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Meta-analysis

The effects of vitamin E on the intensity of primary dysmenorrhea: A systematic review and meta-analysis

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SUMMARY

Background & aims: Primary dysmenorrhea (PD) refers to the presence of painful menstrual cramps due to increased synthesis of prostaglandins. Vitamin E inhibits the release of arachidonic acid and its conversion to prostaglandins through its antioxidant properties. This study sought to examine the effects of oral vitamin E supplementation on PD intensity (primary outcome) and its side effects (secondary outcomes).

Methods: In this systematic review and meta-analysis, databases in English and Persian, including PubMed, Cochrane Library, Google Scholar, Scopus, Web of Science, SID, and Magiran, were systematically searched until August 30, 2021. The study included all randomized, controlled clinical trials comparing oral vitamin E to placebo in healthy women with PD and measuring PD severity as a primary or secondary outcome. The quality of the included articles was assessed using the Cochrane Handbook, and the meta-analysis was performed using RevMan software. Given the continuous nature of the data and the utilization of different tools in the extracted articles, the meta-analysis results were reported using standardized mean difference (SDM) and 95% confidence interval (95% CI). A subgroup analysis was performed in low-dose (100 units), moderate-dose (200 units), and high-dose (400 units) categories. The quality of evidence was examined according to the GRADE approach.

Results: Eight articles with a sample size of 1002 people were entered into this systematic review. The results of meta-analysis revealed that vitamin E consumption significantly reduced PD mean intensity in the first month ($n = 7$ records; $SDM = -1.16$; $95\%CI: -2.16$ to -0.17 ; $I^2 = 31.9\%$; $P = 0.02$) and the second month ($n = 8$ records; $SDM = -1.83$; $95\%CI: -2.90$ to -0.77 ; $I^2 = 76.3\%$; $P < 0.0001$) compared with placebo. Serious side effects were not reported in vitamin E recipients.

Conclusion: Vitamin E could be an adjunctive treatment for women with PD. However, higher-quality clinical trials with larger sample sizes are recommended for a more definite conclusion.

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1. Introduction

Primary dysmenorrhea (PD) is defined as the presence of painful menstrual cramps without apparent pelvic pathology. It commences with the onset of the menstrual cycle and lasts for 12–48 h [1]. Its prevalence among women of reproductive age is estimated

at 16 to 91 percent globally [2] and approximately 74–90 percent in Iranian women [3]. The condition is considered a principal concern in public health, and the World Health Organization refers to it as the primary cause of chronic pelvic pain [4]. In addition to its substantial economic burden [5], it affects various aspects of life, leading to impaired daily activities [6,7] and reduced sleep quality [8,9]. It may also affect the patient's mood and cause depression, stress, and anxiety [7,10,11].

PD's exact pathogenesis is unknown. Potential mechanisms explaining PD pathogenesis include vasopressin levels, cytokine

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gene expression profiles, prolactin levels in the luteal phase, nighttime body temperature, and morning estrogen concentrations [12]. Some studies have considered prostaglandins responsible for contractions in PD [1]. Prostaglandins and leukotrienes cause vasoconstriction and myometrial contraction, resulting in uterine ischemia [12], whereas reactive oxygen species induce oxidative stress during ischemia [13].

Various approaches are used to alleviate dysmenorrhea, including Complementary therapies, nutritional alternatives, vitamins, psychotherapy, transcutaneous electrical nerve stimulation, oral contraceptives, and non-steroidal anti-inflammatory drugs (NSAIDs) [14,15]. Complementary treatments and natural compounds are used in the control and treatment of inflammation and oxidative stress in chronic diseases, especially dysmenorrhea. For example, *Nigella sativa* has anti-oxidative and anti-inflammatory properties, so it can be used in controlling chronic diseases such as type 2 diabetes, cardiovascular, and rheumatoid arthritis diseases [16]. Curcumin exerts has anti-inflammatory and anti-cancer effects through controlling various lncRNAs [17]. Pycnogenol can be used for traumatic brain injury patients to reduce inflammation and oxidative stress [18]. Also propolis and melatonin can be used as a pharmaceutical agents in patients with primary sepsis due to their anti-inflammatory, anti-infection and anti-oxidative [19]. High doses of vitamin D supplementation have been linked with a reduced pain severity of dysmenorrhea. The relationship between calcium intake and dysmenorrhea can be attributed to the function of calcium in reducing contractions. Low calcium levels aggravate spasticity and uterine contractions, while vitamin D levels affect calcium homeostasis and can be effective in improving dysmenorrhea [20].

Oral contraceptive pills and NSAIDs constitute the standard treatment for dysmenorrhea. NSAIDs act as an anti-prostaglandin with proven efficacy, and their side effects include complaints about the gastrointestinal tract, mild neurological symptoms, and cardiovascular complications [21,22]. Despite the limited evidence on the effectiveness of oral contraceptive pills in treating dysmenorrhea [23], they are still in use [4].

Vitamin E was first discovered by Evans et al., in 1936 [24]. It has antioxidant and anti-inflammatory properties. Intake of antioxidants such as vitamin E has been proposed to prevent aging and degenerative diseases such as cancer, cardiovascular disease, sensory disorders, and weakened immune system [25]. Vitamin E may reduce dysmenorrhea pain by inhibiting the release of arachidonic acid [26].

Two reviews have been undertaken on the impact of dietary supplements and micronutrients on dysmenorrhea. Pattanittum et al.'s systematic review [27,28] and Saei et al.'s study (2020) [4] reviewed two and four studies, respectively, where vitamin E was compared with placebo in terms of efficiency. However, the reviews reported inconsistent results.

The number of studies in this field has expanded over time, and the currently published reviews both have presented contradictory results and failed to consider the associated side effects. Hence, given the high prevalence of PD and its significance in improving women's health, we decided to perform a review study to determine the effect of vitamin E supplementation on PD intensity (primary outcome) and the side effects of vitamin E intake (secondary outcomes).

2. Methods

The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.

2.1. PICOS

2.1.1. Type of participants

Healthy women with PD were included in the study.

2.1.2. Type of interventions

All clinical trials administering oral vitamin E as an intervention were included, regardless of manners of preparation, treatment duration, and medication dose.

2.1.3. Comparison group

Placebo-controlled trials were included.

2.1.4. Type of outcome measures

Only trials measuring PD intensity as a primary or secondary outcome were included.

2.1.5. Type of studies

All randomized controlled clinical trials published in English and Persian were included in this systematic review. Reports published in languages other than English and Persian, before-after clinical trials, quasi-experimental studies, reprint articles, review articles, and letters to the editor were excluded.

2.2. Search methods

Databases in English, including PubMed, Cochrane Library, Google Scholar, Scopus, and Web of Science, as well as databases in Persian, namely Magiran, Irandoc, and SID, were searched systematically until August 30, 2021, using the keywords *tocopherol*, *alpha-tocopherol*, *vitamin E* [Mesh], *dysmenorrhea* [Mesh], *painful menstruation*, *pelvic pain*, *painful period*, and *primary dysmenorrhea*.

For instance, the strategic search for the PubMed database was as follows.

((("Vitamin E" [Mesh]) OR (alpha tocopherol)) OR (tocopherol)) AND (((("Dysmenorrhea" [Mesh]) OR (Pelvic Pain)) OR (Painful Period)) OR (Painful Menstruation)) OR (Primary dysmenorrhea))

2.3. Selection of studies

Two authors (MA, MM) independently reviewed the retrieved articles according to titles, abstracts, and full texts in terms of eligibility. In case there was disagreement regarding the eligibility of a specific work, a consensus was obtained via discussion; otherwise, the third author (MM) was consulted.

2.4. Data extraction

Two authors (MA, MM) independently developed a data extraction form, as per Cochrane's Handbook for Systematic Reviews of Interventions [29], which extracted information on the author's name, year of publication, country, type of clinical trial, final sample size, age of participants, intervention, comparison group, follow-up duration, outcomes, outcome measurement tools, and side effects.

Based on the parameters mentioned in the Cochrane Handbook [30], two authors (MM, MA) independently assessed the risk of bias for allocation sequence, allocation concealment, participant and personnel blinding, outcome assessor blinding, incomplete outcome data, and the selective reporting for all studies as low risk, high risk, and unclear risk. Judgments were then reconciled between the two researchers, and consultation was made with the third researcher (MM) if an agreement was not reached.

Quality of evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation system, which contained five components: the risk of bias, indirectness of evidence, imprecision of results, unexplained heterogeneity or inconsistency of results, and publication bias. The quality is assessed as one of four categories, namely, high, moderate, low, or very low [31].

2.5. Data analysis

RevMan software was utilized for meta-analysis [32]. Given the continuous nature of the data and the use of different tools for measuring outcomes, a standardized mean difference (SDM) with a 95% confidence interval (CI) was reported. Heterogeneity was measured using the squared (I^2) statistic. Due to the high heterogeneity, the dose-based subgroup analysis was performed in low-dose (100 units), moderate-dose (200 units), and high-dose (400 units) categories. Further, random effects were used instead of fixed effects due to high heterogeneity. High heterogeneity was

interpreted as per the Cochrane Handbook guidelines: 50%–90% indicating substantial heterogeneity and 75%–100% suggesting considerable heterogeneity. Since the number of included studies in the meta-analysis was lower than 10, the funnel plot was not used to assess the publication bias [30].

3. Results

3.1. Results of the search

A total of 450 articles were extracted from the databases. After duplicates were removed, there remained 371 articles for examination. Of these, 297 were screened for titles, 63 for abstracts, and 11 for full texts. Eventually, eight articles with a sample size of 1002 people were entered into this systematic review (Fig. 1). Of these, seven studies were included in the meta-analysis for PD intensity in the first month and eight for PD intensity in the second month.

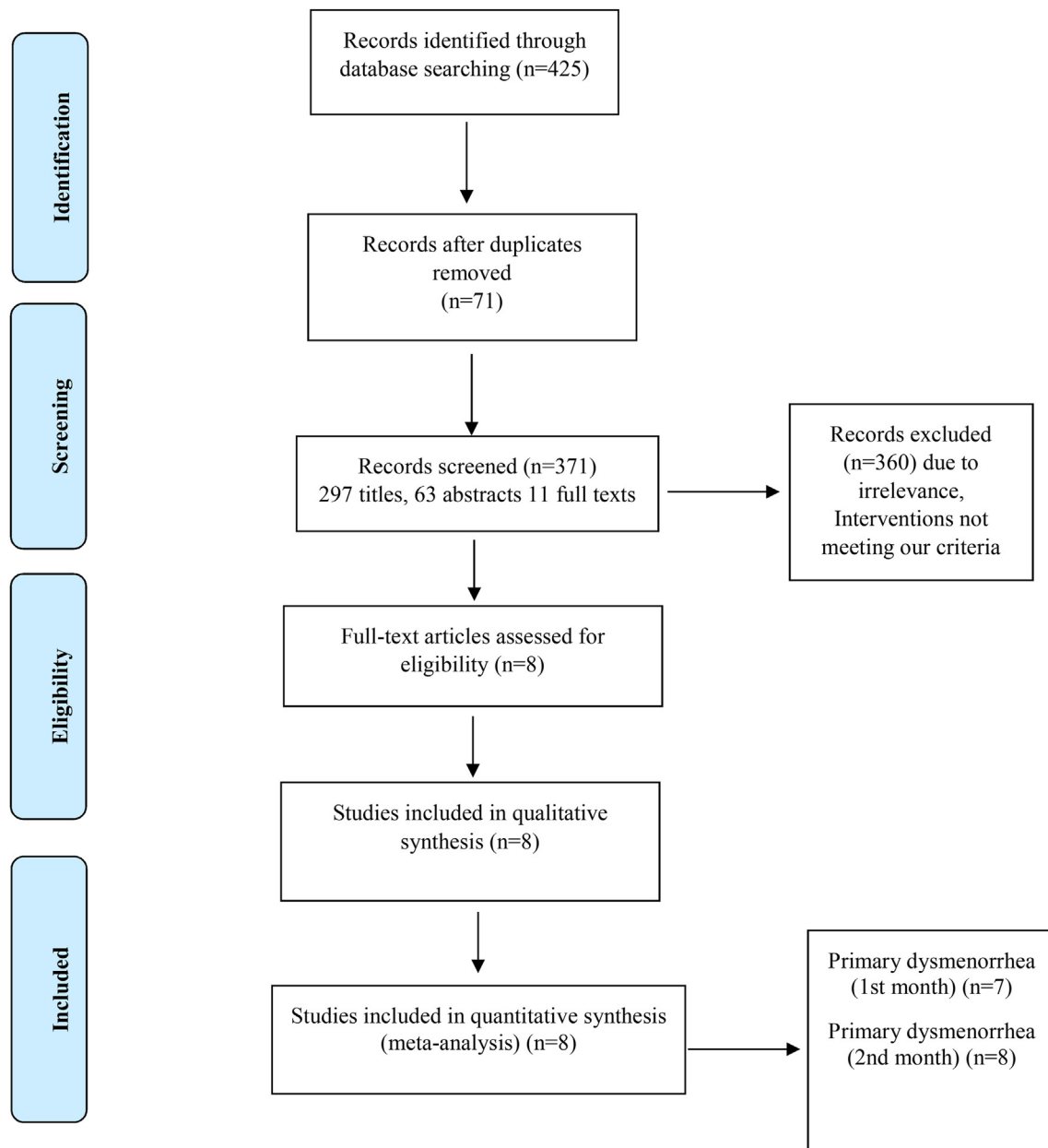


Fig. 1. PRISMA flow diagram illustrating the data extraction process.

Table 1

Characteristics of included studies.

First author	Date of publication	country	Type of clinical trial	Sample size	Age of participants (Years)	Intervention (dosage + months of treatment)	Comparison (dosage + months of treatment)	Duration of follow up	Outcomes	Outcome measurement	Results	Adverse events
Sadeghi et al.	2018	Iran	randomized double-blinded placebo-controlled trial	Vitamin E (n = 25) Placebo (n = 25) Vitamin E– Omega 3 (n = 25)	18–25	The daily dose of vitamin E (Alfa-tocopherol acetate) was 200 international units (IU). (two days before and three days after the beginning of menstruation).	placebo was packed in similar capsules and wrapped in alike wrappings. (two days before and three days after the beginning of menstruation). For 8-week period on patients with primary dysmenorrhea	2 cycles	Severity of the pain	Visual Analog Scale (VAS).	Vitamin E for five days during the beginning of menstruation significantly decreased the intensity of pain due to primary dysmenorrhea.	It was not mentioned.
Pakniat et al.	2019	Iran	Single-blind clinical trial	Vitamin E (n = 50) Placebo (n = 50) Vitamin D (n = 50) Ginger (n = 50)	18–25	100-unit vitamin E capsule as a soft gelatin capsule twice daily; (total of 5 days).	Placebo capsule twice per day; (total of 5 days).	2 cycles	Severity of the pain	VAS	The pain severity decreased in the vitamin E group,	Mild nausea was observed in 2 women in the placebo group
Nazari et al.	2018	Iran	Double-blinded randomized clinical trial	Vitamin E (n = 40) Placebo (n = 40) Monstrogel (n = 40)	18–30	200 mg Vitamin E, every 8 h, from the first day of starting pain for 3 days during two menstrual cycles	Placebo capsule every 8 h, from the first day of starting pain for 3 days during two menstrual cycles.	2 cycles	Severity of the pain	Multidimensional speech scale	Vitamin E can reduce the intensity of primary dysmenorrhea	It was not mentioned.
Vilvapriya et al.	2018	India	A randomized placebo-controlled trial	Vitamin E (n = 30) Placebo (n = 30)	17–25	Two hundred units of vitamin E (each tablet twice daily). Treatment began two days before the beginning of menstruation and continued through the first three days of bleeding.	Placebo tablets (each tablet twice daily). The treatment began two days before the beginning of menstruation and continued through the first three days of bleeding.	3 cycles	Severity of the pain	VAS	Vitamin E helps to relieve pain in primary dysmenorrhoea.	It was not mentioned.
Moslemi et al.	2012	Iran	Randomized single-blind, placebo-controlled trial	Vitamin E (n = 25) Fennel extract (n = 25) Placebo (n = 25)	18–26	100 unit vitamin E used treatment four times a day from the onset of bleeding and continued through three days	Cap placebo four times a day from the onset of bleeding and continued through three days	2 cycles	Severity of the pain	Multidimensional speech criteria (MDSC)	Vitamin E can reduce the intensity of primary dysmenorrhea	It was not mentioned.
Ziaei et al.	2001	Iran	Randomized placebo-controlled trial	Vitamin E (n = 50) Placebo (n = 50)	16–18	Vit E 100 units (5 tablets a day for 5 days; two days before and 3 days after the beginning of menstruation)	A day for 5 days; two days before and 3 days after the beginning of menstruation)	2 cycles	Severity of the pain	VAS	Vitamin E can reduce the intensity of primary dysmenorrhea	It was not mentioned.
Ziaei et al.	2005	Iran	Randomized, double-blind, placebo-controlled trial	Vitamin E (n = 139) Placebo (n = 139)	15–17	Vitamin E 200 units twice daily for five days (two days before and three days after the beginning of menstruation).	Twice per day for 5 days; two days before and 3 days after the beginning of menstruation)	4 cycles	Severity of the pain	VAS	Vitamin E can reduce the intensity of primary dysmenorrhea	There were no adverse effects

(continued on next page)

Table 1 (continued)

First author	Date of publication	country	Type of clinical trial	Sample size	Age of participants (Years)	Intervention (dosage + months of treatment)	Comparison (dosage + months of treatment)	Duration of follow up	Outcomes	Outcome measurement	Results	Adverse events
Kashanian et al.	2010	Iran	Randomized, double-blind, placebo-controlled trial	vitamin E (n = 42) Placebo (n = 52)	18–25	Vitamin E 400 IU daily for 2 days before the beginning of menstruation and continuing for 5 days.	A placebo was administered 2 days before and the first 3 days of menstruation.	2 cycles	Severity of the pain	VAS	Vitamin E can reduce the intensity of primary dysmenorrhea	It was not mentioned.

3.2. Characteristics of studies

All records were randomized controlled clinical trials [1,26,33–38]. Table 1 shows the characteristics of the included studies.

3.3. Outcome measures

PD intensity was measured using the Visual Analog Scale (VAS) and multidimensional speech scale in six [1,26,33–35,37] and two studies [37,38], respectively. The VAS scale is a ruler graded from 0 (lowest pain intensity) to 10 cm (most severe pain imaginable) [39]. The MDSC tool consists of four degrees. Grade 0 denotes an absence of painful menstruation that does not interfere with daily activities. Grade 1 indicates mild menstruation pain that rarely interferes with daily activities and requires minimal painkiller intake. Grade 2 suggests moderate pain intensity and impairs daily activities. However, there is no need to be absent from school or work. Grade 3 indicates severe pain so that the person cannot perform daily activities, and there are severe systemic symptoms [40].

3.4. Risk of bias in included studies

Random sequence generation was assessed as low-risk in five studies [1,34,35,37,38] and unclear in three [26,33,36]. Allocation concealment was unclear in all studies due to an absence of reference to this issue. Blinding of participants and personnel was low-risk in six studies [33–38] and unclear in two studies [1,26]. Blinding of the outcome assessor was considered low-risk in four studies [33–35,38], unclear in three studies [1,26,36], and high-risk in one study [37] as the outcome assessor was not blind to the intervention outcome.

Incomplete outcome data were assessed as low risk in five studies [1,26,34,36,38] because all participants had completed the study. In three studies [33,35,37], such data were evaluated as high-risk because of the imbalance in the number of participants in the study groups and the attrition of participants. Selective reporting was low-risk in all studies since all expected outcomes were reported (Figs. 2 and 3).

3.5. Effects of vitamin E

Below is a summary of the results associated with vitamin E supplementation in the studies included in this review. Notably, none of the studies reported any adverse effects. The results detailed below concern the end of the second cycle.

In Sadeghi et al.'s (2018) study, the mean (SD: standard deviation) of PD intensity in the vitamin E group was 6.03 (1), which was lower than that of the placebo group, i.e., 7.03 (1.1). However, the difference was not statistically significant ($P = 0.927$) [36]. In Pakniat et al.'s (2019) study, the mean (SD) of PD intensity in the vitamin E group was 5.32 (0.68). The severity was significantly lower than that of the placebo group, 6.0 (0.70) ($P < 0.0001$) [1]. In the study of Vilvapriya et al. (2018), the mean (SD) of PD intensity in the group that used vitamin E was 4.77 (1.357), which was less severe than that of the placebo group, i.e., 5.33 (1.124). Nonetheless, the difference was not statistically significant ($P < 0.083$) [26]. In the study of Nazari et al. (2018), the mean (SD) of intensity in the vitamin E group was 1.07 (0.27), which was significantly lower than that of the placebo group, i.e., 7.68 (0.79) ($P < 0.0001$) [38]. In the study by Ziaei et al. (2005), the mean (SD) of intensity in the group of participants receiving vitamin E was 3 (1.84), which was significantly lower than that of the placebo group, that is, 5 (2.21) ($P < 0.0001$) [35]. In Ziaei

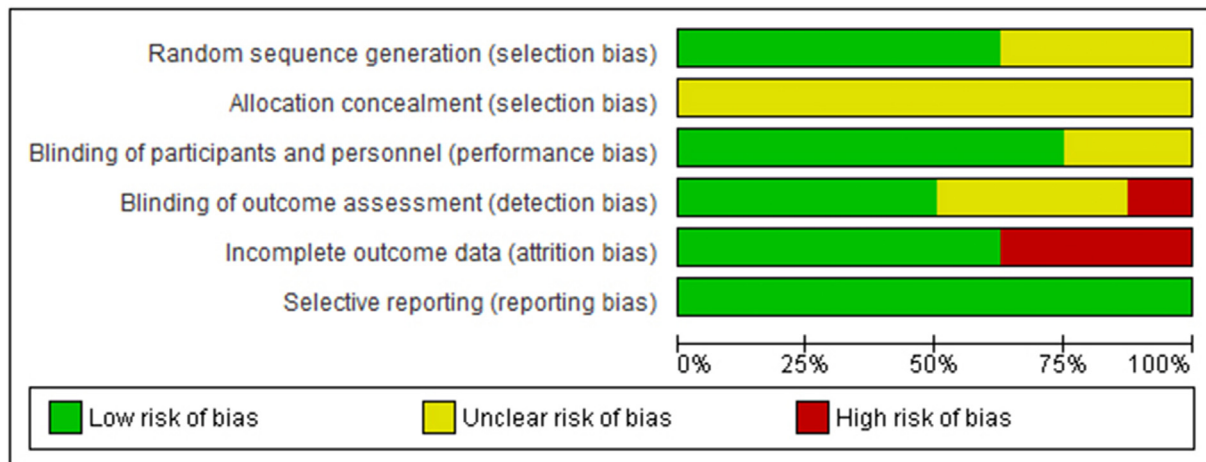


Fig. 2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

et al.'s (2001) study, the mean (SD) of PD intensity was 3.5 (3.68) in the group receiving vitamin E, which was significantly lower than that of the placebo group, i.e., 4.3 (3.31) ($P < 0.02$) [34]. In Kashanian et al.'s (2010) study, the mean (SD) of PD intensity in the vitamin E group was 4.7 (1.8). The value was lower than that of the placebo group, i.e., 5.3 (2.0), although not significantly ($P = 0.6$) [33]. In the study of Moslemi et al. (2012), the mean (SD) of PD intensity in the group of participants who used vitamin E was 2.15 (0.93), which was lower than that of the placebo group, that is, 2.24 (0.67). The difference was not statistically significant, however ($P = 0.19$) [37].

3.6. Synthesis of results

The results of the random effects meta-analysis on seven studies (544 participants) revealed that the use of vitamin E in the first month significantly reduced the average severity of PD compared with placebo (SDM: -1.16 ; 95% CI: -2.16 to -0.17 ; I^2 : 31.9%; $P = 0.02$) (Fig. 4).

The results of the random effects meta-analysis on eight studies (822 participants) showed that the use of vitamin E in the second month significantly reduced the average intensity of PD compared with placebo (SDM: -1.83 ; 95% CI: -2.90 to -0.77 ; I^2 : 76.3.9%; $P < 0.0001$) (Fig. 5).

The evidence for comparing vitamin E and placebo groups regarding PD intensity in the first month was of low quality according to the GRADE system. As regards the second month, the available evidence was of moderate quality, meaning that the results were close to reality with low confidence. Table 2 summarizes the results of the GRADE approach used to assess the quality of evidence.

4. Discussion

4.1. Main finding and interpretation

The present study intended to perform a systematic review and meta-analysis of the literature to determine the effect of vitamin E supplementation on PD intensity. The results showed that vitamin E significantly reduced the severity of PD in the first and second months of the administration. Similar results are reported in another review [4] of a final set of four articles examining the effect of various micronutrients, including vitamin E, on PD pain management. Cochrane's review of two studies examining dietary

supplements for dysmenorrhea showed that vitamin E did not significantly reduce the severity of dysmenorrhea [28]. However, more studies are included in the present study, and the side effects of vitamin E are also investigated.

In this study, meta-analyses revealed substantial heterogeneity in included studies, which may affect the results. Therefore, the random effect model was used instead of fixed model. Significant heterogeneity is characterized primarily by the use of a fixed effect model without an explicit rationale for its selection and a lack of reservations and explanations of the likely causes of the heterogeneity. Using a model with random effects alleviates these problems [41].

Given the inflammatory effects and increased levels of prostaglandins during PD, the decline in PD intensity can be attributed to vitamins' antioxidant and anti-inflammatory properties. The secretory phase releases three times the amount of prostaglandins as the follicular phase, which peaks during menstruation [42]. Prostaglandins E2 and F2 α , derived from arachidonic acid, serve crucial functions [20]. Prostaglandin-induced uterine muscle contractions cause colic, spasm, and labor-like pain in the lower abdomen and back [21]. Therefore, one of the fundamental treatment goals is to reduce prostaglandin levels in the body [1]. Approximately 80% of women who experience dysmenorrhea recover upon taking prostaglandin inhibitors [43]. Vitamin E is a highly potent antioxidant that inhibits the formation of reactive oxygen species molecules via lipid oxidation during the release of free radicals [44]. The antioxidant properties of vitamin E isomers often depend on the number of methyl groups attached to the chromium ring [45]. Vitamin E's antioxidant properties inhibit phospholipid peroxidation and suppress the production of the arachidonic acid and its conversion to prostaglandins [1]. Additionally, vitamin E has been shown to increase internal opioids and alleviate pain [26].

Vitamin E's anti-inflammatory function has not been perfectly understood, although it may involve dephosphorylation of protein kinase C (PKC). α -Tocopherol can activate activator protein 1 (AP-1), which can phosphorylate PKC(α) and suppress smooth muscle cell proliferation [46]. Vitamin E may inhibit the ability of inflammatory cytokines such as IL-6 to stimulate CRP (C-reactive protein) synthesis in the liver [47]. In the study by Mucuk et al. (2021), higher CRP, an indicator of the inflammatory response, was found in the dysmenorrhea group [48]. This may be due to the fact that dysmenorrhea is an inflammatory disorder. CRP, a significant indicator of the inflammatory response, is widely used

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Kashanian et al 2010	?	?	+	+	-	+
Moslemi et al 2012	+	?	+	-	-	+
Nazari et al 2018	+	?	+	+	+	+
Pakniat et al 2019	+	?	?	?	+	+
Sadeghi et al 2018	?	?	+	?	+	+
Vilvapriya et al 2018	?	?	?	?	+	+
Ziaei et al 2001	+	?	+	+	+	+
Ziaei et al 2005	+	?	+	+	-	+

Fig. 3. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

to measure the level of inflammation. During the menstrual cycle, CRP levels fluctuate, falling during the follicular phase with higher estrogen levels and rising during the luteal phase with higher progesterone levels [49–51]. The results of a meta-analysis indicate that vitamin E supplementation in the form of α -tocopherol or γ -tocopherol reduces the serum level of CRP [52].

The majority of the studies did not mention the side effects associated with vitamin E administration. Only two studies [1,32] reported no side effects for certain. One study found that moderate doses of vitamin E (800 IU) did not increase bleeding time or platelet aggregation in the body and did not cause serious bleeding side effects [53]. Another study examining the effects of vitamin E in people suffering from menorrhagic with uterine dysfunction revealed that

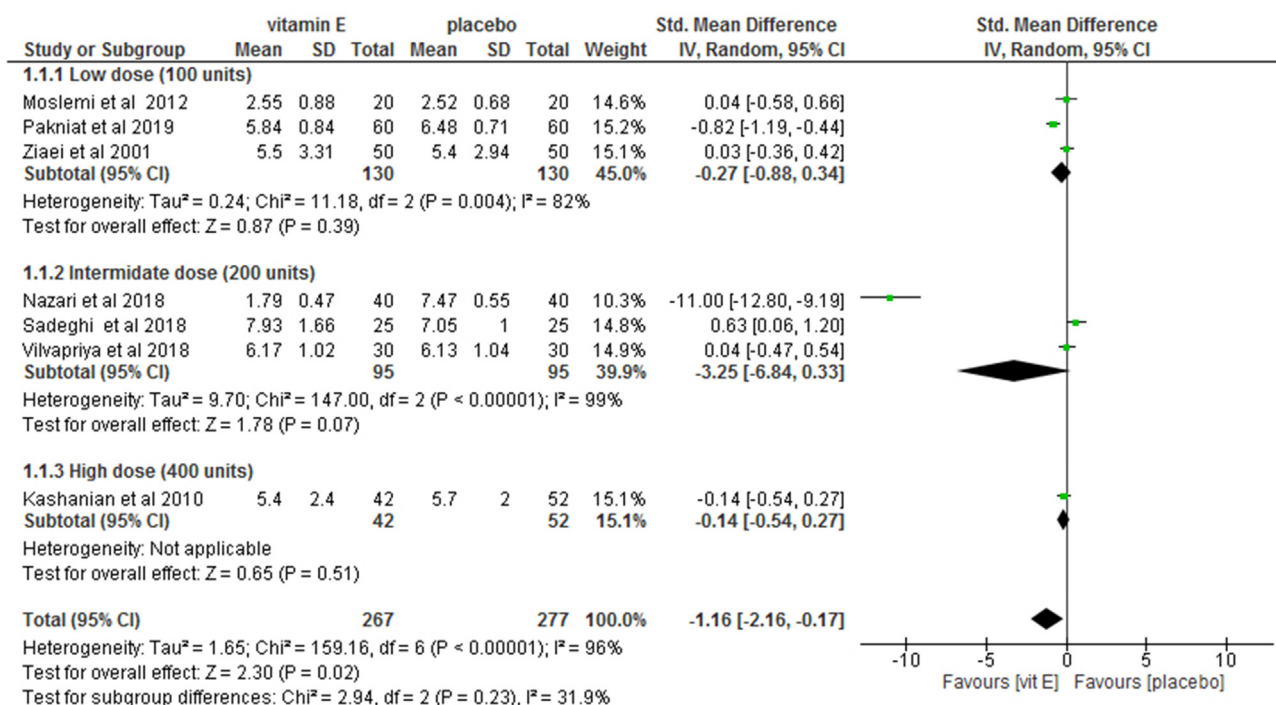


Fig. 4. Vit E versus placebo on the intensity of pain of primary dysmenorrhea (1st month).

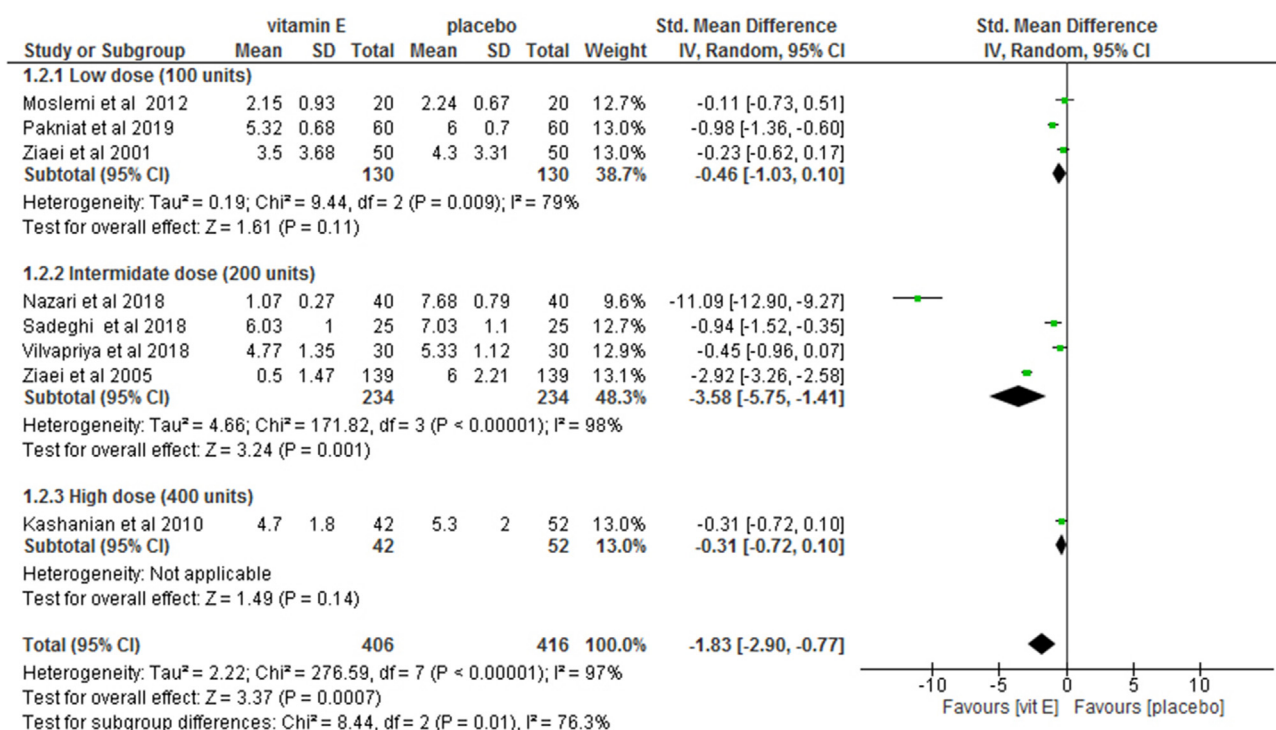


Fig. 5. Vit E versus placebo on the intensity of pain of primary dysmenorrhea (2nd month).

vitamin E had no side effects; rather, it was linked with a high level of satisfaction and acceptance [54]. Hence vitamin E seems to have the potential to replace non-steroidal anti-inflammatory drugs (NSAIDs), which are known to have specific side effects.

Fatty acids exert anti-inflammatory effects via a variety of mechanisms. Many of these anti-inflammatory actions are induced by or at least connected with changes in the composition of cell membrane fatty acids [55].

Table 2
Quality assessment of included studies according to the GRADE approach.

Quality assessment		SMD (95% CI) ^c					Certainty
No. Of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Certainty
7	Vit E versus placebo on the pain intensity of primary dysmenorrhea (1st month) Randomized controlled trials	Serious risk of bias	Very serious inconsistency ^a	No serious indirectness	No serious imprecision	Undetected	Low ⊕⊕ OO
8	Vit E versus placebo on the pain intensity of primary dysmenorrhea (2 nd month) Randomized controlled trials	Serious risk of bias	No serious inconsistency ^b	No serious indirectness	No serious imprecision	Undetected	Moderate ⊕⊕⊕ O

^a Downgraded two level due to severe heterogeneity and the effect sizes in studies were not in the same direction.

^b Despite the high heterogeneity in the meta-analysis, downgrading was not considered because the effect sizes in most of them were in the same direction.

^c Standard Mean Difference (95% Confidence Interval).

4.2. Strengths and limitations

One of the strengths of the present review is that selective reporting was low-risk, as all trials reported all expected outcomes. Moreover, the study protocol has been registered in the PROSPERO database (CRD42021276609). Its limitations concern the small number of included studies, allocation concealment in all studies as unclear risk, and the high-risk status of incomplete outcome data in some studies, which can affect the study results. This study included only healthy women. As such, conclusions may not be readily generalizable to individuals suffering from disorders. Additionally, only Persian and English papers were evaluated, which may have affected the retrieval of additional relevant research.

5. Conclusion

The results showed that using vitamin E significantly reduced the intensity of PD pain compared to placebo, and the effect was more pronounced in the second month than in the first. Given vitamin E's beneficial effect in reducing the severity of PD pain, it might be employed as an adjunctive treatment for women with PD. However, it is advised to undertake clinical trials with higher quality and larger sample sizes for a definitive conclusion.

Ethics approval

Not applicable.

Funding

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Authors' contributions

MA and MM performed an initial search of databases and contributed substantially to writing the manuscript. MA and MM reviewed studies to investigate eligibility criteria. MM (corresponding author) and SMAC regulated methods, performed the meta-analysis, and supervised the drafting of the manuscript. All authors read and approved the final draft.

Declaration of competing interest

The authors declare that they have no competing interests.

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