Dysmenorrhea

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Dysmenorrhea is the leading cause of recurrent short-term school absence in adolescent girls and a common problem in women of reproductive age. Risk factors for dysmenorrhea include nulliparity, heavy menstrual flow, smoking, and depression. Empiric therapy can be initiated based on a typical history of painful menses and a negative physical examination. Nonsteroidal anti-inflammatory drugs are the initial therapy of choice in patients with presumptive primary dysmenorrhea. Oral contraceptives and depo-medroxyprogesterone acetate also may be considered. If pain relief is insufficient, prolonged-cycle oral contraceptives or intravaginal use of oral contraceptive pills can be considered. In women who do not desire hormonal contraception, there is some evidence of benefit with the use of topical heat; the Japanese herbal remedy toki-shakuyaku-san; thiamine, vitamin E, and fish oil supplements; a low-fat vegetarian diet; and acupressure. If dysmenorrhea remains uncontrolled with any of these approaches, pelvic ultrasonography should be performed and referral for laparoscopy should be considered to rule out secondary causes of dysmenorrhea. In patients with severe refractory primary dysmenorrhea, additional safe alternatives for women who want to conceive include transcutaneous electric nerve stimulation, acupuncture, nifedipine, and terbutaline. Otherwise, the use of danazol or leuprolide may be considered and, rarely, hysterectomy. The effectiveness of surgical interruption of the pelvic nerve pathways has not been established. (Am Fam Physician 2005;71:285-91, 292. Copyright© 2005 American Academy of Family Physicians.)

ILLUSTRATION BY JOAN BECK

See page 225 for definitions of strength-of-recommendation labels.

▶ **Patient information:** A handout on dysmenorrhea, written by the author of this article, is provided on page 292.

EB CME

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Primary dysmenorrhea, which is defined as painful menses in women with normal pelvic anatomy, usually begins during adolescence. It is characterized by crampy pelvic pain beginning shortly before or at the onset of menses and lasting one to three days. Dysmenorrhea also may be secondary to pelvic organ pathology.

The prevalence of dysmenorrhea is highest in adolescent women, with estimates ranging from 20 to 90 percent, depending on the measurement method used.[1-3] About 15 percent of adolescent girls report severe dysmenorrhea,[1,4] and it is the leading cause of recurrent short-term school absenteeism in adolescent girls in the United States.[2,5] A longitudinal study[6] of a representative cohort of Swedish women found a prevalence of dysmenorrhea of 90 percent in women 19 years of age and 67 percent in women 24 years of age. Ten percent of the 24-year-olds reported pain that interfered with daily function. Most adolescents self-medicate with over-the-counter medicines, and few consult a physician about dysmenorrhea.[1-3]

Pathogenesis

Dysmenorrhea is thought to be caused by the release of prostaglandins in the menstrual fluid, which causes uterine contractions and pain. Vasopressin also may play a role by increasing uterine contractility and causing ischemic pain as a result of vasoconstriction. Elevated vasopressin levels have been reported in women with primary dysmenorrhea.

The relationship between endometriosis and dysmenorrhea is not clear. Endometriosis may be asymptomatic, or it may be associated with pelvic pain that is not limited to the menstrual period and the low anterior pelvis. In one study[7] of women undergoing elective sterilization, no difference was found in the prevalence of dysmenorrhea in women with and women without an incidental finding of endometriosis. However, an observational study[8] of women undergoing laparoscopy for infertility supported a

relationship between dysmenorrhea and the severity of endometriosis.

Risk Factors

Young age and nulliparity are associated with dysmenorrhea.[4,9] However, one longitudinal study[6] found that age was not a risk factor after controlling for parity and other factors, and that dysmenorrhea improved after childbirth. Heavy menstrual flow is associated with dysmenorrhea.[4,5,9] *Table 1* lists risk factors for dysmenorrhea.

Behavioral risk factors are of interest because of the potential to intervene. Several observational studies[6,10,11] have found an association between smoking and dysmenorrhea. In women 14 to 20 years of age, attempts to lose weight are associated with increased menstrual pain independent of body mass index.[12] However, the evidence of an association between overweight and dysmenorrhea is inconsistent.[4,6,10] Other behaviors such as physical activity and alcohol consumption have not been associated consistently with dysmenorrhea.[10,11]

Mental health problems are another potentially modifiable risk factor. Depression, anxiety, and disruption of social support networks have been associated with menstrual pain.[13] An association between poor self-rated overall health and dysmenorrhea has been noted,[9] but socioeconomic status is not associated consistently with dysmenorrhea.[5,9]

Although there has been concern that tubal sterilization may be a risk factor for dysmenorrhea, a cross-sectional study[14] found no difference in menstrual pain in women with and women without tubal sterilization.

TABLE 1
Risk Factors for Dysmenorrhea

Age < 20 years
Attempts to lose weight
Depression/anxiety
Disruption of social networks
Heavy menses
Nulliparity
Smoking

Diagnosis

In most patients who present with menstrual pain, empiric therapy may be prescribed with the presumptive diagnosis of primary dysmenorrhea, based on a typical history of low anterior pelvic pain beginning in adolescence and associated specifically with menstrual periods. A history that is inconsistent and/or physical findings of a pelvic mass, abnormal vaginal discharge, or pelvic tenderness that is not limited to the time of the menstrual period suggest a diagnosis of secondary dysmenorrhea. It is appropriate to perform only an abdominal examination in young adolescents with a typical history who have never been sexually active. A pelvic examination should be performed in females who have been sexually active to screen for sexually transmitted diseases such as chlamydial infection.

When the history and physical examination suggest other pelvic pathology, the evaluation should follow accordingly, usually with pelvic ultrasonography as the initial diagnostic test to rule out anatomic abnormalities such as mass lesions. In patients with severe dysmenorrhea that is unresponsive to initial treatment, ultrasonography is useful to detect ovarian cysts and endometriomas.[15] It also has reasonably good ability to detect advanced stage 3 or 4 endometriosis; its concordance with surgical staging is 84 percent.[16] Sonovaginography (i.e., transvaginal ultrasonography with saline infusion of the uterus) appears to be better than transvaginal sonography alone in diagnosing rectovaginal endometriosis.[17] Magnetic resonance imaging is limited in its ability to diagnose

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endometriosis (sensitivity, 69 percent; specificity, 75 percent).[18] The reference standard test for diagnosis and staging of endometriosis is laparoscopy or laparotomy with biopsy. It should be considered when first-line therapies are ineffective and dysmenorrhea causes functional impairment.

Therapy

Table 2[19-32] lists therapies for dysmenorrhea and the strength of evidence to support their efficacy. Many of the standard treatments have not been well studied. The recommendations reflect a balance between the available evidence and an assessment of benefit, harm, and cost. *Table 3* provides dosing and cost information for prescription drugs used in the treatment of dysmenorrhea.

NSAIDS

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the best-established initial therapy for dysmenorrhea.[19] They have a direct analgesic effect through inhibition of prostaglandin synthesis, and they decrease the volume of menstrual flow. These effects probably are common to all NSAIDs. Two meta-analyses[33,34] of randomized controlled trials (RCTs) of NSAIDs and acetaminophen found that all of the NSAIDs studied (i.e., ibuprofen [Motrin], naproxen [Naprosyn], mefenamic acid [Ponstel], and aspirin) were effective in treating women with dysmenorrhea, and all of the NSAIDs were more effective than acetaminophen.[19] Small studies[22,23] of cyclooxygenase-2 inhibitors have shown efficacy similar to that of NSAIDs in the treatment of dysmenorrhea. NSAIDs may be most effective when therapy is started before the onset of menstrual pain and flow, although therapy need not be continued after the end of the flow.

ORAL CONTRACEPTIVE PILLS

Treatment of dysmenorrhea is a well-accepted off-label use for oral contraceptive pills (OCPs). The proposed mechanism of action is reduced prostaglandin release during menstruation. Consistent observational data support a beneficial effect from oral contraceptives in the treatment of dysmenorrhea, and in one exploratory RCT[35] of women who took desogestrel-containing OCPs, these women had less pain during menses than women who received placebo. An observational study[36] of dysmenorrhea severity in women who

TABLE 2
Treatments for Dysmenorrhea

Intervention	*Strength of recommendation*
Effective	
NSAIDs[19]	A
Probably effective	
Danazol (Danocrine)*	B
Extended-cycle oral contraceptives*	B
Hysterectomy*	B
Leuprolide acetate (Lupron)*	B
Depo-medroxyprogesterone acetate (Depo-Provera)*	B
Possibly effective	
Acupuncture/acupressure[20,21]	B
COX-2 inhibitors[22,23]	B
Fish oil supplements[24]	B
Levonorgestrel intrauterine system (Mirena)[25]	B
Low-fat vegetarian diet[26]	B
Oral contraceptives (intravaginal administration)[27]	B
Oral contraceptives (oral administration)†	B
Thiamine supplementation[19]	B
Toki-shakuyaku-san (Japanese herb)[19]	B
Topical heat[19]	B
Transcutaneous electric nerve stimulation[19]	B
Vitamin E supplementation[19]	B
Uncertain effectiveness	
Behavioral interventions including exercise[19]	C
Glyceryl trinitrate	C
Nifedipine (Procardia)[28]	C
Surgical interruption of pelvic nerve pathways[29]	C
Terbutaline (Bricanyl)[30]	C
Ineffective	
Spinal manipulation[31,32]	B

NSAIDs = nonsteroidal anti-inflammatory drugs; COX-2 = cyclooxygenase-2.

A = consistent, good-quality, patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, opinion, or case series. *See page 225 for more information.*

NOTE: *At the time of publication new information had appeared regarding the safety of COX-2 inhibitors. Because they appear to increase the risk of myocardial infarction, the decision to use these agents should only be made after a discussion of risks and benefits with the patient.*

**—Mechanism: suppression of menses.*

†—Based on consistent observational data.

Information from references 19 through 32.

TABLE 3
Agents Used in the Treatment of Dysmenorrhea

Agent	*Dosage*	*Cost (generic)**
Danazol (Danocrine)	100 or 200 mg twice daily	$172 to 286 (153 to 257)
Leuprolide acetate (Lupron)	3.75 mg IM monthly	473
NSAIDs†		
Diclofenac (Voltaren)	50 mg three times daily	22 (12 to 16)
Ibuprofen (Motrin)	800 mg three times daily	6 (3 to 5)
Mefenamic acid (Ponstel)	Initial dose: 500 mg, followed by 250 mg four times daily	23
Naproxen (Naprosyn)	500 to 550 mg twice daily	13 (9 to 10)
Oral contraceptives	1 tablet daily	22 to 36

IM = intramuscularly; NSAIDs = nonsteroidal anti-inflammatory drugs; COX-2 = cyclooxygenase-2.

**—Estimated cost to the pharmacist for one month's therapy based on average wholesale prices in Red book. Montvale, N.J.: Medical Economics Data, 2004. Cost to the patient will be higher, depending on prescription filling fee.*

†—Cost for NSAIDs assumes four days of therapy per month.

used different forms of contraception showed lower mean scores in users of monophasic formulations compared with triphasics. However, a Cochrane review[37] found insufficient evidence from RCTs to draw conclusions about the effectiveness of OCPs in treating dysmenorrhea.

OTHER HORMONAL METHODS

Several other off-label methods exist for treating dysmenorrhea with hormonal contraceptives. Most women who receive depo-medroxyprogesterone acetate (Depo-Provera) are amenorrheic within the first year of use. Similarly, extended-cycle use of OCPs (i.e., usually taking OCPs for 12 weeks followed by one week off) leads to less-frequent menstrual periods. In a retrospective review,[38] 21 percent of women who chose extended-cycle regimens did so primarily for treatment of dysmenorrhea. Observational data[39] from users of the levonorgestrel intrauterine device (Mirena) showed a decrease in prevalence of dysmenorrhea from 60 percent before use of the device to 29 percent after 36 months of use.

An intravaginal contraceptive is more effective and associated with fewer side effects than the same agent in an oral form.

A novel treatment approach is intravaginal administration of standard OCPs (i.e., 30 mcg of ethinyl estradiol and 150 mg of levonorgestrel daily); an RCT[27] of 150 women found fewer systemic side effects and less dysmenorrhea with the intravaginal approach (21 percent with intravaginal use versus 44 percent with standard oral administration; number needed to treat, 4; $P < .001$). Contraceptive patches appear to be less effective than OCPs taken orally in treating women with dysmenorrhea.[40]

OTHER PHARMACOLOGIC TREATMENTS

Several medications that induce uterine relaxation have been proposed for treatment of dysmenorrhea. In one RCT,[41] it was found that glyceryl trinitrate is less effective than diclofenac and is associated with a high incidence of headache. Early uncontrolled pilot studies[28,30] of oral nifedipine and intravenous terbutaline showed promise, but further study on these drugs is needed.

Treatment to suppress the menstrual cycle with danazol (Danocrine) or leuprolide acetate (Lupron) may be considered, rarely, in refractory cases. These are expensive therapies with significant side effects; they usually are reserved for treatment of conditions other than primary dysmenorrhea, such as endometriosis and chronic pelvic pain that is not limited to the time of the menstrual period.

LIFESTYLE MODIFICATION

Few studies have examined the effect of lifestyle-modification interventions in the management of dysmenorrhea. One cross-over study[26] of a low-fat vegetarian diet versus placebo pill showed decreased duration and intensity of dysmenorrhea in women in the intervention group. Although some studies have reported a benefit with exercise, the effect is questionable because participants were not blinded to the study hypothesis.[19] Smoking cessation has not been studied as an intervention to manage dysmenorrhea.

Complementary and Alternative Medicines

SUPPLEMENTS

Thiamine at a dosage of 100 mg daily was found to be effective in treating dysmenorrhea in a double-blind RCT of more than 500 East Indian women aged 12 to 21 years with moderate to severe symptoms.[19] It is unclear whether thiamine would be effective in U.S. women, whose diet may be quite different from that of Indian women. A single RCT of vitamin E found that 2,500 IU taken daily for five days starting two days before menstruation was more effective than placebo in treating dysmenorrhea.[19] A small RCT[24] of omega-3 polyunsaturated fatty acids found that 2 g daily of a fish oil supplement significantly reduced pain compared with placebo. High intake of fish n-3 fatty acid also was associated with less average symptom severity in an observational study of Danish women.[42]

HERBAL REMEDIES

The Japanese herbal remedy toki-shakuyaku-san (TSS) has been shown in an RCT to be better than placebo in the treatment of women with dysmenorrhea.[19] Because this product is not regulated, the ingredients and effectiveness may vary among formulations. It does not appear to suppress fertility or ovulation. There are insufficient data to evaluate other herbal products.[19]

PHYSICAL TREATMENTS

Limited evidence from RCTs suggests that acupuncture and acupressure are effective in treating dysmenorrhea. In a study[20] of acupuncture versus sham acupuncture, 91 percent of patients in the treatment group had pain relief compared with 36 percent of control patients. Patients in the treatment group had a 41 percent reduction in use of pain medication, while no difference was noted in control patients.[20] A study[21] of acupressure at a point on the hand found pain relief similar to that in patients who took ibuprofen and better than that in patients who received sham acupressure. A study[43] of acupressure underwear was inconclusive because of lack of blinding.

A single small study[44] of transcutaneous electric nerve stimulation (TENS) suggested that TENS is more effective in treating dysmenorrhea than a sham procedure, with 42 percent of women reporting good to excellent pain relief with TENS compared with 3 percent of control patients. However, a systematic review[45] found insufficient evidence to determine if TENS is effective. In a study[46] of a topical heated patch compared with low-dose ibuprofen (i.e., 400 mg three times daily) and placebo, the heated patch was as effective as ibuprofen.

Nonsteroidal anti-inflammatory drugs are the initial therapy of choice in patients with primary dysmenorrhea.

A well-designed study[31] of spinal manipulative therapy versus a sham procedure showed similar pain relief in both groups. In addition, a systematic review[32] of spinal manipulation in the treatment of dysmenorrhea concluded that there is no evidence to suggest effectiveness.

Surgical Therapies

In rare instances, a surgical approach may be considered for women with severe, refractory dysmenorrhea. Refractory dysmenorrhea is an accepted indication for hysterectomy. Laparoscopic uterine nerve ablation (LUNA) and presacral neurectomy also have been used in refractory cases. Observational data[47] show that at one year after the procedure, pain relief persisted in 82 percent of women having presacral neurectomy and in only 51 percent having LUNA. Information about long-term outcomes is relatively lacking. A Cochrane meta-analysis[29] of surgical interruption of pelvic nerve pathways as a treatment for dysmenorrhea concluded that evidence was insufficient to recommend the procedure, regardless of the cause of the dysmenorrhea.

Approach to the Patient

NSAIDs are the initial therapy of choice in patients with presumptive primary dysmenorrhea. Because all NSAIDs are equal in efficacy, agent selection should be guided by cost, convenience, and patient preference, with ibuprofen or naproxen being a good choice for most patients. If hormonal contraception is desired, monophasic OCPs

and depo-medroxyprogesterone acetate also may be considered. If relief is insufficient, the physician may consider prolonged-cycle OCP use or intravaginal use of OCPs.

In women who do not desire hormonal contraception, topical heat; TSS; thiamine, vitamin E, or fish oil supplements; a low-fat vegetarian diet; and acupressure are relatively simple and inexpensive alternatives that can be used alone or in combination. If dysmenorrhea is not controlled with any of these approaches, pelvic ultrasonography should be performed and referral for laparoscopy should be considered to rule out secondary causes of dysmenorrhea.[48,49] In severe refractory primary dysmenorrhea, additional safe alternatives for women who want to conceive are (in order of clinical preference) TENS, acupuncture, nifedipine (Procardia), and terbutaline (Bricanyl). Otherwise, danazol or leuprolide may be considered and, rarely, hysterectomy.

Therapies on the Horizon

Several of the therapeutic approaches discussed in this article deserve further study before we can say definitively whether they are effective. Two options may become available in the near future: (1) a vasopressin-receptor antagonist is being tested. Because vasopressin appears to be involved in the pathogenesis of dysmenorrhea, vasopressin-receptor antagonists are theoretically useful. However, studies[50-53] to date have not shown consistent evidence of efficacy. And (2) a frameless levonorgestrel IUD has been introduced in Europe, where it is being used in the management of primary and secondary dysmenorrhea.[54] The frameless device decreases menstrual flow and provides contraceptive efficacy similar to that of currently available IUDs.

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