

Evaluating the effects of vitamin D and vitamin E supplement on premenstrual syndrome: A randomized, double-blind, controlled trial

Hajar Dadkhah¹, Elham Ebrahimi², Nahid Fathizadeh¹

ABSTRACT

Background: Premenstrual syndrome (PMS) can cause problems in daily work and relationships.

Materials and Methods: Eighty-six women were randomly assigned to two intervention groups and one control group. Patients were asked to fill out the PMS Daily Symptoms Record for 2 months, and then the participants were randomly assigned to one of the three study groups. Medical intervention was carried out for 2 months with the participants in each group receiving either a tablet containing 200 mg vitamin D, 100 mg vitamin E, or a placebo each day, respectively. After 2 months, the results of pre- and post-intervention were compared. $P < 0.005$ was considered significant.

Results: After the intervention, the mean score of the syndrome significantly decreased in all the three groups (12, 16, and 8 participants had decreased scores in vitamin D, vitamin E, and placebo, respectively). The differences between groups were not significant ($P > 0.05$).

Conclusions: Supplemental therapy with vitamins D and E is an effective and affordable treatment for PMS.

Key words: Premenstrual syndrome, randomized clinical trial, supplementation therapy, vitamin D, vitamin E

INTRODUCTION

Premenstrual syndrome (PMS) was first described by Frank as premenstrual tension syndrome, 70 years ago.^[1] It affects millions of women around the world.^[2] It has been estimated that 80–90% of women experience the symptoms of PMS in their reproductive age. Among those who suffer, the symptoms are severe in

3–8%.^[3] The diagnostic criteria of the American Psychiatry Association for diagnosis of PMS are as follows: At least five of the following symptoms and signs are present in the Daily Symptom Record form during the last week of the luteal phase up to the first 4 days of the next menstrual cycle for at least two cycles; the signs and symptoms interfere with the daily life and relationship of the individual; and the symptoms do not originate from the aggravation of psychiatric disorders.^[4] Various etiologies have been proposed to explain the underlying cause of the syndrome, and thus different therapeutic approaches have been introduced for treatment of the disease. This can be largely due to the multifaceted nature of the disorder and the role of different biological, psychological, and social factors in its development, as well as the overlap of the symptoms of the syndrome with those of many different psychological and gynecological diseases.^[5] One of the treatment approaches proposed for the syndrome is supplementing the diet with vitamins D and E. Many

¹Nursing and Midwifery Care Research Center, Faculty of Nursing and Midwifery, Isfahan University of Medical Sciences, Isfahan, Iran,

²Department of Reproductive Health, Student Research Committee, School of Nursing and Midwifery, Shahroud University of Medical Sciences, Shahroud, Iran

Address for correspondence: Dr. Elham Ebrahimi, School of Nursing and Midwifery, Hafte Teer Square, Shahroud, Iran.

E-mail: ebrahimi_308@yahoo.com

Submitted: 13-Dec-14; Accepted: 20-Sep-15

Access this article online

Quick Response Code:



Website:
www.ijnmrjournal.net

DOI:
10.4103/1735-9066.178237

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite: Dadkhah H, Ebrahimi E, Fathizadeh N. Evaluating the effects of vitamin D and vitamin E supplement on premenstrual syndrome: A randomized, double-blind, controlled trial. Iranian J Nursing Midwifery Res 2016;21:159-64.

studies have been carried out on the effectiveness of these supplements, but so far, no decisive result has been obtained in this regard, and further well-designed studies are required to confirm their effectiveness and safety.

Calcium and vitamin D may influence the development of PMS through their relationship to endogenous estrogens. Vitamin D has been observed to fluctuate during the menstrual cycle. The vitamin D level of serum of women with PMS in luteal phase is lower than that in women without the syndrome.^[6] This relationship is justified through the effect of this vitamin in calcium metabolism.^[7] In a cross-sectional study, it was demonstrated that there is a reverse association between vitamin D from food sources and the risk of PMS.^[8] In another study conducted by the same author, it was shown that women who absorb vitamin D and calcium equivalent of four servings per day have a significantly lower risk of having PMS.^[9] Additional data provides support for a biological relationship between calcium, vitamin D, and PMS, including the observation of an increased risk of osteoporosis after menopause in women with PMS.^[10]

Researchers demonstrated that vitamin E supplements cause significant improvement in the physical symptoms of women with PMS.^[11] In a clinical randomized trial study, it was shown that in the group receiving vitamin E, there were statistically meaningful differences in the physical and mental symptoms after the treatment.^[12] Thus, considering what have been mentioned above, the importance of the occurrence of the syndrome in relation to personal and social problems, as well as the affordability, availability, and safety of vitamin D and vitamin E supplements, the current study was carried out to determine the effect of vitamins D and E, and the placebo on PMS symptoms.

MATERIALS AND METHODS

Design

This study was a double-blind, placebo-controlled clinical trial with parallel design that was performed in two health centers in Isfahan, Iran between September 2011 and July 2012.

Study subjects

The study was carried out in two steps. In the first step, 130 women who referred to routine health care were randomly selected. After verifying that the inclusion and exclusion criteria were met and filling out the questionnaire regarding the symptoms of a primary diagnosis of PMS, the patients were evaluated for depression and anxiety using Beck's depression test and Holmes' anxiety criteria'. If a participant was not affected by depression or anxiety disorder, she was asked to fill out the PMS Daily Symptom Record form

for 2 months prospectively. One hundred and nineteen of the original 130 women selected to enter the study were asked to fill out the Daily Symptom Record form for 2 months. The study population consisted of women aged 15–45 years who were referred to the selected health centers for receiving routine health care, affected by PMS according to the criteria of the American Psychiatry Association, and also met the inclusion criteria. After 2 months, 113 women returned the questionnaires. Of these, 86 were affected by the syndrome as indicated by the data analysis. The 86 women were randomly assigned to three groups. Allocation was based on number codes which were hidden in sealed envelopes, with each group consisting of approximately 28 participants.

In the second step, the participants were asked to continue regularly recording their daily symptoms and also to begin taking the tablet they were given from the first day of the menstrual cycle to the start of the next cycle. Among the participants, 30, 28, and 28 participants in the vitamin D, vitamin E, and placebo groups followed the study to the end. The severity of symptoms was determined using the Daily Symptom Record form and symptom rating. The participants rated their daily symptoms as zero (not having), 1 (mild), 2 (moderate), or 3 (severe). The rating was explained as follows: Zero means not having the symptom; 1 (mild) means the symptoms are present, but do not interfere with daily activities such as education and work; 2 (moderate) indicates the symptoms affect the daily activities moderately; and 3 means the symptom prevents the person from taking part in normal daily activities. In this study, the coding method was used for blinding, in which the medicine boxes were coded and then handed to the researcher. Only at the end of the study and after decoding were the contents of the boxes specified for the researcher and study subjects. The exclusion criteria were: Pregnancy, willingness to use hormonal contraceptive methods or taking any hormonal treatment or doing exercise, not taking the drug or not filling out the forms regularly, and unwillingness to continue the treatment.

Ethical considerations

The Ethical Committee of Isfahan University of Medical Sciences approved the study protocol. The researcher explained the study and possible side effects of medications to all the eligible women who were candidates for study. Then, if they agreed to participate, the researcher provided them with consent form and replies to probably questions. Each participant completed the informed consent form before enrolling in the study. Participants could leave the study at any time of the study. They were also not required to pay for additional care.

Intervention

On confirmation of PMS being present in the participants after 2 months, they were randomly assigned to three groups, each consisting of approximately 28 participants. The participants of vitamin D group received one vitamin D tablet (200 mg) daily. The participants of vitamin E group received a tablet containing 100 mg vitamin E, apparently similar to the vitamin D tablet, daily. Each day, the participants of the placebo group received one placebo tablet, apparently similar to the tablets of the two other groups. In this step, the participants were asked to continue regularly recording their daily symptoms and also to begin taking the tablet each day from the first day of the menstrual cycle to the start of the next cycle.

Data collection

Obstetric and demographic information of patients was collected through interviews and reviewing the patients' records on file. The severity of PMS symptoms was assessed by a Daily Rating Test (DRT). Four trained midwives explained to the participants how to fill out the Daily Symptom Record form and followed up with them by phone each week throughout the 4 months of the study (before and after intervention). They recorded the data about symptom severity and probable adverse effects of the drug during the study.

Statistical analysis

We used one-way analysis of variance (ANOVA), paired *t*-test, Chi-square test, and Kruskal–Wallis for comparison of qualitative and quantitative variables. *P* value less than 0.05 was considered statistically significant.

RESULTS

Participant enrollment in the study is shown in Figure 1. No significant difference was observed in the demographic and

obstetric characteristics between the three groups before intervention [Table 1]. Moreover, the findings showed that after intervention, the PMS symptom scores were significantly different with regard to the mean score of the PMS symptoms before the menstrual cycles ($P < 0.05$; $P = 0.000$). However, the three groups were not significantly different in this respect after the treatment ($P = 0.30$). Table 2 shows the mean score of the PMS symptoms before and after the intervention in the three groups. The decrease was the greatest in the vitamin E group and was the lowest in the placebo group. To simplify the comparison of effectiveness of each treatment, we categorized the 30 recorded symptoms into five subgroups, according to Abraham's classification, and then evaluated the effect of each treatment on the symptoms [Table 3].

DISCUSSION

With regard to the periodic and chronic nature of the syndrome, administration of supplements seems to be feasible and safe. Although supplement therapy is utilized for this purpose, to our knowledge, there are few standard randomized controlled trials on this method. This study demonstrated significant reduction in premenstrual score after 2 months in each of the three groups. The results indicated that vitamin E was slightly more effective than vitamin D and placebo in decreasing the PMS symptoms, but there was no significant difference between the three groups.

Khajehei *et al.* carried out a study to determine the potential effect of calcium plus vitamin D and demonstrated that after 2 months of treatment with 500 mg of calcium plus 200 mg of vitamin D, symptom severity decreased significantly. The decrease in calcium plus vitamin D and placebo groups was significantly different.^[3]

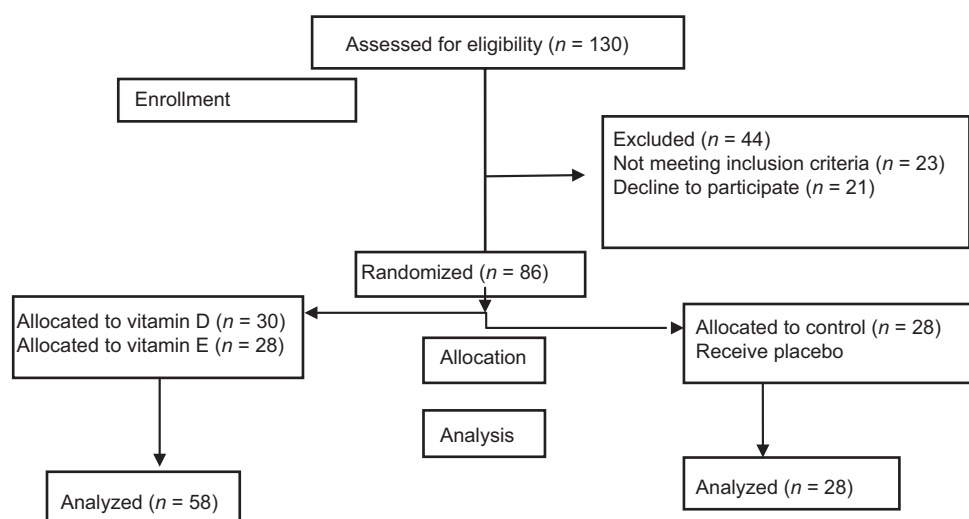


Figure 1: Flowchart of participants' enrollment in the study

Table 1: Obstetric and demographic characteristics of the study subjects

Group (mean±SD)	Vitamin D	Vitamin E	Placebo	F test	P
Age	30.9±6.97	30.82±6.14	29.64±5.51	0.36	0.6
BMI	23.70±5.78	24.29±3.67	23.62±3.61	0.18	0.8
Contraception					
Age at menarche	13.10±1.66	13.64±1.47	13.42±1.75	0.18	0.8
Mens D	7±1.70	7.32±1.58	6.96±1.40	0.44	0.6
Mens I	27.3±2.56	26.67±3.26	28.32±2	2.97	0.05

SD: Standard deviation, Mens D: Menstrual duration, Mens I: Menstrual interval, BMI: Body mass index

Table 2: Mean PMS scores before and after the intervention in the three groups

Group	Vitamin D	Vitamin E	Placebo
Before the intervention	37.49 (10.72)	38.94 (14.29)	35.21 (13.62)
After the intervention	25.5 (11.52)	22.82 (11.56)	27.74 (12.38)
P value	<0.0001	<0.0001	0.0001

Values are expressed as mean (SD), t-test 4.74, F 0.18. PMS: Premenstrual syndrome

Table 3: Comparison of changes in mean premenstrual syndrome scores before and after the intervention in each group

	Vitamin D	Vitamin E	Placebo	P
Craving	-1.88 (1.12)	-2.69 (1.46)	-0.4 (0.79)	<0.0001
Depression	-4.57 (2.8)	-5.52 (3.31)	-2.15 (1.93)	0.0001
Water retention	-1.7 (1.21)	-1.49 (1.11)	-1.02 (0.63)	0.041
Anxiety	-3.4 (1.58)	-3.12 (1.13)	-2.3 (2.16)	0.007
Somatic changes	-2.21 (1.60)	-2.26 (1.53)	-0.99 (0.68)	0.001

Values are expressed as mean (SD). The mean changes are negative due to the reduction of syndrome symptoms after the intervention in comparison to before the intervention

The difference observed between Khajehei *et al.*'s study and the current study can also be partly explained by the difference in the PMS score severity. For instance, in the Khajehei *et al.* study, the syndrome score in the placebo group was higher than in the other groups, whereas in our study, there was no significant difference in the mean score of the PMS symptoms between the groups.

In another study on the effect of vitamin D and calcium on premenstrual migraine, Thys-Jacobs *et al.* reported that with daily administration of 1200 mg of calcium and 1600 IU of vitamin D, the group which received calcium and vitamin D experienced a significant decrease in the severity of premenstrual migraine compared with the placebo group ($P < 0.05$).^[7] The difference observed between the study carried out by Thys-Jacobs *et al.* and the current study could be, in part, because of the higher mean score of PMS in the participants of Thys-Jacobs *et al.*'s study. In their study, all the patients suffered from severe PMS (60 vs 36 in our study) and because of that, the placebo seemed

to have less of an effect than the treatment received by the other group.

In a study carried out by Bertone-Johnson *et al.*, it was demonstrated that women with a high intake of vitamin D from foods have a significantly lower risk of PMS. These dietary intakes corresponded to approximately 1200 mg of calcium and 400 IU of vitamin D from food sources.^[9]

In another study carried out by Bertone-Johnson *et al.* on the effect of vitamin E and placebo on PMS, it was demonstrated that vitamin E (100 mg/day) and placebo had a similar effect on syndrome severity.^[13]

London *et al.* also conducted a study on vitamin E and placebo in 1987. They reported that using 400 IU of vitamin E can alleviate the symptoms of PMS, but no significant difference was found between the two groups.^[14]

Also, Dolatian *et al.* assessed the effectiveness of vitamin E, vitamin B6, and placebo on PMS in 93 patients in Tehran. They found that 100 mg of vitamin E, 40 mg of vitamin B6, or placebo, all had a similar effect in the treatment of PMS.^[15]

Pourmohsen *et al.*, in their study on the effect of calcium, vitamin E, and placebo, reported that after 3 months of intervention with 1000 mg of calcium plus 400 IU of vitamin E, the severity of symptoms showed a significant decrease in the intervention versus placebo group.^[16] The difference between our study and the study by Pourmohsen *et al.* can probably be explained by the longer duration (2 vs 3 months) of treatment and the synergic effect of calcium and vitamin E on PMS in their study. Reviewing various studies on the effect of vitamin E on PMS symptoms indicates that at least 2 months are required for presentation of the therapeutic effects of vitamin E.^[15] Also, it shows that combination therapy with vitamin E and calcium is more effective than vitamin E or calcium alone.

The efficacy of vitamin D and other compounds on each symptom of PMS can be compared from Table 2. Depression-related symptoms are associated with the greatest reduction. The results showed that vitamin E most efficiently reduced depression-related symptoms of PMS. In the study performed by Dolatian *et al.*, vitamin E caused a significant reduction in the mood symptoms of PMS. In the study by London *et al.*, vitamin E efficiently reduced irritability, stress, and low social activities;^[14] these symptoms fall in the subgroup of depression-related symptoms of PMS in our study. The study of Pourmohsen *et al.* reported that intervention with 1000 mg of calcium

plus 400 IU of vitamin E decreased the severity of all the PMS symptoms.^[16] There is no contradiction between the results of the two studies because reviewing various studies on the effect of calcium on PMS symptoms indicates that calcium has the highest effectiveness in relieving the somatic-related symptoms of PMS^[6,9] and the results of the above studies showed that vitamin E has the highest effectiveness in relieving mood-related symptoms. Therefore, the combination of calcium and vitamin D can affect the mood and physical symptoms of PMS at the same time. Unfortunately, studies which have evaluated the effect of vitamin D on PMS are not performed. The details and results of our study can be helpful in this regard.

With respect to the placebo effect, it should be noted that in the studies carried out on PMS, the placebo effect on the syndrome is considerable.^[17] Response to placebo was different, ranging from 0.3 to 0.4, and it seems that paying attention to the women under study can bring about a positive psychological effect in the treatment of PMS.^[18]

The current study had some limitations, including a short intervention period (2 months) and a low sample size, which may have affected both the effectiveness and the side effects noted. Additionally, women in this study had different nutritional regimens that could be a substantial confounder.

CONCLUSION

The current study was undertaken with the goal of finding an effective compound with no side effects to reduce the symptoms of PMS and its direct and indirect economic and social effects. According to this study, vitamins D and E are an effective and affordable treatment for PMS. All compounds used in the current study had no side effects, were effective, non-chemical, and acceptable by most groups of women in the society. Hence, health groups, especially midwives, can compare the effectiveness of the compound on their specific patients and select the most appropriate treatment for each individual. Moreover, in cases where the patient is prohibited from using chemical drugs to treat PMS, such as those on oral contraceptive pills and gonadotropin releasing hormone (GnRH) agonists, the use of these compounds seems effective. However, the prescription of high dosages of every drug should be handled with caution.

Acknowledgment

This study was approved by the Isfahan University of Medical Sciences research Deputy (project no. 290147) and funded by the Research Chancellor of Isfahan University of Medical Sciences. The authors would like to acknowledge this respectable deputy for financial support.

Financial support and sponsorship

This study was approved by Isfahan University of Medical Sciences research deputy (project no. 290147) and funded by the Research Chancellor of Isfahan University of Medical Sciences.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Frank RT. The hormonal causes of premenstrual tension. *Arch Neurol Psychiatry* 1931;26:1053-7.
2. Shin KR, Ha JY, Park HJ, Heitkemper M. The effect of hand acupuncture therapy and hand moxibustion therapy on premenstrual syndrome among Korean women. *West J Nurs Res* 2008;31:171-86.
3. Khajehei M, Abdali K, Parsanezhad ME, Tabatabaee HR. Effect of treatment with dydrogesterone or calcium plus vitamin D on the severity of premenstrual syndrome. *Int J Gynaecol Obstet* 2009;105:158-61.
4. Bakhshani NM, Mousavi MN, Khodabandeh G. Prevalence and severity of premenstrual symptoms among Iranian female university students. *J Pak Med Assoc* 2009;59:205-8.
5. Jurgens T, Whelan AM. Advising patients on the use of natural health products to treat premenstrual syndrome. *Can Pharm J* 2009;142:228-33.
6. Thys-Jacobs S. Micronutrients and the premenstrual syndrome: The case for calcium. *J Am Coll Nutr* 2000;19:220-7.
7. Thys-Jacobs S, Starkey P, Bernstein D, Tian J. Calcium carbonate and the premenstrual syndrome: Effects on premenstrual and menstrual symptoms. *Premenstrual Syndrome study Group. Am J Obstet Gynecol* 1998;179:444-52.
8. Bertone-johnson ER, Hankinson SE, Johnson SR, Manson JE. A simple method for assessing premenstrual syndrome in large prospective studies. *J Reprod Med* 2007;52:779-86.
9. Bertone-johnson ER, Hankinson SE, Johnson SR, Willett WC, Manson JE. Calcium and vitamin D intake and risk of incident premenstrual syndrome. *Arch Intern Med* 2005;165:1264-52.
10. Lee SJ, Kanis JA. An association between osteoporosis and premenstrual symptoms and postmenopausal symptoms. *Bone Miner* 1994;24:127-34.
11. Bendich A. The potential for dietary supplements to reduce premenstrual syndrome (PMS) symptoms. *J Am Coll Nutr* 2000;19:3-12.
12. Mandana Z, Azar A. Comparison of the effect of vitamin E, VitB6, calcium and Omega-3 on the treatment of premenstrual syndrome: A clinical randomized trial. *Annual Research and Review in Biology* 2014;4:1141-9.
13. Johnson SR. Clinician's approach to the diagnosis and management of premenstrual syndrome. *Clin Obstet Gynecol* 1992;35:637-57.
14. London RS, Murphy L, Kitlowski KE, Reynolds MA. Efficacy of alpha-tocopherol in the treatment of the premenstrual syndrome. *J Reprod Med* 1987;32:400-4.
15. Dolatian M, Montazeri SH, Velaei N, Ahmadi M. Comparative effects of vitamin B6 and vitamin E on symptoms of premenstrual syndrome. *J Zanjan Univ Med Sci* 2002;37:5-10.

16. Pourmohsen M, Zoneamat KA, Taavoni S, Hosseini AF. Effect of combined calcium and vitamin E consumption on premenstrual syndrome. *J Iran Nursing Tehran Univ Med Sci Health Services* 2010;23:8-14.
17. London RS, Bradley L, Chiamori NY. Effect of a nutritional supplement on premenstrual symptomatology in women with premenstrual syndrome: A double-blind longitudinal study. *J Am Coll Nutr* 1991;10:494-9.
18. Salamat S, Ismail KM, O'Brien S. Premenstrual syndrome. *Obstet Gynaecol Reprod Med* 2008;18:29-52.