



## Review Article

# The Effect of Micronutrients on Pain Management of Primary Dysmenorrhea: a Systematic Review and Meta-Analysis

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## ABSTRACT

**Introduction:** Primary dysmenorrhea is considered as one of the main problems in women. This review study aimed to characterize the effect of micronutrients on primary dysmenorrhea.

**Methods:** In this systematic and meta-analysis study, the articles were searched at Cochrane library, PubMed, Scopus, Web of Science databases. The searching process was conducted with the key terms related to dysmenorrhea and micronutrients. Risk of bias assessment was performed, using Rev Man 5.3 software. In view of the heterogeneity of some of the studies, they were analyzed, using a qualitative method (n=10), and only 6 studies were included in Meta analyze. STATA statistical software version 11 was used for the analysis.

**Results:** In this study, finally 16 clinical trials were investigated. Most micronutrients studied in the relevant articles had anti-inflammatory and analgesic properties with a desirable effect on dysmenorrhea pain relief. Vitamins (K, D, B1, and E) and calcium, magnesium, zinc sulfate and boron contributed effectively to dysmenorrhea pain management. Two months after the intervention, there was a significant mean decrease in the pain score for the vitamin D intervention group (SMD: -1.02, 95% CI: -1.9 to -0.14, P =0.024), as well as in the vitamin E intervention group compared to placebo group (SMD: -0.47, 95% CI: -0.74 to -0.2, P = 0.001).

**Conclusion:** Despite the paucity of related research, the studies indicated the potential effects of micronutrients on reducing the pain severity in primary dysmenorrhea. But more studies are needed to confirm the safety and effectiveness of various types of micronutrients on primary dysmenorrhea.

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## Introduction

Dysmenorrhea is a common menstrual symptom known as menstrual pain or menstrual cramps, its overall prevalence in women of reproductive age is estimated to be 16-91%,<sup>1</sup> and its prevalence in Iranian women is estimated 71%.<sup>2</sup> Dysmenorrhea is generally categorized into two distinct types: primary and secondary. Primary dysmenorrhea is defined as a painful menstruation without any pelvic pathology.<sup>3,4</sup> Primary dysmenorrhea is considered as one of the main problems in women and in public health so that WHO refers to it as the main cause of chronic pelvic pain.<sup>5</sup> In fact, in addition to its huge economic burden,<sup>6</sup> dysmenorrhea affects different dimensions of life and causes limitations in daily activities<sup>7,8</sup> and low sleep quality,<sup>9,10</sup> as well as negatively affect the patient's mood, lead to depression, stress and anxiety.<sup>8,11,12</sup> Although the main cause of primary dysmenorrhea is not well recognized, most studies show an increase in the levels of prostaglandins E<sub>2α</sub> (PGE<sub>2α</sub>), F<sub>2α</sub> (PGF<sub>2α</sub>), and leukotriene during menstruation and this, in turn, results in more uterine muscle contractions

and cramps.<sup>4,13,14</sup> In case of primary dysmenorrhea, different treatment methods and dietary supplements including non-invasive interventions, treatment methods based on dietary plan and vitamins, herbal medicine, drug therapy.<sup>15</sup> Standard treatment for dysmenorrhea is non-steroidal anti-inflammatory drugs (NSAIDs) and oral contraceptive (OC) pills. NSAIDs act as anti-prostaglandins with an approved effectiveness and their side-effects include complaints about digestive system, mild nervous symptoms and cardiovascular complications.<sup>15,16</sup> Despite little evidence for the effectiveness of contraceptive pills in the treatment of dysmenorrhea,<sup>17</sup> they are still used to this end. About half of women, after one year of using hormonal contraceptives, stopped taking them due to their side-effects.<sup>18</sup>

In general, micronutrients include necessary vitamins and minerals. They are essential for preserving physiological function of the body; deficiency of micronutrients can have a wide range of negative effects on human health.<sup>17</sup> Micronutrients are supplied in the market in different forms of pills, capsules, soft gels and

gel caps. All around the world, women suffer from deficiency or insufficient intake of some types of micronutrients. The evidence shows that in women of reproductive age, iron, folate, vitamin D, and zinc deficiency is highly prevalent<sup>18</sup> as the reproductive role of women results in more need for intake of some micronutrients.<sup>19</sup> Poor diet and lifestyle have a key role in menstrual cycle and its hormonal changes in women.<sup>20</sup>

Women experience menstrual disorders because of nutrition status.<sup>21</sup> Nowadays dietary pattern is an alternative valuable approach in risk of different disorders.<sup>22</sup> Most women attempt to use alternative medicine such as dietary therapy to relieve menstrual pain.<sup>23</sup> A standard treatment for this problem is to use anti-inflammatory drugs. Many Micronutrients play an effective antioxidant and anti-inflammatory role in biological anti-inflammatory activities of the body.

Thus, since dysmenorrhea is considered one of the main problems of women during their course of life and micronutrients are widely used for treatment of dysmenorrhea, and with regard to their easy accessibility and non-prescription sale, it is essential to establish some practical and comprehensive evidence on their effective dose, effectiveness and drug interactions. Also, there isn't any review study in this regard. Therefore; this study was intended to investigate evidences related to the effectiveness of micronutrients in treating primary dysmenorrhea in a systematic review and meta-analysis.

## Materials and methods

This study is a systematic review and meta-analysis of randomized controlled trials (RCTs), assessing published articles in English (clinical trials) from 2000 to 2017 (except for one study -Zangane et al.-which was indexed in Scopus with an English abstract, and its full text was included in Persian), searching through databases, including PubMed, Scopus, Web of science and Cochrane library. The search was based on the following as related to the Dysmenorrhea and micronutrients keywords: [Dysmenorrhea OR Menstrual Pain OR Painful Menstruation] AND [Vitamin A OR Retinol OR Vitamin D OR vitamin D3 OR Cholecalciferol OR Vitamin E OR Tocopherol OR Alpha Tocopherol OR Vitamin B1 OR Thiamin OR Vitamin B6 OR Pyridoxine OR Pyridoxal OR Pyridoxamine OR Vitamin B2 OR Riboflavin OR Biotin OR Avidin OR Vitamin B12 OR Cobalamin OR Vitamin C OR Ascorbic Acid OR Niacin OR Nicotinic acid OR Vitamin B3 OR Vitamin PP OR Folic acid OR Folate OR Vitamin B9 OR Vitamin K1 OR vitamin K2 OR vitamin K3 OR menaquinone OR phytonadione OR Mephyton OR Calcium OR Ca OR Magnesium OR Mg OR Iron OR Fe OR Chromium OR Cr OR Copper OR Cu OR Fluorides OR Iodine OR Manganese OR Mn OR Molybdenum OR Mo OR Selenium OR Se OR Zinc OR Zn Boron OR Sodium pentaborate].

In PubMed, the articles were limited to clinical trials. Thus, in all data bases, advanced search was used. Figure1 shows the flowchart of article selections.

The inclusion criteria of this review are only the published studies, with the following PICO criteria in timeframe 2000 to 2017 and the studies without these criteria were excluded. We extracted the following information from each study: author/s, year of publication, location of the study, sample size, study design, findings. After the data had been extracted, they were checked by the authors for discrepancies in order to minimize the possibility of errors.

Criteria for considering studies for this review:

*Selection of studies:*

Types of participants: all clinical trials with inclusion criteria of healthy women experiencing primary dysmenorrhea.

Types of interventions: all clinical trials involving micronutrients treatment for primary dysmenorrhea versus placebo, no treatment or any treatment for primary dysmenorrhea.

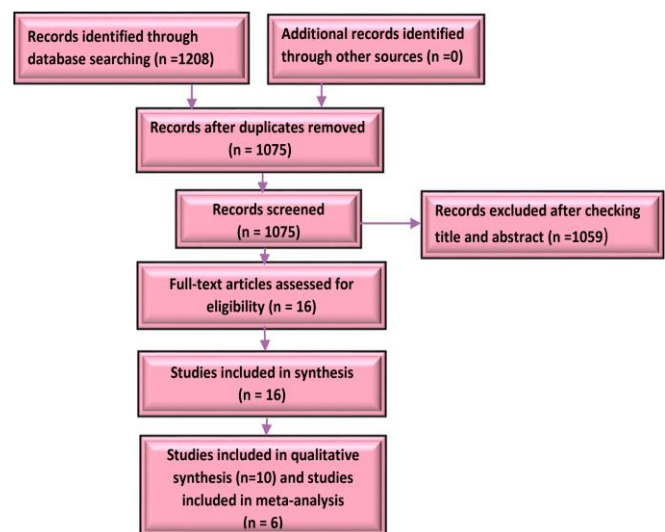
Types of comparator/control: placebo, no treatment or other usual treatments

Types of outcome measures: primary dysmenorrhea pain, measured by standardized scales such as visual analogue scale, numeric rating scale, multi-dimensional speech criteria. The side-effects which reported by studies were recorded.

Primary outcome: severity menstrual pain relief according standard pain measure scale.

Secondary outcome: perception other treatment during study, improvement in other menstrual symptoms, adverse effect of each intervention in participants of studies.

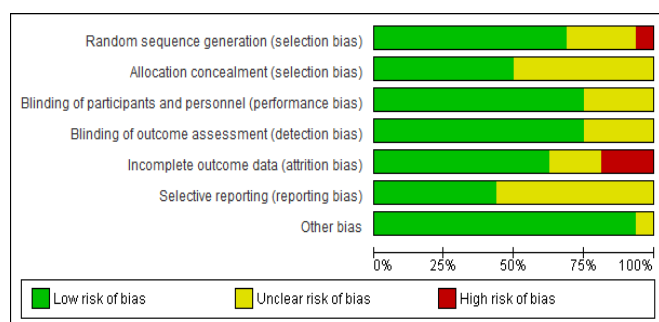
Risk of bias: we used the Cochrane risk of bias tool, including selection bias (random sequence generation, allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting) and other bias.<sup>24</sup> According to this tool, the methodological quality was judged on a three-degree scale "high", "low", "unclear". Figure 2 shows the methodological quality graph.



**Figure 1.** Flowchart of study

Data analyze: in studies about vitamin D and vitamin E included in met-analysis. The mean and standard deviation of pain score in intervention and placebo groups were extracted. In studies which reported median and interquartile range, the mean and standard deviation was estimated.<sup>25</sup> The score of pain intensity were extracted in standard range of VAS 0-10 in one scale with score 0-3 the score range transformed to standard range 0-10.<sup>26</sup> We calculated the mean difference with confidence interval 95% for primary dysmenorrhea outcome.

Because of heterogeneity ( $I^2 > 50\%$ ) the overall effect was calculated by random effect model. The STATA statistical software version 11 was used for the analysis.



**Figure 2.** Methodological quality graph: review authors' judgments about each methodological quality

## Results

In this study, 16 clinical trials were included in a qualitative synthesis: out of 16 articles, with 1871 participants, 4 articles were about Vitamin E, 3 were about Vitamin D, 2 were about Vitamin B1, 3 were about Zinc, one was about vitamin K, one was about Vitamin D and Calcium, one was about Calcium carbonate and Magnesium stearate and one was about Boron. Most studies have demonstrated a positive effect on reducing pain of primary dysmenorrhea; however, no adverse effect has been reported. The age range of the participants was 13-40 years. The evaluated studies are summarized in (Table 1).

### Risk of bias report

Random sequence generation was judged in 11 articles as 'low risk' and in 4 article 'unclear risk' and in Zangane et al.,<sup>27</sup> study the random sequence generation was judged 'high risk' because of using the days of week method. Allocation concealment was judged in 8 articles 'low risk' and in 8 articles authors had not clearly described the allocation concealment methods. Blinding (performance bias) was judged as 'low risk' in 12 articles and 'unclear risk' in 4 articles as the blinding of the participants and personnel had not been adequately clarified. Blinding of outcome assessment was judged as 'low risk' in 12 articles, but in 4 articles the authors had not clearly described the detection bias. Incomplete outcome data were judged as 'low risk' in 10 articles and 'unclear risk', and in the remaining they were judged as 'high risk' in Moini et al.,<sup>28</sup> study more than 10% drop

out rate in study group, Kashanian et al.,<sup>29</sup> only 42 (from 60) participants in the intervention group and 52 (from 60) of the control group completed the study. The dropout was 26 (from 120). In Moslemi's et al., study<sup>30</sup> the dropout rate was 16%. Selective reporting was judged 'low risk' in 7 articles and in 9 articles authors had not clearly described it. Other bias was judged 'low risk' in 15 articles.

The main result of the study reports is provided below:

### Vitamin D

The effect of vitamin D alone in three studies, and that of vitamin D and calcium together in another study were investigated in Lasco et al.,<sup>31</sup> Moini et al.,<sup>28</sup> and Zangane et al.,<sup>27</sup> and the results suggested their positive effects on dysmenorrhea pain management. Lasco et al., and Zangane et al., studies were included in meta-analysis, but in Moini et al., study the participants had vitamin D deficiency and this study had a different population, so it was not included in the analysis. The result showed that in one month after the intervention, there was not a significant mean decrease in pain score for the vitamin D intervention group compared to placebo (standardized mean difference -0.5, 95% CI: -1.6 to 0.6,  $P = 0.36$ ).

However, two months after the intervention, there was a significant mean decrease in pain score for the vitamin D intervention group compared to placebo (standardized mean difference -1.02, 95% CI: -1.9 to -0.14,  $P = 0.024$ ).

### Calcium and Magnesium

In study by Zarei et al.,<sup>32</sup> calcium was prescribed alone, and with vitamin D, and vitamin D level in blood was unknown, in which case the pain severity reduction was reported, but in vitamin D and calcium group, this decrease was significant; however, it was stated that this significant decrease might have been achieved by chance as lack of experimental information on calcium and vitamin D levels in blood was considered an important limitation of this study. In Mohammad Alizadeh Charandabi et al.,<sup>33</sup> study on 63 students, calcium intervention, combined calcium- magnesium intervention and placebo were compared and the results showed that combined calcium- magnesium had better outcome than calcium intervention with mean difference -1.1 (-1.4 to -0.8).

### Vitamin E

About 26.6% of the studies in this review article were about the positive effects of vitamin E on alleviation of primary dysmenorrhea pain. In Ziaei's et al., study<sup>34</sup> 100 IU of vitamin E per day was used for 5 days in a cycle up to 2 cycles and in another study by Ziaei et al.,<sup>35</sup> 200 IU per day was used for 2 cycles. In Moslemi's et al., study<sup>30</sup> 400 IU of vitamin E per day was used for the first 3 days after the onset of the cycle for 2 cycles and in a study by Kashanian et al.,<sup>29</sup> 400 IU was prescribed for the first two days of period for 4 cycles. All studies showed a significant reduction in pain severity in the intervention group. The result showed that one month after the intervention, there was not a significant mean decrease in pain score for the vitamin E intervention group compared to placebo (standardized mean difference -

**Table 1.** The characterize of included studies

Author	Method	Subjects	Intervention	Measure	Outcome	Adverse effects
Wade et al., <sup>41</sup>	DBRCT	80 chinese women aged 14–25 years	Group1: single injection of vitamin K3 Group 2:vitamin K3 acupuncture point injection Control group: Saline in spleen 6	NRS	The mean pain decreased by 4.9 points (P<0.001) in the group A and 4.7 points (P<0.001) in the group B and 6.6 point decrease in pain an acupuncture point injection of vitamin K3 in SP6. Mean difference: a vs B:-0.708, A vs standard: 1.113, B vs standard: 1.821. In all groups the menstrual distress post treatment was reduced	Mild discomfort at the injection site
Moini et al., <sup>28</sup>	DBRCT	50 women aged 18–30 years with vit d deficiency	50 000 IU oral vit D / once per week Control group: Placebo	VAS	After eight weeks of treatment , pain severity decreased significantly in treatment group (P<0.001) Two month after intervention, number of NSAID intake in intervention group significantly decreased [0.91 (1.08) in Vit D versus 2.11 (1.08) in placebo]	Was not reported
Zarei et al., <sup>32</sup>	Randomized placebo-controlled trial	85 students with 18 to 32 years	Group1: one tablet/day of 1000mg calcium15000 IU vitamin D3 Group2:calcium-alone1000 mg Control group: Placebo	VAS	The mean pain severity was lower in the both calcium-vitamin D (-0.7, 95% CI -1.6 to 0.3) and calcium-alone (-1.6, CI95% -2.6 to -0.6), but the difference was statistically significant only in the calcium-alone group, there were no significant differences were found between calcium-vitamin D vs. placebo (-7.7, -32.0 to 16.7), there was an increase in mean of physical health and mental health in calcium-vitamin D group (mean difference 3.3 and 7.1, respectively), calcium-alone group (6.7 and 9.9), and only a slight change in the placebo group .	Constipation and headache
Zangene et al., <sup>27</sup>	DBRCT	54 girl18-30 years	A single dose of 300,000 IU of vitamin D was prescribed 5 days before the beginning of menstruation, for three consecutive cycles Control group: Placebo	VAS	At first, pain severity was high in both groups, and then it decreased in the first months. In placebo group, pain severity did not decrease in the second and third months, but it increased. Though pain severity decreased in the second and third months in the group of Vitamin D. Mefnamic acid intake in intervention group was 40% and in placebo group was 62.1% (P=0.09).	Was not reported
Lasco et al., <sup>31</sup>	DBRCT	40 italian women 18 to 40 years	20 women received a single oral dose of cholecalciferol (300 000 IU/1mL) .5 days before the putative beginning of their next menstrual cycle Control group: Placebo	VAS	There were significant reduction of pain in the vitamin D group compared with the placebo group (P<0.001). The intervention groups don't use NSAIDS but in the placebo group at least one NSAID use in 40% of women.	Was not reported
Hosseini et al., <sup>40</sup>	DBRCT	240 female student 13 to18 years	1)Vit B1 (100 mg/day) 2) Fish oil pearl 500 ,mg/day 3)Vit B1 100 mg/day and fish oil pearl 500 mg/day Control group: Placebo	VAS	In all three experimental groups (vitamin B1, fish oil, combination therapy) severity of pain significantly reduced (P<0.001) versus control group (p=0.79). In all experimental groups pain duration reduce (P<0.05) versus the control group (p=0.32).	Was not reported
Kashania et al., <sup>29</sup>	DBRCT	94 women 18-25years	400 IU/day of vitamin E was prescribed starting 2 days before the beginning of menstruation and continuing for a total of 5 days, for 2 consecutive cycles, Control group: Placebo	VAS	Pain severity during the first and second months of treatment with vitamin E and placebo was lower than the pain severity before treatment (P<0.05). The pain reduction in second month in study group is greater than other group.	Was not reported
Moslemi et al., <sup>30</sup>	Single blind placebo-controlled trial	65 single female students who suffered from primary dysmenorrhea	1) The 100-unit vitamin E capsules every 6 h for 3 days after their menstruation started for 2 consecutive menstrual cycles. 2) 46 mg fennel Control group: Placebo	MDSC	In the fennel extract group and vitamin E group, the pain severity was lower compare to before treatment (P<0.001) reduction was greater in fennel extract group (P<0.019).	Was not reported
Ziaei et al., <sup>34</sup>	Randomized placebo-controlled trial	100 girls aged 16–18 years	Vit E 100 IU (5 tablets a day for 5days; two days before and 3 days after the beginning of menstruation). Control group: Placebo	VAS	The pain severity in the two groups (treatment and control groups) was reduced after treatment, but the reduction was greater in the group treated with vitamin E (P<0.05).	Was not reported

**Table 1. (Continued)** The characterize of included studies

Author	Method	Subjects	Intervention	Measure	Outcome	Adverse effects
Ziaei et al., <sup>35</sup>	DBRCT	278 girls aged 15–17 years	vitamin E 200 units twice a day, beginning 2 days before the start of menstruation and continued the first 3 days of bleeding Control group: Placebo	VAS	There were statistically significant reductions in pain score in both groups at 2 and 4 months but the reduction was significantly greater in the vitamin E group than other group ( $P < 0.001$ ). Reduction in pain duration and menstrual blood loss in intervention group significantly greater than placebo ( $P < 0.05$ ).	Without adverse effects
Zekavat et al., <sup>36</sup>	DBRCT	120 females aged 14–18 years	50 mg/day zinc beginning on the first day of menses and continuing until three days prior to the end of menses. Control group: Placebo	VAS	In the first month there was no significant difference in pain severity between the groups ( $P = 0.497$ ). In the second and third month, pain severity and duration in the zinc group were lower than the other group ( $P < 0.001$ ). After intervention reduction in pain duration in intervention group significantly greater than placebo ( $P < 0.05$ ).	Without adverse effects
Teimoori et al., <sup>38</sup>	DBRCT	200 participants 18–26 years	Zinc sulfate capsules 220 mg once daily and mefenamic acid capsules 250 mg 3 times daily Control group: Placebo	VAS	The difference in pain levels before and after treatment in the intervention group was 4.1(2.8), and in the control group was 2.9(1.7) ( $P > 0.050$ ).	Was not reported
Kashefi et al., <sup>37</sup>	Randomized placebo-controlled trial	137 students 15–18 years	220 mg zinc sulfate for 4 days, from the day before the commencement of menstruation to the third day of their menstrual bleeding Control group: Placebo	PVAS	Compared with the placebo group, participants receiving zinc sulfate reported more reduction of pain ( $P < 0.05$ ). In zinc group mean pain score before intervention was 8.01 and first month 6.18, two month after intervention was 3.12.	Diarrhea, headache, and heartburn
Zafari et al., <sup>39</sup>	Clinical trial	152 girls 18 to 22 years	100 mg/day vitamin B1 during the luteal phase Control group: 400 mg ibuprofen when their pain started	MDSC	In the first month after intervention there was no difference between the severity of pain in the two groups ( $P = 0.414$ ), but there was difference in the second and third months ( $P < 0.001$ ).	Was not reported
Charandabi Mohammad-Alizadeh et al., <sup>33</sup>	DBRCT	63 student 18–21 years	Group1: 600 mg calcium carbonate and 300 mg magnesium stearate Group2: 600 mg calcium carbonate Control group: placebo	VAS	The outcomes in calcium- magnesium and calcium alone groups had better than the placebo group in pain severity, pain relief and rest length. In pain relief and rest length the calcium-magnesium group had significantly better outcomes than the calcium group but not in the Ibuprofen group.	Without adverse effects
Nikkhah et al., <sup>41</sup>	Triple-blind randomized clinical trial	113 university students 18–25 years	10 mg/day Boron from 2 days before the menstrual flow until its third day Control group: placebo	VAS	After the intervention, the severity and duration of pain were significantly lower in the treatment group than placebo group ( $P < 0.05$ ).	Without major side effects

DBRCT: Double-Blind Placebo-Controlled Randomized Clinical Trials, VAS: Visual Analogue Scale, NRS: Numeric Rating Scale, PVAS: pain visual analog scale, MDSC: multi-dimensional speech criteria



0.07, 95% CI: -0.42 to -0.29,  $P = 0.718$ ).

Two months into the intervention, however, there was a significant mean decrease in the pain score for the vitamin E intervention group compared to placebo group (standardized mean difference -0.47, 95% CI: -0.74 to -0.2,  $P = 0.001$ ).

#### Zinc

In this study, 3 clinical trials were included, administration of zinc micronutrient also significantly reduced dysmenorrhea. In a study by Zekavat et al.,<sup>36</sup> 50 mg/day zinc was used on the first 3 days for 3 cycles and in the study by Kashefi et al.,<sup>37</sup> 220 mg zinc (3 times a day to 4 days) was used for 2 months, and in Teimoori et al.'s study<sup>38</sup> 250 mg/day zinc and Mefenamic acid capsules (250) were administered for 3 menstrual cycles. Since mefenamic acid was used with zinc as a pain killer in Teimoori et al.'s study, the synergic effect of mefenamic acid may illustrate a significant reduction of pain severity.

Although pain alleviation was significant in the second month in Kashefi's et al., study, it wasn't significant between the treatment and placebo groups during the first month. In addition, the decrease in pain severity in the first month was not significant between the two groups in Zekavat's et al., study but it was significant in the second and third months. Therefore, it seems that duration of administration is important in this case.

#### Vitamin B1

Another micronutrient studied in this research was vitamin B1, which was investigated in two clinical trials. In a study by Zafari et al.,<sup>39</sup> vitamin B1 was compared with ibuprofen and it was reported that there was no significant difference in pain reduction between the two groups, but due to its poor side effects, use of vitamin B1 was recommended. In a study by Hosseinlou et al.,<sup>40</sup> vitamin B1 group alone, fish-oil capsule group, mix of vitamin B1 and fish oil group finally all three groups were compared with placebo group and it was reported that there was a significant reduction in pain severity for all treatment groups.

#### Vitamin k

In one clinical trial, injection of vitamin K3 in SP6 caused a significant reduction in the severity of dysmenorrhea pain (decrease from 8.0 to 1.5,  $P < 0.001$ ) in the saline injection group (from 7.9 to 3.0,  $P < 0.001$ ) in the vitamin K3 muscle injection group (decrease from 8.0 to 3.3,  $P < 0.001$ ).<sup>41</sup>

#### Boron

Boron was one of the nutrients that was studied only in one clinical trial on primary dysmenorrhea in which a significant decrease in the severity and duration of pain in the treatment group was observed.<sup>42</sup>

## Discussion

The results of current study indicated the effectiveness of various types of micronutrients [vitamins (K, D, B1, and E) and minerals (calcium, magnesium, zinc sulfate and boron)] on alleviation of the severity of primary

dysmenorrhea pain. In this study, the largest number of articles on the vitamin group related to vitamin E (25%) and to zinc in the minerals group. The results of a systematic study by Cochran showed that no strong evidence existed on the effectiveness of a variety of dietary supplements herbal and non-herbal (fish oil, melatonin, vitamins B1 and E, and Zinc sulfate) for improvement of dysmenorrhea pain.<sup>43</sup>

The results of our study showed that two months after vitamin D intervention brought about more tangible effect on pain severity than one month after intervention. In a review study by Wu et al., the results indicated that vitamin D supplement effectively alleviated the severity of chronic pain.<sup>44</sup> This micronutrient may be effective in reducing the severity of pain through this mechanism: Vitamin D receptor plays a major role in regulating steroid hormones in the female reproductive system.<sup>45</sup>

The function of biologically active form of vitamin D, called 1, 25-dihydroxyvitamin D, in endometrium causes a reduction in the synthesis of prostaglandins by suppressing cyclooxygenase 2 expressions. Furthermore, elevated inactivation of prostaglandin also has anti-inflammatory effects through up-regulating 15-hydroxyprostaglandin dehydrogenase.<sup>46</sup> However, given the inconsistency of the studies, it seems that clinical trials with a large sample size are needed to investigate administration of vitamin D in women with normal levels of vitamin D who suffer from primary dysmenorrhea to have strong evidence indicating the therapeutic effects of this micronutrient on primary dysmenorrhea. In addition, as the optimal level of vitamin D is different in various disorders, it is recommended that the cut-off point for vitamin D level should be specified to be effective in improvement of dysmenorrhea, because if administration of this vitamin leads to its excessive amounts in blood, toxicity develops and causes abnormal level of steroid hormones,<sup>45</sup> and other disrupted parameters in blood.<sup>47</sup>

The result of our study showed that two months after vitamin E intervention had more effect on pain severity than one month after intervention. The results of a meta-analysis by Kharaghani et al., in three studies also showed that vitamin E reduces dysmenorrhea pain to 7%.<sup>48</sup> The mechanism of action for vitamin E can be due to its antioxidant effect which reduces arachidonic acid release and thereby reduces its conversion to pain-inducing prostaglandins.<sup>49</sup> Additionally, it is known to have anti-inflammatory properties by acting on the enzymes and proteins of inflammatory pathways.<sup>50,51</sup> Considering the large sample size and appropriate methodology in the above studies, it is possible to talk more confidently about the effectiveness of this vitamin in relieving pain in dysmenorrhea. However, in order to confirm its safe therapeutic effect and to determine its standard therapeutic dose, more evidence is needed.

The results of case-series by Eby showed that zinc consumption reduces dysmenorrhea and uterine cramps,<sup>52</sup> which are consistent with the results of the current study. There are various hypotheses about the

effectiveness of zinc in dysmenorrhea. Zinc reduces production of prostaglandins,<sup>52</sup> and inhibits prostaglandin- and leukotriene-dependent metabolisms which induces dysmenorrhea<sup>53,54</sup> and consequently, alleviates uterine cramps. In many cases, dysmenorrhea pain and discomfort are due to generation of oxygen free radicals. There is an enzyme that deactivates superoxide free radicals, which are present in the uterus. Zinc has antioxidant and anti-inflammatory properties<sup>55</sup> and its use can control the inflammation associated with dysmenorrhea and increase blood flow in the uterine arteries.<sup>56</sup> However, in general, due to heterogeneity of the studies, it is not possible to confirm the analgesic effects of this micronutrient.

Also, the results of the current review study demonstrated that calcium micronutrient alone and together with magnesium<sup>33</sup> and also with vitamin D (in another study) can reduce dysmenorrhea. Calcium is a stabilizing agent and regulates the ability of muscular cells to respond to neural stimuli. High blood calcium leads to a reduction in the excitability of nerves and muscles, and its reverse state reduces spasm and muscle contraction.<sup>57</sup> The results obtained by Thys-Jacobs et al., showed that serum calcium levels were reduced in the last half of the luteal phase and in menstrual bleeding.<sup>58</sup>

In another clinical trial, the administration of 4 mg of K3 caused a significant reduction in the severity of dysmenorrhea pain.<sup>41</sup> Boron was one of the nutrients that was studied only in one clinical trial on primary dysmenorrhea in which a significant decrease in the severity and duration of pain in the treatment group was observed.<sup>42</sup> As little is known about vitamins K and B1, calcium, magnesium and boron, more studies are needed to shed light on their effectiveness.

In general, several review studies have examined the effects of different methods such as massage therapy, acupuncture, medicinal herbs and Nonsteroidal anti-inflammatory drugs like ibuprofen and mefenamic acid on the severity of primary dysmenorrhea.<sup>59-62</sup> But the important point in our study which examined the effectiveness of micro-nutrients in primary dysmenorrhea is that in various studies, micronutrients had been prescribed along with or without the conventional treatment of dysmenorrhea (NSAIDs).

Moreover, the administered doses of different types of micronutrients and the duration of their administration in different menstrual cycles, as well as lack of information on whether the subjects in the studies had normal levels of the respective micronutrient or not, did not allow a comparison of pain severity reduction by each single micronutrient. However, despite weak evidence, our studies suggest that there is a potential effect of nutrients on dysmenorrhea. But more studies are needed to confirm the effectiveness of various types of micronutrients. One of the strengths of this study is that the effectiveness of a large variety of micronutrients on primary dysmenorrhea has been examined.

One of the limitations of this study was that due to the very limited number of studies on vitamins and minerals

and the heterogeneity of studies, it was not possible to perform a meta-analysis. Another limitation of the study was that Gray literature was not searched because there was no access to all of these documents worldwide. Therefore, it is suggested that other studies should be conducted to examine such documentation. A similar review study is recommended on the effect of micronutrients on the treatment of secondary dysmenorrhea.

## Conclusion

In spite of poor evidence, the studies examined in this review article indicate that there are potential effects of micronutrients on reducing the pain severity of primary dysmenorrhea. But more studies are needed to confirm the safety and effectiveness of various types of micronutrients and for determine the optimal dose of micronutrients.

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## Ethical issues

None to be declared.

## Conflict of interest

The authors declare no conflict of interest in this study.

## Research Highlights

### What is the current knowledge?

There are various pharmacological treatments for primary dysmenorrhea, but these treatments have some side effects. On the other hand now, poor diet and lifestyle lead to micronutrient deficiency in women, which a key role in menstrual cycle disorders in women.

### What is new here?

This study reviews the potential effects of micronutrients on reducing the pain severity in primary dysmenorrhea.

## Author's contributions

MSG and GO contributed to the study design; MSGZK, FRF, VG and GO contributed to the execution and analysis; MSG, MA and ZK contributed to manuscript drafting and all authors contributed to the critical discussion and approval of final version of the manuscript.

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