



# The Effect of Zinc Supplementation on the Improvement of Premenstrual Symptoms in Female University Students: a Randomized Clinical Trial Study

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## Abstract

Zinc is an essential microelement that plays many important functions in the body. It is crucial for the regulation of cell growth, hormone release, immunological response, and reproduction. Thus, this trial aimed to evaluate the effects of zinc supplementation in comparison with placebo on the improvement of premenstrual symptoms in female university students. This triple-masked, randomized, placebo-controlled, parallel trial was conducted among 69 female students aged 18–35 with premenstrual syndrome that living in dormitories of Hamadan University of Medical Sciences, in west of Iran. Participants were randomly assigned to two groups of equal number; one group received 220 mg of elemental zinc ( $n=33$ ) and the other group received placebo ( $n=36$ ) on a regular daily for 24 weeks. The premenstrual syndrome was assessed by Premenstrual Symptoms Screening Tool-Adolescent (PSST-A) questionnaire for all participants. Chi-square and  $t$ -student tests were used to compare the percentage or mean of parameters between two groups. All statistical analysis conducted by SPSS version 16. The mean age in the intervention group was  $25.64 \pm 0.53$  years, and in the control group was  $24.38 \pm 0.51$  years ( $P=0.087$ ). After 24 weeks of intervention, PMS physical and psychological symptoms such as anger, anxiety, depressed mood, overeating, breast tenderness, headaches, muscle pain, bloating, and weight gain significantly decreased in zinc group compared to placebo group ( $P<0.001$ ). We observed a significant increase in relationship with friends, classmates, and coworkers ( $p=0.003$ ) after 24 weeks of intervention with zinc compared to placebo. In conclusion, zinc, as a simple and inexpensive treatment, was associated with improvement of PMS symptoms. Given that this is among the first studies to evaluate the effect of zinc supplementation on PMS, additional studies are warranted to confirm these findings.

**Keywords** Zinc · Premenstrual syndrome · Randomized controlled trial

## Introduction

Premenstrual syndrome (PMS) involves a set of clinically significant physical and psychological manifestations during the luteal phase of the menstrual cycle. This syndrome causes significant distress and impaired functional capacity in individuals. Usually, the symptoms following PMS disappear shortly after the onset of menstruation [1]. Evidence indicates that the prevalence of PMS is close to 50% in women at reproductive age worldwide [2]. Most patients experience mild to moderate symptoms of the syndrome, and only about 2.5–3% experience severe symptoms that can interfere with their daily functioning. Female university students are among women with the higher rate of PMS [1, 3].

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There are about 200 different symptoms associated with PMS, the three most important of which are mood swings, stress, and anxiety. Common emotional and non-specific symptoms following PMS include stress, anxiety, insomnia, headache, fatigue, mood swings, increased emotional sensitivity, and changes in libido [4]. Formal definitions absolutely require the presence of emotional symptoms as the main complaint of PMS; The presence of physical symptoms associated with the menstrual cycle include changes in appetite, nausea, constipation, swelling or tenderness of the breast, menstrual cycle acne, fatigue, and joint or muscle pain [4, 5].

The etiology of PMS is unknown [1]. It is believed that this syndrome is not a single disorder but is a set of symptoms of biological origin that also includes psychological and social aspects. Therefore, efforts have been made for pharmacological and non-pharmacological treatment [6]. Treatment is usually based on symptom relief and reduces the effects of PMS on the patient daily routine activities. For example, combinations of pharmacotherapies including diuretics, painkillers, antihistamines, antidepressants, and anti-anxiety are used to treat the same symptom [1].

Recently, more attention has been paid to other treatments that are mostly based on clinical experience and reduce the prevalence and severity of annoying PMS by unknown mechanisms. These treatments include mineral deficiency replacement including calcium, magnesium, vitamin B6, and vitamin E supplements, as well as various diets such as primrose oil or a high-carbohydrate diet, which have recently received much attention [7].

Serum zinc concentrations fluctuate throughout the menstrual cycle. In PMS women, serum zinc level is significantly lower than the normal women. Zinc supplements may reduce the negative effects of PMS in women. This mineral is able to regulate the secretion of progesterone as a hormone that increases the risk of premenstrual syndrome. Zinc supplements in women prevent painful menstruation. It also plays a vital role in the physical development of the gastrointestinal tract and immune system [8, 9]. So far, very few studies have examined the beneficial effects of zinc supplementation on biochemical and genetic factors associated with PMS. Also, due to the fact that zinc participates in some metabolic and signaling pathways, therefore, the administration of this drug may further improve the symptoms in patients with PMS. Given the antioxidant role, antidepressant activity, and anti-inflammatory action of zinc supplement, so it seems to alleviate PMS symptoms [10–12]. There is little information about the effect of zinc supplement on PMS complications; therefore, this study was conducted to investigate the effect of zinc supplement on the symptoms of women with premenstrual syndrome.

## Materials and Methods

### Study Design and Setting

This study was a double-blind randomized clinical trial that was conducted on female students aged 18–35 with PMS living in dormitories of Hamadan University of Medical Sciences, Hamadan (west of Iran), from February to April 2021.

### Eligibility Criteria

Inclusion criteria included patients with moderate to severe PMS in the age range of 18–35 years who were studying at Hamadan University of Medical Sciences and were willing to participate in the study. Patients with symptoms of malnutrition (Marasmus, Kwashiorkor, Marasmus-Kwashiorkor) and need zinc replacement or any signs of severe malnutrition, symptoms of systemic disease (sepsis, acute meningitis, hemodynamic instability), diarrhea with 3 or more watery stools in the last 24 h, known intolerance or sensitivity to zinc or zinc-containing compounds, smoking, being in a stressful situation, and having a history of mental illness were considered as exclusion criteria.

### Intervention

Patients randomly were divided into two groups. The control group received the placebo and the intervention group received 220 mg zinc sulfate capsules (containing 50 mg zinc) that were administered for 3 months. Patients were evaluated for symptoms at initiation, 1 month, 3 month, and 6 month after running the study.

### Randomization and Blinding

Balanced block randomization (block size, 4) was used to allocate patients into two groups and 43 patients finally were assigned to each group. Moreover, because neither the participants nor the experimenters know who is receiving a particular treatment, therefore, the study was double-blind.

### Measurement Tool

Prior to the study, patients were asked to complete and sign an informed consent form if they wished to participate in the study. After the patients entered the study, demographic information including age, education, marital status, and occupation were asked and recorded.

In this study, PSST questionnaire was used to assess the severity of PMS. The PSST questionnaire consists of 19 questions that have two parts: the first part which includes

14 questions related to mood, physical, and behavioral symptoms; and the second part which measures the effect of these symptoms on people's lives and consists of 5 questions. This questionnaire was designed by McMaster University of Canada and standardized in Persian by Siahbazi et al. in the Iranian population [13]. The validity and reliability indices of the Persian version of this questionnaire in the above study were presented at an acceptable level so that Cronbach's alpha index was higher than 0.7 that indicates the acceptable internal consistency. Moreover, its face and content validity in this study was approved by the panel of experts. This questionnaire completed by the patients at the beginning of the study, 1 month, 3, and 6 months after the beginning of the study.

### Statistical Analysis

All quantitative data were presented as mean  $\pm$  SD. Chi-square test was used to compare the percentage or frequency of parameters between two groups. Comparison of the continuous variables between two groups was done using independent Student sample-*t* test. Using ANCOVA, the mean score of PSST-A components (adjusting for baseline score), between two groups, was compared in the investigated time periods. Moreover, changes in the score of PSST-A components over time between the two groups were performed

using repeated measures ANOVA test. In this study,  $p < 0.05$  was considered statistically significant. The SPSS software (IBM, version 23) was applied for data analysis.

### Ethical Considerations

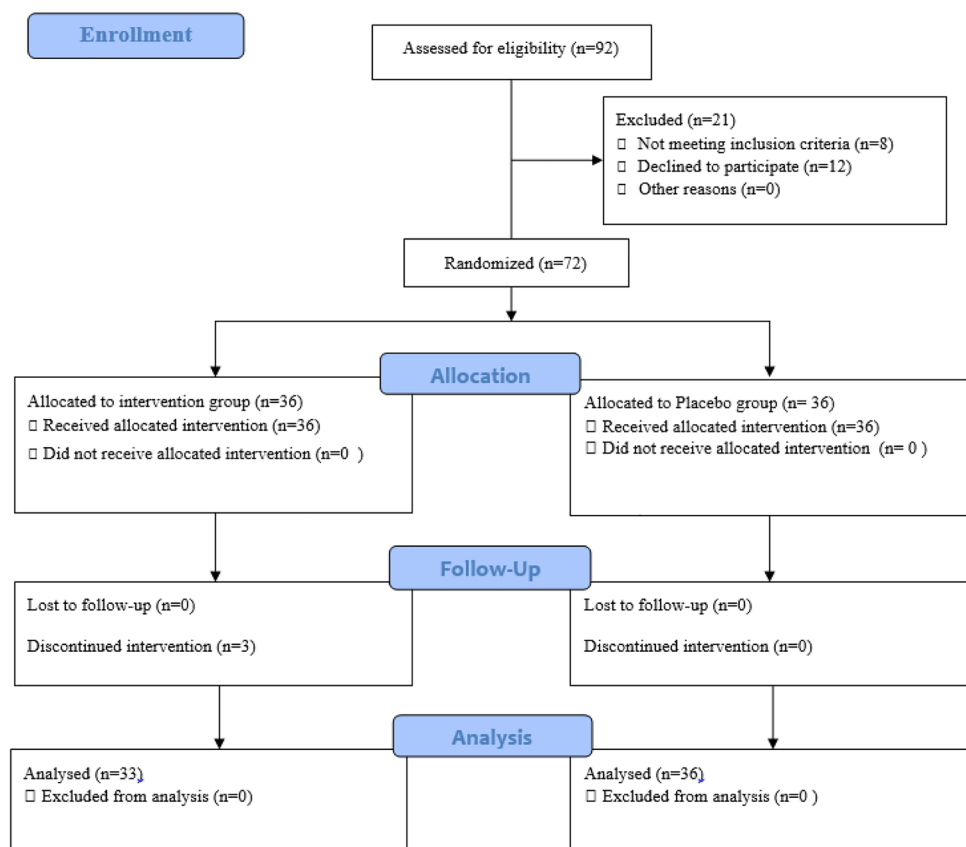
Ethical approval for the study was obtained from the ethics committee of Hamadan University of Medical Sciences according to Helsinki declaration. This clinical trial was registered by the Iranian Registry of Clinical Trials (IRCT) on 2020-03-14 and the IRCT ID was IRCT20120215009014N347.

### Results

Figure 1 shows the process of patients selecting and follow-up in two groups. Of the 92 investigated patients, 21 of them were excluded due to not meeting the inclusion criteria or decline for participation. After equally allocation of patients (36 patients in each group), 3 patients discontinued the study in the intervention group.

Table 1 shows the distribution of individual characteristics of the participants in zinc sulfate and placebo groups. The majority of participants in the intervention group ( $n = 33$ ) and placebo group ( $n = 36$ ) were Ph.D. students. The

**Fig. 1** CONSORT diagram regarding follow-up of the patients in the two groups



**Table 1** Distribution of individual characteristics of the participants in the intervention and control groups

Variable	Zinc sulfate group ( <i>n</i> = 45) <i>n</i> (%)	Control group ( <i>n</i> = 45) <i>n</i> (%)	<i>P</i> -value
Age (mean ± SD)	25.64 ± 0.53	24.38 ± 0.51	0.087*
Education			
Diploma	0 (0.00)	1 (2.22)	0.201**
BSc	9 (20.00)	3 (6.67)	
MSc	3 (6.67)	5 (11.11)	
PhD	33 (73.33)	36 (80.00)	
Marital status			
Single	18 (40.00)	14 (31.11)	0.378***
Married	27 (60.00)	31 (68.89)	
Occupation			
Stager	3 (6.67)	1 (2.22)	0.767**
Intern	2 (4.44)	3 (6.67)	
Medical student	34 (75.56)	37 (82.22)	
Assistant	2 (4.44)	2 (4.44)	
Resident	1 (2.22)	0 (0.00)	
Midwife	1 (2.22)	0 (0.00)	
Clerkship			

\*Student *t*-test, \*\* Fisher exact test, \*\*\*Chi-square test

mean age in the intervention group was 25.64 ± 0.53 years, and in the control group was 24.38 ± 0.51 years (*P* = 0.087).

According to the results presented in the table, there was no statistically significant difference between the zinc sulfate supplementation and placebo groups regarding the individual features that might affect the treatment.

In Table 2, we compared the mean score of PSST-A components at the baseline between the intervention and control groups. As shown, there was not a significant difference between two groups in this regard (*P* > 0.05).

Table 3 shows the mean score of each item in the PSST-A questionnaire on the 1st, 3th, and 6th months after the intervention. This table also shows the changes in the mean difference between the intervention and control group in each period of intervention. The mean score of anger and irritability 1 month after intervention in the zinc sulfate supplementation group was 3.65 ± 0.59 and in the control group was 3.94 ± 0.61, which was significantly different between the intervention and control groups (*P* = 0.001). This significant difference was also seen in the third and sixth months of the study. The mean score of anxiety and tension 1 month after intervention in the zinc sulfate group was 3.79 ± 0.89 and in the placebo group was 3.80 ± 0.89, which statistically different between intervention and control groups (the mean of anxiety in the group receiving zinc was 0.85 less than the control group). Also, the means of work efficiency, relationship with friends, classmates, and family members, social life activities, and responsibility in the home in the intervention group were higher than the control group. Results of the

**Table 2** Comparison of the mean score of PSST-A components among the intervention (zinc sulfate) and control (placebo)

PSST-A components	Zinc sulfate group ( <i>n</i> = 45) Mean ± SD	Control group ( <i>n</i> = 45) Mean ± SD	<i>P</i> -value*
Anger/irritability	3.42 ± 0.11	3.36 ± 0.11	0.674
Anxiety/tension	3.58 ± 0.11	3.47 ± 0.12	0.518
Tearful/increased sensitivity to rejection	3.84 ± 0.14	3.78 ± 0.09	0.707
Depressed mood/hopelessness	3.42 ± 0.14	4.00 ± 0.05	0.053
Decreased interest in work activities	3.80 ± 0.13	4.07 ± 0.09	0.103
Decreased interest in home activities	3.67 ± 0.13	3.93 ± 0.09	0.092
Decreased interest in social activities	3.47 ± 0.11	3.58 ± 0.09	0.459
Difficulty concentrating	4.13 ± 0.12	4.13 ± 0.10	1.000
Fatigue/lack of energy	3.75 ± 0.18	4.00 ± 0.12	0.261
Overeating/food cravings	3.18 ± 0.15	3.27 ± 0.14	0.669
Insomnia	3.49 ± 0.12	3.84 ± 0.10	0.056
hypersomnia	3.62 ± 0.13	4.00 ± 0.10	0.023
Feeling overwhelmed or out of control	3.44 ± 0.12	3.58 ± 0.09	0.374
Physical symptom	3.20 ± 0.11	3.09 ± 0.12	0.498
School or work efficiency	4.27 ± 0.13	4.38 ± 0.11	0.516
Relationship with friends, classmates	3.55 ± 0.13	3.49 ± 0.13	0.717
Relationship with family	3.93 ± 0.12	3.80 ± 0.14	0.467
Social life activity	3.64 ± 0.12	3.75 ± 0.07	0.059
Home responsibility	3.93 ± 0.13	3.80 ± 0.13	0.467

\*Student *t*-test

**Table 3** Comparison of the score of PSST-A components between the intervention and control groups and time period

PSST-A components	Zinc sulfate group Mean $\pm$ SD	Placebo group Mean $\pm$ SD	P-value*	P-value for: **		
				Treatment effect	Time effect	Interaction treatment and time
Anger/irritability						
After 1 month	3.65 $\pm$ 0.59	3.94 $\pm$ 0.61	0.001	0.014	0.49	0.25
After 3 month	3.53 $\pm$ 0.42	3.91 $\pm$ 0.73	0.001			
After 6 month	3.04 $\pm$ 0.41	3.89 $\pm$ 1.02	0.001			
Anxiety/tension						
After 1 month	3.79 $\pm$ 0.89	3.80 $\pm$ 0.89	0.001	<0.001	0.86	0.17
After 3 month	3.65 $\pm$ 0.61	3.76 $\pm$ 0.83	0.037			
After 6 month	3.21 $\pm$ 0.48	3.79 $\pm$ 0.86	0.001			
Tearful/increased sensitivity to rejection						
After 1 month	4.17 $\pm$ 0.48	4.32 $\pm$ 0.94	0.027	0.84	0.48	0.31
After 3 month	3.96 $\pm$ 0.53	4.28 $\pm$ 0.96	0.001			
After 6 month	3.69 $\pm$ 0.42	4.30 $\pm$ 0.85	0.001			
Depressed mood/hopelessness						
After 1 month	4.08 $\pm$ 0.39	4.11 $\pm$ 0.76	0.001	0.02	0.21	0.87
After 3 month	3.83 $\pm$ 0.53	4.07 $\pm$ 1.25	0.001			
After 6 month	3.05 $\pm$ 0.52	3.96 $\pm$ 0.89	0.001			
Decreased interest in work activities						
After 1 month	3.83 $\pm$ 0.53	4.04 $\pm$ 0.90	0.004	0.41	0.23	0.42
After 3 month	3.60 $\pm$ 0.41	3.92 $\pm$ 1.11	0.011			
After 6 month	3.12 $\pm$ .014	4.00 $\pm$ 0.89	0.001			
Decreased interest in home activities						
After 1 month	3.97 $\pm$ 0.54	4.09 $\pm$ 0.93	0.018	0.27	0.39	0.48
After 3 month	3.88 $\pm$ 0.38	4.01 $\pm$ 1.08	0.001			
After 6 month	3.65 $\pm$ 0.23	3.98 $\pm$ 0.83	0.001			
Decreased interest in social activities						
After 1 month	4.16 $\pm$ 0.51	4.25 $\pm$ 0.87	0.006	0.16	0.86	0.42
After 3 month	3.77 $\pm$ 0.46	4.19 $\pm$ 1.02	0.013			
After 6 month	3.82 $\pm$ 0.43	4.19 $\pm$ 1.08	0.020			
Difficulty concentrating						
After 1 month	4.02 $\pm$ 0.53	4.13 $\pm$ 0.95	0.001	0.56	0.35	0.41
After 3 month	3.84 $\pm$ 0.42	4.11 $\pm$ 1.08	0.001			
After 6 month	3.09 $\pm$ 0.81	4.06 $\pm$ 0.67	0.001			
Fatigue/lack of energy						
After 1 month	4.16 $\pm$ 1.01	4.53 $\pm$ 1.04	0.009	0.78	0.68	0.18
After 3 month	4.07 $\pm$ 0.50	4.50 $\pm$ 0.85	0.023			
After 6 month	3.90 $\pm$ 0.42	4.49 $\pm$ 0.73	0.001			
Overeating/food cravings						
After 1 month	3.74 $\pm$ 0.79	4.01 $\pm$ 0.83	0.001	<0.001	0.40	0.50
After 3 month	3.58 $\pm$ 0.51	3.97 $\pm$ 0.96	0.001			
After 6 month	3.19 $\pm$ 0.32	4.00 $\pm$ 0.78	0.001			
Insomnia						
After 1 month	3.86 $\pm$ 0.67	4.08 $\pm$ 0.66	0.048	0.48	0.99	0.88
After 3 month	3.42 $\pm$ 0.61	4.10 $\pm$ 0.74	0.001			
After 6 month	3.13 $\pm$ 0.21	4.09 $\pm$ 0.90	0.023			
Hypersomnia						
After 1 month	4.01 $\pm$ 0.63	4.13 $\pm$ 1.00	0.001	0.98	0.28	0.98
After 3 month	3.72 $\pm$ 0.49	4.07 $\pm$ 0.93	0.001			
After 6 month	3.08 $\pm$ 0.53	4.11 $\pm$ 0.77	0.001			
Feeling overwhelmed or out of control						
After 1 month	3.95 $\pm$ 0.58	4.16 $\pm$ 0.76	0.016	0.27	0.94	0.74
After 3 month	3.79 $\pm$ 0.39	3.98 $\pm$ 1.25	0.001			
After 6 month	3.56 $\pm$ 0.08	3.96 $\pm$ 1.08	0.009			

**Table 3** (continued)

PSST-A components	Zinc sulfate group Mean ± SD	Placebo group Mean ± SD	P-value*	P-value for: **		
				Treatment effect	Time effect	Interaction treatment and time
Physical symptom (breast tenderness, headaches, muscle pain, bloating, and weight gain)						
After 1 month	3.63 ± 0.66	3.76 ± 1.18	0.230	<0.001	0.49	0.21
After 3 month	3.55 ± 0.64	3.72 ± 0.93	0.054			
After 6 month	3.23 ± 0.16	3.75 ±1.01	0.048			
School/work efficiency						
After 1 month	4.43 ± 0.62	4.30 ± 1.08	0.035	0.66	0.04	0.77
After 3 month	4.32 ± 0.80	3.91 ± 1.25	0.002			
After 6 month	4.06 ± 0.39	3.54 ± 0.91	0.002			
Relationship with friends, classmates, and coworkers						
After 1 month	3.93 ± 0.52	3.81 ± 0.88	0.021	0.003	0.63	0.52
After 3 month	3.91 ± 0.63	3.61 ± 1.10	0.001			
After 6 month	3.94 ± 0.24	3.19 ± 0.91	0.036			
Relationship with family						
After 1 month	4.39 ± 0.48	4.25 ± 0.66	0.030	0.17	0.03	0.16
After 3 month	4.36 ± 0.35	4.08 ± 0.85	0.001			
After 6 month	4.41 ± 0.27	3.62 ± 0.73	0.001			
Social life activity						
After 1 month	4.02 ± 0.50	3.88 ± 0.79	0.001	0.77	0.78	0.33
After 3 month	4.03 ± 0.52	3.54 ± 0.96	0.023			
After 6 month	4.02 ± 0.54	3.14 ± 1.07	0.001			
Home responsibility						
After 1 month	4.39 ± 0.48	4.04 ± 0.66	0.008	0.06	0.36	0.62
After 3 month	4.20 ± 0.61	4.04 ± 0.81	0.001			
After 6 month	3.99 ± 0.25	3.83 ± 0.85	0.001			

\* ANCOVA test, \*\*repeated measure ANOVA

repeated measure ANOVA indicate no significant interaction between treatment and time for all components ( $P > 0.05$ ).

## Discussion

Premenstrual syndrome is one of the most common disorders of reproductive age [14]. This study showed that zinc supplementation compared to placebo was effective on all dimensions of the PSST-A questionnaire.

The control placebo group also had lower scores after intervention, but only in the first month of the study. The positive role of placebo has been reported by others [15], suggesting that the response to placebo in published trials on psychological aspects of disorders or treatment of pain is highly effective [16].

Zinc supplement has an anti-inflammatory effect [17]. This property reduces the production of prostaglandins and leukotriene by inhibiting the cyclooxygenase and lipoxygenase pathways and reduces the severity of the physical symptoms of PMS and improves physical function and physical pain [18].

Many of the symptoms of PMS, such as depression, sleep disorders, anxiety, aggression, and difficulty concentrating, are due to a decrease in the neurotransmitter serotonin [19]. Zinc supplementation affects the levels of neurotransmitters such as serotonin, which are responsible for behavioral and emotional symptoms [20]. Furthermore, zinc is also required for the production and modulation of melatonin and GABAs [21, 22], which helps regulate dopamine function, an important factor in PMS and its treatment [23].

In healthy people, the activity of oxidants and antioxidants is in balance. Loss of this balance causes oxidative stress. According to the results of some studies, the level of total antioxidant capacity (TAC) in patients with premenstrual syndrome decreases. A decrease in TAC is associated with an increase in the production of free radicals and a decrease in the level of defense antioxidants. Zinc supplement has antioxidant activity; As a result, the antioxidant activity of zinc is effective in improving all dimensions of the PSST-A questionnaire [24].

The study of Siabhazi et al. [9] as the effect of zinc sulfate supplementation on premenstrual syndrome and quality

of life showed that the prevalence of this syndrome in the zinc sulfate group was significantly reduced during the study period. The mean scores of health-related quality of life in the physical and mental components in the intervention group improved significantly. Therefore, it was consistent with the results of the present study.

One of the strengths of this study was blinding and its limitations were individual, personality, and genetic differences of research units that could be controlled to some extent through random selection of samples. Also, some PMS confounders were not studied, such as relationship status, lifestyle, and physical activity. In addition, we did not measure blood zinc concentration to monitor alterations in zinc levels before and during treatment.

## Conclusion

In conclusion, zinc, as a simple and inexpensive treatment, was associated with improvement of PMS symptoms. Given that this is among the first studies to evaluate the effect of zinc supplementation on PMS, additional studies are warranted to confirm these findings.

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**Author Contribution** MA, SK, and HP developed the original idea and the protocol, abstracted, and prepared the manuscript. AP and AA participated in the study design and analyzed the data. MA and SK contributed to the study design and data gathering. All authors read and approved the final manuscript.

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**Data Availability** The data that support the findings of the study are available from the corresponding author in SPSS form upon reasonable request.

**Code availability** Not applicable.

## Declarations

**Ethics Approval and Consent to Participate** Institutional review board approval was obtained from the ethics committees of Hamadan University of Medical Sciences.

**Consent for Publication** Written and informed consent was obtained from the patients.

**Conflict of Interest** The authors declare no competing interests.

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