments for neurology, anesthesia and psychiatry (36). Based on the results of these studies, zinc was essential for producing and regulating melatonin and GABA, which could help control dopamine function. Additionally, zinc supplementation could improve aggressive behaviors and impulsivity by increasing the synthesis of melatonin and serotonin (23).

Ahmadi et al. carried out a study in 2022 to assess the effect of zinc supplementation on the improvement of PMS symptoms in female students (18-35 years old). The intervention group received one 220 mg zinc sulfate capsule (containing 50 mg zinc) and the control group received a placebo capsule daily for 24 w. The results of this study showed a significant decrease in physical and psychological symptoms in the intervention group, compared to the placebo group ($p < 0.001$). Moreover, the intervention group demonstrated a significant increase in their relationships with friends, classmates and colleagues, compared to the placebo group ($p = 0.003$) (21).

Observational studies

Since studies have shown that serum zinc levels may be associated with PMS, the authors briefly reviewed studies that majorly compared serum zinc levels between individuals with PMS and healthy controls.

A cross-sectional study was carried out in 2019 by Fatemi et al. with the aim of comparing the serum levels of several elements, including zinc, in PMS patients and healthy individuals. In this study, 300 female students (19-21 years old) were divided into two groups of healthy people (controls) and people with PMS. The prevalence of PMS was reported as approximately 41.5% and no significant difference was reported in the serum zinc level between the PMS group and the healthy group ($p = 0.521$) (26). In another study, Bahrami et al. designed a cross-sectional study on the association of zinc levels with common complaints in women of reproductive age, including PMS, primary dysmenorrhea (PD) and irritable bowel syndrome (IBS). In this study, 448 adult girls were classified into four groups of PMS, PD, PD and PMS, and normal groups. When the groups were compared for serum zinc levels, they detected no significant differences in serum zinc levels within the four groups ($p > 0.05$) (24). In a study, Mira et al. did not observe any significant difference in zinc levels between people with PMS and the control group during follicular or luteal phase (29). Based on a study by Juber et al., due to an imbalance of estrogen and progesterone hormones in PMS, decreased intake of zinc was reported, which led to decreased sensitivity to sweet taste. In this study, seven people (18-24 years old) were included to investigate the relationship between sensitivity to sweets and serum zinc levels. Serum analysis revealed no significant difference in zinc levels between the PMS group and the control group and no correlations were detected between sweet taste sensitivity and serum zinc levels ($p > 0.05$) (28). In contrast to previous studies, the results of the study by Fathizadeh et al. in 2015, who assessed the serum zinc concentration in women with PMS compared to healthy people, showed that the serum zinc concentration was lesser in PMS patients than in controls ($p < 0.01$ and $p < 0.05$, respectively). During the luteal phase, a decrease in serum zinc levels presents, for which several hypotheses are described. Some suggest that this may be due to estrogen levels, inflammatory factors such as interleukin-1 enhancement and regulation of progesterone and prolactin activities (27). Das and Chowdhury suggested that zinc was taken up by endometrial tissue during the luteal phase to regulate progesterone and estradiol binding receptors (13). A study was carried out by Posaci et al. in 1994 with the aim of investigating plasma zinc levels in women (20-45 years old) with PMS. Plasma zinc levels were assessed in 40 women with PMTS and 20 healthy individuals (control group). The results indicated that the mean zinc level and the Zn/Cu ratio during the luteal phase were significantly lesser in the PMTS group than in the control group ($p < 0.05$), while a significant difference was not detected during the follicular phase ($p > 0.05$) (30). Additionally, Chuong et al. assessed the association between zinc levels and PMS. In this case-control study, 23 young women (24–39 years old) were included. After PMS diagnosis by questionnaire, the women were divided into two groups of PMS patients and controls. When the blood serum of people with PMS was compared with that of the control group, it was detected that the serum zinc level ($p < 0.05$) and the zinc:copper ratio ($p < 0.05$) were significantly lesser in the PMS group in the luteal phase (25). As previously stated, studies have shown no significant difference in the serum zinc levels of people with PMS, compared to healthy individuals. However, sudden fluctuations in neurotransmitters and sex hormones during the luteal phase in PMS patients can cause an increased need for essential elements, including zinc. A slight decrease in

zinc levels can lead to unpleasant symptoms of PMS. Therefore, consuming zinc can help individuals manage PMS symptoms (37).

Based on Table 2, the authors categorized the assessed factors in the RCTs. Of these studies, two studies showed the effects of zinc supplementation on quality of life in women with PMS. Siahbazi et al. (23) investigated that supplementation with zinc improved quality of life for physical and psychological symptoms. However, Jafari et al. (22) detected no significant difference in the psychological aspects of quality of life; however, positive effects of zinc supplementation on physical symptoms were observed.

Regarding the effect of zinc supplementation on improving PMS symptoms, three studies (16, 21, 23) reported improvements in PMS symptoms. Only one study reported that zinc supplementation decreased the prevalence of PMS (22). The quality of sleep was assessed in a study by Jafari et al. (22) and no changes were detected in their investigations. In another study, zinc supplementation increased the levels of biochemical factors such as TAC and BDNF in patients with PMS (23).

The characteristics of the observational studies are present in Table 3. The serum zinc concentration in the PMS group was significantly lesser than that in the control group in three studies and this difference was mostly in the luteal phase (25, 26, 30). The other articles did not detect significant differences in serum zinc levels between the case and control groups (24, 27, 29). The zinc/copper ratio (Zn/Cu) was assessed in three studies; in two of them, (25, 30) Zn/Cu significantly decreased and in one of them, (24) no significant changes were recorded.

The quality of the observational and interventional studies was assessed using Newcastle-Ottawa and Jadad scales, respectively. The observational studies received a moderate score, while the RCTs were considered as high quality studies.

Based on this search, this systematic study is one of the first studies on zinc and PMS. Significant limitations were seen in the interventional and observational studies. First, the number of RCTs was limited and the factors assessed in RCTs were heterogeneous; hence, the authors were unable to made a statistically accurate conclusion. Additionally, not all RCTs used similar files for zinc. Second, in observational studies, a time gap was seen between the published articles and studies were outdated. Hence, this caused lack of access to the necessary information. Furthermore, most of the studies were carried out in Iran and the authors might not be able to link the results to other societies worldwide.

Effects of other supplements on PMS

The effects of supplementation with other elements on physical and psychological PMS symptoms have been studied, with brief results outlined later. In 2021, Bahrami et al. carried out a triple-blind clinical trial to assess the effects of a 500 mg curcumin supplement on patients with PMS. The trial lasted for three cycles, starting 7 d before and ending 3 d after the menstrual cycle. The participants were divided into two groups of intervention (n = 62) and placebo (n = 62). The results showed that the two groups experienced a decrease in PSST scores; however, the curcumin group showed a greater decrease than that the placebo group did (24).

In a study by Ghanbari in 2009, it was shown that administering 500 mg of calcium carbonate supplement (twice a day) in PMS was associated to a significant decrease in PMS symptoms, including fatigue, appetite changes and depression (38).

In a study by Behboudi et al., 95 women received 1 g of fish oil daily for 10 d, starting 8 d before and ending 2 d after menstruation, for three consecutive cycles. The study detected that physical and mental symptoms decreased significantly in the two groups; however, the intervention group showed greater improvement, leading to an enhanced quality of life for women with PMS (39).

Based on a study by Higuchi1 et al, consuming 180 mg of gamma tocopherol during the luteal phase of the first and second menstrual cycle could significantly decrease symptoms of fatigue, sensitivity and irritability. Additionally, the supplement could improve PMS symptoms linked to water retention during the luteal phase, possibly due to the diuretic characteristics of gamma tocopherol (40).

Kendall et al. in 1987 carried out a study to assess effects of B6 supplementation on women with PMS. The research detected that administering 150 mg of this supplement daily for 2 m resulted in improvement of certain PMS symptoms such as dizziness, vomiting and behavioral changes in the intervention group. However, it is noteworthy that a low dose of B6 can potentially cause toxicity. As a result, caution is advised when using this supplement (41).

Souza study in 2000 detected that a 1-m combined dose of 50 mg B6 and 200 mg magnesium only effectively decreased anxiety-linked symptoms in 44 people with PMS (42). Abdollahi carried out a study in 2019 involving 130 girls with vitamin D deficiency and PMS. Girls received 2000 IU of vitamin D every other day for 12 w. The study showed no significant changes after the supplementation. However, intragroup comparison revealed a significant decrease in variables such as fatigue, anxiety and some physical symptoms (43). Most studies used PSST (24, 39, 43) questionnaire to assess PMS symptoms, while others used MDQ (40) and MHQ (42) questionnaires.

Strengths and Limitations of This Study

The study included several strengths and limitations. One major limitation was the limited number of RCTs and the heterogeneous factors assessed, which weakened the ability to made a statistically accurate conclusion. Additionally, there was variability in the files used for zinc across various RCTs. The time gap and outdated nature of some observational studies further limited access to the necessary information. Moreover, a majority of studies were carried out in Iran, which limited the generalizability of the findings to other societies worldwide. This regional focus poseed challenges in relating the study results to broader global populations.

Conclusions

In summary, this systematic search revealed several fundamental limitations in the current research on zinc supplementation for PMS. These included a lack of sufficient RCTs and significant heterogeneity in study outcomes. Observational studies lacked the necessary data to carry out a meta-analysis. Despite these limitations, a significant decrease in zinc levels was generally observed in individuals with PMS. The results from existing RCTs indicated that zinc supplementation could significantly decrease physical and psychological symptoms associated with PMS.

Regarding these findings, there is an urgent need of further comprehensive studies in this field. Future RCTs should include larger sample sizes and longer intervention times in diverse populations to provide further robust evidence. Additionally, observational studies should be updated to offer further heterogeneous and comprehensive data. This helps better understand the potential benefits of zinc supplementation for PMS and guide clinical practice.

Declarations

Ethics approval and consent to participate

Not applicable.

Availability of data and materials

All the data analyzed during this study are included in this published article.

Disclosure statement

No potential conflict of interest was reported by the authors.

Abbreviations

PMS: Premenstrual Syndrome
RCTs: Randomized Controlled Trials
PSST: Premenstrual Symptoms Screening Tool
QoL: Quality of Life
ZS: Zinc Sulfate
ZG: Zinc Gluconate
BDNF: Brain-Derived Neurotrophic Factor
TAC: Total Antioxidant Capacity
GABA: Gamma-Aminobutyric Acid
PD: Primary Dysmenorrhea
IBS: Irritable Bowel Syndrome
Zn/Cu: Zinc/Copper Ratio
IU: International Units
MDQ: Menstrual Distress Questionnaire
MHQ: Menstrual Health Questionnaire
PMDD: Premenstrual Dysphoric Disorder
hs-CRP: High-Sensitivity C-Reactive Protein
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: International Prospective Register of Systematic Reviews
ISI: Institute for Scientific Information
NOS: Newcastle-Ottawa Scale

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