

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of December 21, 2021. No. 32343. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical Culture Sciences (Field of Medical sciences and health sciences); Health Sciences (Field of Medical Sciences and Health Sciences). Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 21 grudnia 2021 r. Lp. 32343. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).  
© The Authors 2022;  
This article is published with open access at Licensee Open Journal Systems of Nicolaus Copernicus University in Torun, Poland  
Open Access. This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author (s) and source are credited. This is an open access article licensed under the terms of the Creative Commons Attribution Non commercial license Share alike. (<http://creativecommons.org/licenses/by-nc-sa/4.0/>) which permits unrestricted, non commercial use, distribution and reproduction in any medium, provided the work is properly cited.  
The authors declare that there is no conflict of interests regarding the publication of this paper.  
Received: 01.09.2022. Revised: 02.09.2022. Accepted: 15.09.2022.

## Latest reports of primary dysmenorrhea

Anna Łopuszyńska (1), Łukasz Ochyra (1),

Mateusz Pawlicki (1), Halina Pieciewicz-Szczęsna (2)

(1) Student Scientific Association at Department of Epidemiology and Clinical Research  
Methodology Medical University of Lublin, ul. Radziwiłłowska 11, Lublin 20-080,  
Poland

(2) Department of Epidemiology and Clinical Research Methodology of the Medical  
University of Lublin, ul. Radziwiłłowska 11, Lublin 20-080, Poland

Corresponding author: Anna Łopuszyńska, [lopuszynskaania@gmail.com](mailto:lopuszynskaania@gmail.com)

ORCID ID:

Anna Łopuszyńska <https://orcid.org/0000-0001-5133-4180>, [lopuszynskaania@gmail.com](mailto:lopuszynskaania@gmail.com)

Łukasz Ochyra <https://orcid.org/0000-0002-8586-3619>, [lukaszochyra98@gmail.com](mailto:lukaszochyra98@gmail.com)

Mateusz Pawlicki <https://orcid.org/0000-0001-8318-6573>, [pawlak32@gmail.com](mailto:pawlak32@gmail.com)

Dr n. med. Halina Pieciewicz-Szczęsna <https://orcid.org/0000-0002-0573-7226>,  
[halpiec@gmail.com](mailto:halpiec@gmail.com)

## **Abstract**

**Introduction:** Primary dysmenorrhea (PD) is a pelvic pain during menstruation in the absence of any pelvic pathologies. This disease mainly affects young women in reproductive age. In addition to pain, patients may experience many other symptoms including: gastrointestinal symptoms, sleep disorders. This contributes to reduction in their mental and physical quality of life.

**Purpose:** the purpose of this review is to draw attention to a problem that affects a large number of society, is often underestimated and largely affects the quality of women's life, as well as to present the latest discoveries and reports on this issue.

**Material and methods:** the scientific literature published in the years 2017-2022 was reviewed in the PubMed scientific database using the following keywords: primary dysmenorrhea, dysmenorrhea.

**Results:** Increased prostaglandin levels, abnormalities in the reward system, oxidative stress, ischemia, and eotaxin may contribute to the development of pain in PD. These findings could open up new diagnostic or therapeutic targets. The first choice in the treatment of PD are NSAIDs, which are taken regularly for many years, so they must be as safe and effective as possible. Research suggests that thiaprofenic acid and ibuprofen are suitable. For alternative treatments TENS, heat, and acupuncture can be effective. Propolis, ginger, valeric acid, hops and exercise are also promising.

**Conclusions:** PD is a varied disease that affects a large number of women. It leads to a reduction in the quality of life, hence it is necessary to conduct further research on a diverse, large group of respondents, in many centers, with the use of systematized pain scales, and lasting for a certain period of time.

**Keywords:** primary dysmenorrhea, dysmenorrhea, gynecology

## **Introduction**

Primary dysmenorrhea (PD) is defined as pelvic pain during menstruation with no pelvic pathology present. This phenomenon occurs mainly in girls and young women in reproductive age and is one of the most common gynecological diseases in this group of people. It is estimated that it affects from 45 to 97% of women [1]. Primary dysmenorrhea

may be accompanied by gastrointestinal symptoms such as nausea, vomiting, flatulence, constipation, diarrhea or indigestion. In addition, women report headaches, dizziness, fatigue, irritability, insomnia and back pain. These symptoms are associated with a reduction in the quality of life, both in the physical and mental spheres, over a period of many years. This disease also contributes to absenteeism from school, university or work, which can lead to lower academic performance and cause economic losses for both employees and employers [2].

## **Purpose**

The purpose of this review is to draw attention to a problem that affects many societies, is often underestimated and largely affects the quality of women's life, as well as to present the latest discoveries and reports on this issue.

## **Material and methods**

The scientific literature published in the years 2017-2022 was reviewed in the PubMed scientific database using the following keywords: primary dysmenorrhea, dysmenorrhea.

## **Results**

### **Pathophysiology**

The mechanism of primary dysmenorrhea is not fully understood, but it has been suggested that it may be caused by prostaglandins, mainly PGF 2, which levels are elevated in women with this condition. Their concentration is the highest in the first two days of the cycle, and it is associated with a decrease in the level of progesterone, this decrease causes their production. Prostaglandins lead to increased uterine tone and contractions, resulting in ischemia and pain [3].

A study by Qi Zhang et al. on 80 women (including 41 patients with PD and 39 women from the control sample) showed that this disease may be connected with abnormalities in the reward system [4]. Functional MRI showed a reduced connection of the left nucleus accumbens with the anterior islet bilaterally and the left amygdala. In the case of the right nucleus accumbens, reduced connectivity was demonstrated with the ventral tegmental area (which correlated negatively with PGF 2 $\alpha$  levels), the left hippocampus, the right orbitofrontal cortex, and the right anterior islet. This study, however, had its limitations. There is a need for a larger research group and for imaging during different stages of the

menstrual cycle. However, these reports allow a better understanding of the mechanism of PD in the nervous system and may contribute to the creation of a new target in the treatment of this disease.

Oxidative stress is a state in which there is no equilibrium between the action of reactive oxygen species and the biological capacity to detoxify reactive intermediates or repair damage caused. This phenomenon, along with the amount of antioxidants, can affect the endothelium of the uterus. Review M. K. Schmidt et al. showed that in patients with PD the levels of malondialdehyde, the major secondary product of lipid peroxidation, and nitric oxide, a non-invasive marker of inflammation, are increased compared to women in the control groups [5]. Conflicting results have been obtained for 3-nitrotyrosine, which is a promising marker of oxidative stress, so more research is needed to reach a consistent conclusion. In the case of antioxidant status, it is suggested that patients with PD have a lower total antioxidant status than women in the control group. Among the enzyme markers, it was shown that the concentration of heme oxygenase 1 is higher and the activity of glutathione peroxidase is lower in PD. However, studies on non-enzymatic markers indicate a higher concentration of adrenomedullin and a lower concentration of vitamin E in women with PD. These reports suggest that oxidative stress and the state of antioxidants may influence the pathomechanism of PD formation.

Ischemia is one of the factors responsible for pain in PD. In a small study by, E. Sen et al., the levels of ischemia-modified albumin (IMA) were measured and the Doppler indices of the uterine arteries (pulsation index and resistance index) were measured in 37 patients with PD and 30 women in the control group [6]. The level of ischemia-modified albumin was significantly higher in subjects with PD during menstruation, but there were no significant differences in the luteal phase. Additionally, a positive correlation was found between IMA and Doppler indices during menstruation. These reports suggest that IMA may be a promising marker of ischemia and pain intensity in the course of PD.

Eosinophils are cells present in the endometrium only in the perimenstrual period, hence E. Gul et al. examined the level of eotaxin, a selective chemotactic protein for eosinophilia, in the first two days of the cycle in 30 women with PD and 30 in the control group [7]. The mean level of eotaxin was  $440.72 \pm 132.17$  in healthy subjects and  $580.8 \pm 195.7$  in patients with PD, and the difference between the groups was statistically significant ( $p = 0.012$ ). However, more research is needed on a larger group of subjects to determine the exact action

of this substance in the pathogenesis of the disease. This is particularly important as approximately 20-25% of patients are treated with failure, and this study could provide a new therapeutic target.

### **Pharmacological treatment**

In the treatment of pain in the case of PD, non-steroidal anti-inflammatory drugs (NSAIDs), oral contraceptives, TENS, heat therapy, aromatherapy, acupuncture or various non-pharmacological agents are used. There are no detailed management guidelines, self-medication is a frequent occurrence, and it may be ineffective. There is also a fear of taking painkillers due to lack of knowledge, possible side effects, or fear of addiction. Therefore, there is a great need for research into the treatment of this condition. NSAIDs are the drugs of first choice because they inhibit the production of prostaglandins that are involved in the pathomechanism of PD. These drugs, however, have numerous side effects and complications of use, hence it is necessary to assess their effectiveness and safety in patients with PD, as they are often used in them for many years. In the meta-analysis by X. Feng et al. evaluated 72 studies with 5723 patients and 13 drugs (nimesulide, rofecoxib, valdecoxib, aspirin, diclofenac, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, naproxen, piroxicam, thiaprofenic acid) [8].

In terms of pain relief, all drugs except aspirin were significantly more effective than placebo. The most effective analgesic effect is flurbiprofen, while piroxicam, thiaprofenic acid and indomethacin were also very effective. Thiaprofenic acid, mefenamic acid and ketoprofen turned out to be the safest, and the worst result was achieved by indomethacin. Taking into account both factors, which are effectiveness and safety, thiaprofenic acid turned out to be optimal.

In the case of the meta-analysis, W. Nie et al. of 35 studies with 4383 participants and 5 drugs (naproxen, ibuprofen, diclofenac, aspirin and ketoprofen) also found that, in addition to aspirin, these substances are more effective than placebo [9]. Diclofenac and ibuprofen turned out to be the most effective in relieving pain, and in terms of safety, ketoprofen and ibuprofen. Taking these two factors into account, ibuprofen turned out to be the most advantageous in this group of drugs. Hormonal agents are often used in the treatment of primary dysmenorrhea, they thin the endometrium, which reduces the production of COX-2 and prostaglandins. The review by F. Oladosu shows that the combination of nomegestrol acetate and 17 $\beta$ -estradiol was more effective in the treatment of pain than agents containing

drospirenone and ethinylestradiol [10]. Similar relief of menstrual pain was observed with the levonorgestrel-releasing inserts as with the oral agents. The comparison of drugs containing ethinylestradiol (EE) and chlormadinone acetate (CMA) at doses of 30 mcg / 2 mg with tablets containing EE and drospirenone (DRSP) 30 mcg / 3 mg once daily in groups of 90 randomly assigned women showed greater efficacy EE / CMA [11]. Additionally, more women in this group reported "significant reduction", "reduction", or no pain. Treatment tolerance and adverse events were comparable in both groups. A review by T. Damm suggests that continuous or prolonged / flexible use of oral contraceptives is more effective in PD than cyclical use [12].

### **Alternative Treatment**

TENS is a transcutaneous nerve stimulation that may be a potential non-pharmacological technique for treating pain in primary dysmenorrhea. This method is minimally invasive, relatively inexpensive, portable, and has a minimal risk of use and a few contraindications. Moreover, it can be used on its own if it is necessary. There are two types of TENS: HF > 50 Hz, which activates large-diameter cutaneous afferents (A $\beta$ ), while small-diameter nerves are not stimulated, and LF, 2-5 Hz, which stimulates the efferent motor nerves that cause phasic muscle contractions. Review by M. Elboim-Gabyzon et al. showed that this method reduced the patients' pain, improved their quality of life and led to the use of fewer pharmacological agents (which resulted in a lower chance of adverse effects) [13]. Additionally, HF TENS has been shown to be more effective in opioid users. During a therapy session, the current intensity should be set to a painless, maximum tolerated level and continuously increased to avoid habituation. Accordingly, this method may prove ineffective in women who cannot achieve and maintain increased intensity. However, there is a need for more and better quality research on a larger group of women, examining the specific duration of the session, its intensity and describing the action based on standardized pain scales.

Local heat treatment (for example hot compresses, hot water bottles) is a commonly used analgesic method among women. In patients with PD, it can reduce tension and relax the abdominal muscles, leading to a decrease in pain levels. In addition, heat can lead to an increase in blood circulation in the pelvis, and this leads to a reduction in congestion and swelling. The work of J. Jo et al. suggests that this treatment method is effective in primary dysmenorrhea and has fewer side effects than NSAIDs or contraceptives that women who want to get pregnant cannot take [14]. This therapy is a promising method of non-

pharmacological pain management, but there are still no multicentre studies that compare different methods of local heat treatment (thermal strips, patches, ceramic belt emitting far infrared rays) in terms of their short-term and long-term effects or cost-effectiveness. There are reports that acupuncture inhibits pain impulses by interacting with mediators such as serotonin and endorphins, by stimulating receptors and nerve pathways [21]. Review by H. L. Woo et al. on acupuncture showed that manual acupuncture and electroacupuncture are more effective methods than no treatment [15]. In comparison with NSAIDs and contraceptives, manual acupuncture and heat acupuncture were also effective in treating pain during PD. This method can be an effective and safe alternative in the management of women with ailments.

The studies of E. Jenabi et al. on 86 young women showed that taking bee propolis for 5 days during two menstrual cycles significantly reduced pain, both after the first and the second month, without side effects [16]. This substance contains isoflavones, which belong to the group of polyphenols and have antiviral, antibacterial and anti-inflammatory properties. Moreover, it has been reported that three p-coumaric acid derivatives can be isolated from bee propolis, which have a smooth muscle relaxant effect. Therefore, this substance may be effective in primary dysmenorrhea and may be an alternative to pharmacological treatment, as it has anti-inflammatory and antispasmodic properties. However, research is needed on a larger group of people, assessing the long-term effect.

Menstrugole is a drug containing approximately 80 mg of dried celery, anise and saffron extract. A study by F. Shobeiri et al. showed that it is an effective analgesic and antispasmodic in primary dysmenorrhea [17]. The antispasmodic effect is due to the content of anethole (an anise component), which has a chemical composition similar to catecholamines. Additionally, the components of the drug have an anti-inflammatory effect. This drug seems to be promising, but the study had some limitation, which is the small number of subjects (79 women) from a particular study group. Research is needed on a larger number of women, more diverse individually.

A meta-analysis by H. W. Lee et al. suggests that fennel may also have an analgesic effect in PD, reducing the level of prostaglandins. The analyzed studies showed that the substance is effective in comparison with both pharmacological treatment and placebo [18]. Fennel can be used in the form of 1-2% oil about 30 drops every eight hours or a capsule containing 30-46 mg fennel extract orally. Most studies suggest dosing from three days before to the third day of the cycle. Only three of the twelve studies focused on the assessment of side effects and

reported conflicting results, so it is important that future studies pay attention to this issue. In addition, subsequent trials should be structured in terms of pain assessment or the presence of control samples to provide the highest quality results.

In the study by H. Pakniat et al. on 200 women, the effects of ginger, vitamin E and vitamin D on primary dysmenorrhea were compared, where before the supplements, the results of the VAS scale (visual analogue scale of pain assessment) amounted to  $7.13 \pm 0.80$ , which indicates a high level of pain [19]. The highest decrease in the level of pain was observed in the ginger group. In the VAS scale the pain was assessed as: after one month of intervention,  $3.72 \pm 1.39$  and after two months,  $3.20 \pm 1.28$ . In the case of vitamin D, the mechanism of action is not yet fully understood, but it was second in terms of effectiveness in the VAS scale: after one month of use,  $5.44 \pm 1.40$ , and after two months,  $5.20 \pm 1.34$ . There are reports that vitamin E reduces the level of pain by increasing the level of  $\beta$ -endorphins, and in the VAS study the assessment was:  $5.84 \pm 0.84$  after one month of use and  $5.32 \pm 0.68$  after two months. A limitation of the study was the fact that these substances were administered together with an analgesic, so one can only compare their effects with each other, and not their independent effect on the analgesic effect in PD. In contrast, this result is satisfactory and promising for adjuvant therapy when NSAIDs are not working well enough.

*Valeriana officinalis* (valerian) has an antispasmodic effect on smooth muscles through cellular depolarization. It blocks calcium channels and opens potassium channels, leading to a decrease in intracellular calcium levels, which leads to relaxation of the uterine muscle. The FDA has classified valerian as a safe drug, and a review by N. Gamathy et al. suggests that 300 mg may be an analgesic and spasmolytic dose [20]. *Humulus lupulus* (common hops) inhibits the cholinergic system, and additionally, the isohumulone contained in it has an analgesic effect. The recommended analgesic dose in PD is 100 mg [20]. *Passiflora incarnata* (passion flower) also increases the GABA inhibitory level and has an analgesic effect. This review shows that these three substances reduce uterine smooth muscle contraction by influencing GABA levels, and a formulation containing 300 mg *Valeriana officinalis*, 30 mg *Humulus lupulus* and 80 mg *Passiflora incarnata* relieves PD pain [20]. Additionally, their safety index is high and holds promise as first-line therapy for this condition.

Exercise in the form of moderate-intensity aerobic exercise can also help with pain in PD. Movement causes blood flow to increase, so that waste products and prostaglandins are carried faster. Moreover, exercises reduce stress levels, improve blood circulation and

increase endorphin levels, which also positively affect this condition. The study by Z. M. Dehnavi et al. on 70 students showed ( $P = 0/041$ ) that after 8 weeks of aerobic exercises for 30 minutes three times a week, the pain intensity decreased [22]. The positive effect of exercises was also demonstrated by R. Heidarimoghadam et al. examining 86 women. For this, the FITT protocol for sport session frequency, exercise intensity, exercise time, and exercise type was used for the experimental group, and the entire study also lasted 8 weeks [23]. A decrease in pain intensity was noticed in the study group. Thus, it is a good and effective method, both for the prevention and alleviation of the course of PD.

## Conclusions

Primary dysmenorrhea is a varied disease that affects many women. This disease can lead to a decrease in their quality of life, as well as to absenteeism from many important events. Many of the respondents report severe pain that must be treated and, if possible, prevented. The mechanism of the formation of this disease entity is not fully understood, and there are still promising studies that may provide new possibilities and therapeutic goals. The drugs of choice are NSAIDs and oral contraceptives, which should be as effective and safe as possible, but they cannot be used in all women, for example those planning a pregnancy or refractory NSAIDs. The ongoing research into alternative treatment methods gives hope for many new therapeutic possibilities. However, there is a great need for large multicentre studies, on a diverse group of women, based on systematized pain scales and lasting an appropriate time. There is also a need for educational programs for younger girls to encourage physical activity and a healthy diet that contains the necessary macro- and micronutrients, which could result in lower pain levels or absences from school.

## Literature:

1. Sharghi M, Mansurkhani SM, Larky DA, Kooti W, Niksefat M, Firoozbakht M, Behzadifar M, Azami M, Servatyari K, Jouybari L. An update and systematic review on the treatment of primary dysmenorrhea. *JBRA Assist Reprod.* 2019 Jan 31;23(1):51-57. doi: 10.5935/1518-0557.20180083. PMID: 30521155; PMCID: PMC6364281.

2. Nagy H, Khan MAB. Dysmenorrhea. 2022 Jul 18. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. PMID: 32809669.
3. Bernardi M, Lazzeri L, Perelli F, Reis FM, Petraglia F. Dysmenorrhea and related disorders. *F1000Res*. 2017 Sep 5;6:1645. doi: 10.12688/f1000research.11682.1. PMID: 28944048; PMCID: PMC5585876.
4. Zhang Q, Yu S, Wang Y, Wang M, Yang Y, Wei W, Guo X, Zeng F, Liang F, Yang J. Abnormal reward system network in primary dysmenorrhea. *Mol Pain*. 2019 Jan-Dec;15:1744806919862096. doi: 10.1177/1744806919862096. PMID: 31286840; PMCID: PMC6616063.
5. Szmidski MK, Granda D, Sicinska E, Kaluza J. Primary Dysmenorrhea in Relation to Oxidative Stress and Antioxidant Status: A Systematic Review of Case-Control Studies. *Antioxidants (Basel)*. 2020 Oct 15;9(10):994. doi: 10.3390/antiox9100994. PMID: 33076228; PMCID: PMC7602455.
6. Sen E, Ozdemir O, Ozdemir S, Atalay CR. The Relationship between Serum Ischemia-Modified Albumin Levels and Uterine Artery Doppler Parameters in Patients with Primary Dysmenorrhea. *Rev Bras Ginecol Obstet*. 2020 Oct;42(10):630-633. doi: 10.1055/s-0040-1715141. Epub 2020 Oct 31. PMID: 33129218.
7. Gul E, Celik Kavak E. Eotaxin levels in patients with primary dysmenorrhea. *J Pain Res*. 2018 Mar 23;11:611-613. doi: 10.2147/JPR.S146603. PMID: 29615846; PMCID: PMC5870633.
8. Feng X, Wang X. Comparison of the efficacy and safety of non-steroidal anti-inflammatory drugs for patients with primary dysmenorrhea: A network meta-analysis. *Mol Pain*. 2018 Jan-Dec;14:1744806918770320. doi: 10.1177/1744806918770320. Epub 2018 Mar 27. PMID: 29587566; PMCID: PMC5987898.
9. Nie W, Xu P, Hao C, Chen Y, Yin Y, Wang L. Efficacy and safety of over-the-counter analgesics for primary dysmenorrhea: A network meta-analysis. *Medicine (Baltimore)*. 2020 May;99(19):e19881. doi: 10.1097/MD.00000000000019881. PMID: 32384431; PMCID: PMC7220209.
10. Oladosu FA, Tu FF, Hellman KM. Nonsteroidal antiinflammatory drug resistance in dysmenorrhea: epidemiology, causes, and treatment. *Am J Obstet Gynecol*. 2018 Apr;218(4):390-400. doi: 10.1016/j.ajog.2017.08.108. Epub 2017 Sep 6. PMID: 28888592; PMCID: PMC5839921.
11. Jaisamrarn U, Santibenchakul S. A comparison of combined oral contraceptives containing chlormadinone acetate versus drospirenone for the treatment of acne and

- dysmenorrhea: a randomized trial. *Contracept Reprod Med*. 2018 Apr 10;3:5. doi: 10.1186/s40834-018-0058-9. PMID: 29662684; PMCID: PMC5891982.
12. Damm T, Lamvu G, Carrillo J, Ouyang C, Feranec J. Continuous vs. cyclic combined hormonal contraceptives for treatment of dysmenorrhea: a systematic review. *Contracept X*. 2019 Jan 24;1:100002. doi: 10.1016/j.conx.2019.100002. PMID: 32550522; PMCID: PMC7286154.
  13. Elboim-Gabyzon M, Kalichman L. Transcutaneous Electrical Nerve Stimulation (TENS) for Primary Dysmenorrhea: An Overview. *Int J Womens Health*. 2020 Jan 8;12:1-10. doi: 10.2147/IJWH.S220523. PMID: 32021488; PMCID: PMC6955615.
  14. Jo J, Lee SH. Heat therapy for primary dysmenorrhea: A systematic review and meta-analysis of its effects on pain relief and quality of life. *Sci Rep*. 2018 Nov 2;8(1):16252. doi: 10.1038/s41598-018-34303-z. PMID: 30389956; PMCID: PMC6214933.
  15. Woo HL, Ji HR, Pak YK, Lee H, Heo SJ, Lee JM, Park KS. The efficacy and safety of acupuncture in women with primary dysmenorrhea: A systematic review and meta-analysis. *Medicine (Baltimore)*. 2018 Jun;97(23):e11007. doi: 10.1097/MD.00000000000011007. PMID: 29879061; PMCID: PMC5999465.
  16. Jenabi E, Fereidooni B, Karami M, Masoumi SZ, Safari M, Khazaei S. The effect of bee prepolis on primary dysmenorrhea: a randomized clinical trial. *Obstet Gynecol Sci*. 2019 Sep;62(5):352-356. doi: 10.5468/ogs.2019.62.5.352. Epub 2019 Jul 26. PMID: 31538079; PMCID: PMC6737054.
  17. Shobeiri F, Nazari S, Nazari S, Jenabi E, Shayan A. Effect of Menstrugole on primary dysmenorrhea: a randomized clinical trial. *Obstet Gynecol Sci*. 2018 Nov;61(6):684-687. doi: 10.5468/ogs.2018.61.6.684. Epub 2018 Oct 11. PMID: 30474015; PMCID: PMC6236095.
  18. Lee HW, Ang L, Lee MS, Alimoradi Z, Kim E. Fennel for Reducing Pain in Primary Dysmenorrhea: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Nutrients*. 2020 Nov 10;12(11):3438. doi: 10.3390/nu12113438. PMID: 33182553; PMCID: PMC7697926.
  19. Pakniat H, Chegini V, Ranjkesh F, Hosseini MA. Comparison of the effect of vitamin E, vitamin D and ginger on the severity of primary dysmenorrhea: a single-blind clinical trial. *Obstet Gynecol Sci*. 2019 Nov;62(6):462-468. doi: 10.5468/ogs.2019.62.6.462. Epub 2019 Oct 15. PMID: 31777743; PMCID: PMC6856484.

20. Gomathy N, Dhanasekar KR, Trayambak D, Amirtha R. Supportive therapy for dysmenorrhea: Time to look beyond mefenamic acid in primary care. *J Family Med Prim Care*. 2019 Nov 15;8(11):3487-3491. doi: 10.4103/jfmpe.jfmpe\_717\_19. PMID: 31803641; PMCID: PMC6881953.
21. Xu Y, Zhao W, Li T, Bu H, Zhao Z, Zhao Y, Song S. Effects of acupoint-stimulation for the treatment of primary dysmenorrhoea compared with NSAIDs: a systematic review and meta-analysis of 19 RCTs. *BMC Complement Altern Med*. 2017 Aug 31;17(1):436. doi: 10.1186/s12906-017-1924-8. PMID: 28859645; PMCID: PMC5580316.
22. Dehnavi ZM, Jafarnejad F, Kamali Z. The Effect of aerobic exercise on primary dysmenorrhea: A clinical trial study. *J Educ Health Promot*. 2018 Jan 10;7:3. doi: 10.4103/jehp.jehp\_79\_17. PMID: 29417063; PMCID: PMC5791467.
23. Heidarimoghadam R, Abdolmaleki E, Kazemi F, Masoumi SZ, Khodakarami B, Mohammadi Y. The Effect of Exercise Plan Based on FITT Protocol on Primary Dysmenorrhea in Medical Students: A Clinical Trial Study. *J Res Health Sci*. 2019 Aug 24;19(3):e00456. PMID: 31586377; PMCID: PMC7183554.