

Tips for Clinicians

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Managing Primary Dysmenorrhea

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Background

Primary dysmenorrhea, or painful menses without identifiable pathology, is the most common gynecologic complaint among adolescent females. Sixty to seventy percent of young women^{1,2} report painful periods and 15% of them report an interruption in daily activity due to menstrual pain.² Dysmenorrhea is the leading cause of school absenteeism among this population.¹ Painful menses typically presents in the adolescent years, about 6–12 months after menarche, or when regular ovulatory cycles are established. Symptoms may last up to 72 hours and may include nausea, vomiting, diarrhea, headache, fatigue, dizziness, and syncope, as well as cramping. Although dysmenorrhea is frequent problem among adolescents, many do not seek help from health care providers.

The most common, classic explanation for menstrual cramping is the overproduction of prostaglandins (PG) within the endometrium. PGs are inflammatory modulators known to cause myometrial contractions and vasoconstriction. Locally, PGs incite uterine contractions and ischemia leading to the cramping pain classic of dysmenorrhea. Through systemic circulation, PGs can reach other end organs, causing nausea, vomiting, bloating, and headaches. The biochemical production of PGs is directly related to an ovulatory menstrual cycle. Prior to each ovulatory cycle, as progesterone is withdrawn, arachidonic acid, an omega-6 fatty acid, is released from endometrial cell wall phospholipids. Free arachidonic acid

then sets into motion the cyclo-oxygenase (COX) and lipooxygenase inflammatory cascades that lead to the production of PGs and leukotrienes. Women with dysmenorrhea often have higher levels of PGs in their menstrual fluid when compared to their pain-free counterparts.³

Traditional Treatments

The majority of treatments for dysmenorrhea make use of knowledge of PG production and act through disruption of specific steps in PG formation. Nonsteroidal anti-inflammatory drugs (NSAIDs) are considered by most to be the first-line treatment for dysmenorrhea. In multiple studies a variety of COX 1 NSAIDs have been found to be significantly more effective than placebo for menstrual pain relief. When compared with each other, no NSAID is clearly superior.⁴ For optimal relief of symptoms, NSAIDs should be administered on a scheduled basis, using adequately high doses. They should be initiated as soon as possible with the onset of menses.

Oral contraceptive pills (OCP) are considered the second-line treatment for dysmenorrhea. By decreasing endometrial growth, OCPs limit the production of PGs. Lower levels of PGs have been reported in the menstrual fluid of women taking OCPs compared to those not taking OCPs.³ In a recent double-blind, randomized, controlled trial by Davis et al comparing adolescents taking 28-day pack OCPs (ethinyl estradiol 20 mcg and levonorgestrel 100 mcg) to those taking placebo, OCP users were found to have significantly less dysmenorrhea and required less additional pain medication.⁵ For patients who show a favorable, but incomplete, response to OCPs taken cyclically, OCPs may be taken continuously to reduce

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the number of painful menses in a year. Furthermore, for those patients showing an inadequate response to combination therapy with NSAIDs and OCPs, consideration of common causes of secondary dysmenorrhea and investigation with ultrasound or laparoscopy may be warranted.

In exploring alternative etiologies for dysmenorrhea, besides PG overproduction, the overproduction of leukotrienes (LE) is a logical proposition. In addition to sharing a similar biochemical production pathway, LEs are similar to PGs in that both are potent smooth muscle-stimulating agents. Unlike PGs, however, the relationship between LEs and dysmenorrhea is less well investigated. It has been shown that some adolescent females with dysmenorrhea have increased concentrations of urinary LEs, and it has been speculated that LEs may be responsible for dysmenorrhea in those 30–40% of patients having pain refractory to cyclo-oxygenase inhibitors.⁶ Montelukast, a leukotriene receptor antagonist, has been studied as a therapy for adolescent dysmenorrhea. Given in doses used to treat asthma, it was found to have no significant effect on dysmenorrhea when compared to placebo.⁷

Nontraditional or Alternative Treatments or Adjunctive Treatments

Dietary modification, including the use of vitamins and herbal supplements, may help with the management of dysmenorrhea. Though the data is sparse, use of these products may play a role as an adjunct to traditional therapy. Several of these treatments, including the doses at which they were studied in the trials described below, are presented in Table 1.

Omega-3 Fatty Acids

Dysmenorrhea has been associated with diets high in omega-6 fatty acids and low in omega-3 fatty acids.

Increased incorporation of omega-3 fatty acids (such as fish oil) into cell wall phospholipids ultimately leads to uterine production of less potent PGs and LEs. In a double blind crossover study by Harel and colleagues, patients taking fish oil were found to have less pain and a decreased need for additional medication when compared to patients taking placebo. Some minor adverse effects associated with the use of fish oil are nausea, acne exacerbation, and difficulty swallowing the capsules.⁸

Fennel Essential Oil

While not affecting the PG pathway, another dietary supplement investigated as a treatment for dysmenorrhea is fennel essential oil (FEO). FEO is a fruit essence derived from the *Foeniculum vulgare* plant that has been used as an antispasmodic for pediatric colic and respiratory disorders.⁹ In the Mediterranean region it has been used to relieve pain with menstruation. In a rat-model study by Ostad, FEO reduced the intensity of uterine contractions induced by oxytocin and prostaglandin E2 (PGE2).¹⁰ In women, Jahromi compared the effect of Sweet Fennel versus mefenamic acid for the treatment of primary dysmenorrhea and found that both treatments reached statistical significance for pain reduction on each day of menses when compared to controls; however, mefenamic acid was more potent on menstrual days 2 and 3. As for adverse effects, fennel is known to contain anethol, which may affect the central nervous system and lead to convulsions; therefore, the use of fennel is contraindicated in patients with epilepsy. Fennel also contains small amounts of coumarins that could effect coagulation and bleeding.¹¹

Vitamins

Vitamin E is a known inhibitor of protein kinase C, thereby inhibiting the release of arachidonic acid from

Table 1. Complementary/Alternative Treatments for Dysmenorrhea

	Drug	Dose
Omega-3 Fatty Acids— Fish Oil ⁸	Mega EPA-1000, General Nutrition Corporation, Pittsburgh, 1080 mg eicosapentaenoic acid, 720 mg docosapentaenoic acid, and 1.5 mg vitamin E	One oral dose twice daily
Fennel Essential Oil ¹¹	Essence of fennel fruit with 2% concentration; oral drops	25 drops orally every 4 hours during menstruation
Vitamin E ¹²	200-unit tablets	One oral tablet twice daily, 2 days prior to and 2 days following the start of menses
Vitamin B ₁ ¹³	100-mg tablets	One tablet orally daily
Magnesium ¹⁶	4.5 mg oral Mg Pidolate	One dose three times daily, 7 days prior to and 3 days following the start of menses
	Magnesiocard (magnesium aspartate hydrochloride) 3 × 5 mmol granulate	One oral dose per day, 1 day prior to and 2 days following the start of menses

cell membrane phospholipids and decreasing PG synthesis. In a double blind, randomized, placebo-controlled trial, Ziaei et al investigated the effects of Vitamin E 200 units twice daily versus placebo in treating dysmenorrhea. While study findings revealed that pain was reduced by both medications, the reduction by vitamin E was significantly greater.¹²

Vitamin B₁ supplementation may improve dysmenorrhea via a reversal of the symptoms common to B₁ deficiency, namely muscle cramping, fatigue, and reduced pain tolerance. When B₁ supplementation was tested against placebo supplementation in a large randomized controlled trial for the treatment of dysmenorrhea, vitamin B₁ was found to have a significantly greater effect on pain reduction than placebo.¹³

Magnesium

Magnesium is another supplement studied for its effect on dysmenorrhea. While its mechanism of action is nonspecific, magnesium may work via a reduction in PGs and/or via a decrease in muscle contractility. Seifert found that women taking magnesium had substantially lower levels of prostaglandin F₂ alpha (PGF₂α) in their menstrual fluid compared to women taking placebo.¹⁴ Magnesium is also a cell membrane stabilizer, and when intracellular levels are reduced, as they are after progesterone withdrawal prior to menses, muscles become more contractile.¹⁵ In small, randomized, double blind controlled trials, magnesium was found to be more effective than placebo for menstrual pain relief. It was also noted to reduce significantly the need for additional medications during menses.¹⁶

Transcutaneous Electrical Nerve Stimulation (TENS)

TENS has been investigated as a means of non-pharmacologic dysmenorrhea treatment. TENS involves the application of electric current to skin electrodes in order to induce pain relief. As it applies to dysmenorrhea, TENS may reduce pain by altering the body's basic ability to perceive pain¹⁷ or by increasing uterine blood flow and decreasing myometrial ischemia.¹⁸ A Cochrane review of TENS for the treatment of dysmenorrhea found high frequency TENS to be more effective for pain relief than placebo/sham TENS. Adverse effects of high frequency TENS include muscle vibrations and tightness, headache, and redness and burning of the skin.¹⁷

Acupuncture

Acupuncture involves the placement of needles into specific skin sites in order to excite receptors and/or nerve fibers that interact with serotonin and endorphins to block pain impulses. As a treatment for dysmenorrhea, one small study by Helms, which

investigated the use of acupuncture versus placebo/sham acupuncture for the treatment of dysmenorrhea, found acupuncture to be significantly more effective for pain relief than placebo.¹⁹

In summary, while NSAIDs and OCPs are considered the first and second line treatments for dysmenorrhea, other potential medical treatments are available. While studies of the aforementioned non-traditional treatments are limited in size and number, these therapies may be of help to patients seeking complementary or alternative therapies.

References

1. Klein J, Litt I: Epidemiology of adolescent dysmenorrhea. *Pediatrics* 1981; 68:661
2. Andresch B, Milsom I: An epidemiologic study of young women with dysmenorrhea. *Am J Obstet Gynecol* 1982; 144:655
3. Chan W, Hill J: Determination of menstrual prostaglandin levels in non-dysmenorrheic and dysmenorrheic subjects. *Prostaglandins* 1978; 15:365
4. Marjoribanks J, Proctor M, Farquhar C: Nonsteroidal anti-inflammatory drugs for primary dysmenorrhea. *Cochrane Database Syst Rev* 2004; (2):CD.
5. Davis A, Westhoff C, O'Connell K, Gallagher N: Oral contraceptives for dysmenorrhea in adolescent girls. *J Obstet Gynecol* 2005; 106:97
6. Schroeder B, Sanfilippo J: Dysmenorrhea and pelvic pain in adolescents. *Pediatr Clin North Am* 1999; 46:555
7. Harel Z, Riggs S, Vaz R, et al: The use of the leukotriene receptor antagonist Montelukast (Singulair) in the management of dysmenorrhea in adolescents. *J Pediatr Adolesc Gynecol* 2004; 17:183
8. Harel Z, Brio F, Kottenhahn R, et al: Supplementation with omega-3 polyunsaturated fatty acids in the management of dysmenorrhea in adolescents. *Am J Obstet Gynecol* 1996; 174:1335
9. Reynolds E: Essential oils and aromatic carminatives. Martindale, *The Extra Pharmacopeia*, 28th ed. Royal Pharmaceutical Society, London 1982: 670
10. Ostad S, Soodi M, Shariffzadeh M, et al: The effect of fennel essential oil on uterine contraction as a model for dysmenorrhea. *Pharmacology and toxicology study. J Ethnopharmacol* 2001; 76:299
11. Jahromi B, Tartifzadeh A, Khadnadideh S: Comparison of fennel and mefenamic acid for the treatment of primary dysmenorrhea. *Int J Gynaecol Obstet* 2003; 80:153
12. Ziaei S, Zakeri M, Kazemnejad A: A randomized control trial of vitamin E in the treatment of primary dysmenorrhea. *BJOG* 2005; 112:466
13. Gokhale L: Curative treatment of primary (spasmodic) dysmenorrhea. *Indian J Med Res* 1996; 103:227
14. Seifert B, Wagler P, Dartsch S, et al: Magnesium, a new therapeutic alternative in primary dysmenorrhea. *Zentralbl Gynakol* 1989; 111:755
15. Balbi C, Musone R, Menditto A, et al: Influence of menstrual factors and dietary habits on menstrual pain in adolescence age. *Eur J Obstet Gynecol* 2000; 91:143

16. Proctor M, Murphy P: Herbal and dietary therapies for primary and secondary dysmenorrhea. *Cochran Database Syst Rev* 2005; (3):CD
17. Proctor M, Smith C, Farquhar C, et al: Transcutaneous electrical nerve stimulation and acupuncture for primary dysmenorrheal. *Cochrane Database Syst Rev* 2004; (2):CD
18. Milsom I, Hedner N, Mannheimer C: A comparative study of the effect of high-intensity transcutaneous nerve stimulation and oral naproxen on intrauterine pressure and menstrual pain in patients with primary dysmenorrhea. *Am J Obstet Gynecol* 1994; 170:123
19. Helms J: Acupuncture for the management of primary dysmenorrhea. *Obstet Gynecol* 1987; 69:61