Primary Dysmenorrhea
Advances in Pathogenesis and Management

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Primary dysmenorrhea is defined as painful menstrual cramps without any evident pathology to account for them. It refers to any degree of perceived cramping pain during menstruation.

**PREVALENCE**
A widely prevalent and common complaint among young women, primary dysmenorrhea is estimated to be present in 40–50% of them,\(^1\) with severe forms giving rise to work or school absenteeism in 15% and the mild forms requiring no medication or occasional over-the-counter (OTC) analgesics in about 30%. In spite of advances in the treatment of primary dysmenorrhea, a recent study of 1,546 menstruating Canadian women found that 60% were having the disorder.\(^2\) Sixty percent of the dysmenorrheic women were having severe or moderate pain. Fifty-one percent reported limitation of activities, and 17% reported absenteeism. Thus, there appears to be underuse of currently available OTC and prescription medications, or there is insufficient dissemination of information about primary dysmenorrhea to targeted young populations.

The prevalence of primary dysmenorrhea decreases with increasing age: prevalence is highest in the 20- to 24-year-old age group and decreases progressively thereafter.\(^3\) There appears to be no relationship with parity when age is factored in. Dysmenorrhea is increased with smoking.\(^2\) Primary dysmenorrhea occurs only during ovulatory cycles.\(^4\) Limited studies have suggested a decline in dysmenorrhea with physical exercises, but critical analysis and other studies do not support any evidence-based relationship between exercise and primary dysmenorrhea.\(^5\)
CLINICAL FEATURES
Primary dysmenorrhea presents with or shortly after menarche. It may start within 6 months after menarche because it occurs only during ovulatory cycles, which may not always be evident at menarche. Although it may occur as late as a year after menarche, it is less likely to do so later when it should raise suspicion of secondary dysmenorrhea.

Characterized by fluctuating, spasmodic menstrual cramps, sometimes referred to as “labor-like” pains that begin only a few hours before or with the onset of menstrual flow, the symptoms of primary dysmenorrhea lasts only 2–3 days. The pains are most intense on the first or second day of the menstrual flow, or more precisely the first 24–36 hours, consistent with the time of maximal prostaglandin release into the menstrual fluid (vide infra). The pains are suprapubic in location with radiation into the inner aspects of the thighs. The cramps are frequently accompanied by backache, nausea, vomiting, and diarrhea in a high percentage of cases. With severe pains, the sufferers may be absent from school or work for a day or two. In the severe forms, the pain may present as an intense acute abdominal episode and may mimic the presentation of an acute ectopic pregnancy. General and pelvic examinations are essentially normal.

The typical history and absence of any positive findings in the physical examination are key diagnostic features. The diagnostic history includes the proximities of the onset of primary dysmenorrhea with menarche, the onset of symptoms with the onset of menstrual flow, and the duration of menstrual cramping and its characteristic description. Thus, primary dysmenorrhea should be diagnosed as a specific entity, but there is no laboratory test for it.

PATHOPHYSIOLOGY
Advances in the last three decades and current understanding suggest that in primary dysmenorrhea there is abnormal and increased prostanoid and possibly eicosanoid secretion, which in turn induces abnormal uterine contractions. The contractions reduce uterine blood flow, leading to uterine hypoxia.

That increased vasoactive prostanoid secretion is responsible for the etiology of primary dysmenorrhea is supported by 1) the striking similarity between the clinical symptoms of primary dysmenorrhea and the uterine contractions and adverse effects observed in prostaglandin-induced abortion and labor, 2) substantial evidence demonstrating and correlating the amount of menstrual prostanoids in women with primary dysmenorrhea compared with eumenorrheic women, and 3) many clinical trials demonstrating the efficacy of cyclooxygenase (COX) inhibitors in relieving the pain of primary dysmenorrhea through prostaglandin suppression and quantitative decrease of menstrual fluid prostaglandins.

Prostanoids
In primary dysmenorrhea, there is increased abnormal uterine contractility, similar to uterine contractility induced with prostaglandins or their analogues for labor or abortion. Symptoms such as nausea, vomiting, and diarrhea occur in 60% or more of patients and are similar to the adverse effects of prostaglandins.

Pickles and his colleagues postulated that “menstrual stimulant” or prostaglandins were elevated in menstrual extracts of women with primary dysmenorrhea compared with eumenorrheic women. With availability of radioimmunoassay and specific antisera, several laboratories, including ours, were able to measure small quantities of prostanoids in endometrium and menstrual fluid with greater precision. In most but not all women with primary dysmenorrhea, there is increased endometrial secretion of menstrual prostaglandin F2α (PGF2α) during the menstrual phase. The release of prostaglandins into the menstrual fluid is a continuous discontinuous process, that is, the amount of menstrual fluid and prostaglandins varies throughout any window of time. The intensity of the menstrual cramps and associated symptoms of dysmenorrhea are directly proportional to the amount of PGF2α released (Fig. 1).

Fig. 1. Correlation between the amounts of prostaglandins in prostaglandin F2α, equivalents released per hour during menstruation and the severity of the dysmenorrhea as reflected by the dysmenorrhea score in a woman with primary dysmenorrhea. Reproduced with permission from Dawood MY. Hormones, prostaglandins and dysmenorrhea. In: Dawood MY, editor. Dysmenorrhea. Baltimore (MD): Williams and Wilkins; 1982. p. 21. Copyright 1982, Lippincott Williams & Wilkins.

When a nonsteroidal anti-inflammatory drug (NSAID) such as ibuprofen is taken during menstruation, the menstrual fluid prostaglandins are significantly inhibited to levels similar to or lower than those found in eumenorrheic women,\textsuperscript{11–20} and clinical relief is obtained. Similarly, when the patient is on a combined oral contraceptive (estrogen and progestin), her menstrual fluid prostaglandins are significantly suppressed, with an accompanying reduction in menstrual fluid volume/bleeding and concomitant relief of pain compared with cycles given placebo or no medication.\textsuperscript{3,12,16,19,21}

Despite advances with prostaglandins in the etiology of primary dysmenorrhea, there are patients with normal laparoscopic finding and severe dysmenorrhea who do not have elevated menstrual \( \text{PGF}_2 \alpha \) to account for the severe cramping.\textsuperscript{11} The prevalence of such patients is currently not known. The role of prostanoids such as thromboxane \( A_2 \), prostacyclin, and leukotrienes in the pathogenesis of primary dysmenorrhea is neither fully understood nor adequately explored. Prostacyclin, a potent vasodilator and uterine relaxant, appears to be reduced in primary dysmenorrhea.\textsuperscript{22} This heightens the uterine activity and vasoconstriction because the uteronic and vasoconstrictive effects of the other prostaglandins are less impeded. Increased leukotriene produced by the 5-lipoxygenase enzyme pathway rather than the COX pathway may account for some forms of primary dysmenorrhea that are not responsive to NSAIDs.\textsuperscript{23} The 5-lipoxygenase pathway for the biosynthesis of leukotrienes is outlined in Figure 2. Human endometrium and myometrium can synthesize leukotrienes,\textsuperscript{23} thus confirming the functional activity of the 5-lipoxygenase pathway and that leukotrienes are involved in myometrial contractions.\textsuperscript{24} In women with primary dysmenorrhea, there are significantly higher concentrations of menstrual leukotrienes,\textsuperscript{25,26} especially leukotriene C\textsubscript{4} and leukotriene D\textsubscript{4}, than in women without dysmenorrhea.\textsuperscript{27} Because specific binding sites for leukotriene C\textsubscript{4} are demonstrable in myometrial cells,\textsuperscript{28} it is likely that leukotrienes contribute to the uterine hypercontractility seen in primary dysmenorrhea.

Prostaglandins and prostanoids are biosynthesized from arachidonic acid through the COX pathway after production of arachidonic acid from hydrolysis of phospholipids by phospholipase (Fig. 3). When pregnancy does not occur, progesterone levels decline during the late luteal phase. This causes labilization of lysosomes and release of their phospholipase enzyme, which then hydrolyzes the cell membrane phospholipids to generate arachidonic acid as well as icosatetraenoic acid. These compounds then serve as the precursors for the COX and lipoxygenase pathways.

**Vasopressin**

Involvement of vasopressin in the pathogenesis of primary dysmenorrhea is still controversial.\textsuperscript{29,30} Increased levels of circulating vasopressin during menstruation reported in women with primary dysmenorrhea\textsuperscript{31} can produce dysrhythmic uterine contractions that reduce uterine blood flow and cause uterine hypoxia. In limited studies, vasopressin antagonists were able to neutralize the effect of endogenous
vasopressin and relieve dysmenorrhea. Other investigators could not confirm elevated plasma vasopressin in women with primary dysmenorrhea and found that the vasopressin antagonist atosiban had no effect on menstrual pain, intrauterine pressure, or uterine artery pulsatility index in dysmenorrheic women.

Uterine Contraction
In normal eumenorrheic women, the uterus has well-defined contraction patterns that are influenced by sex steroids, prostaglandins, and other uterotonic substances throughout the menstrual cycle. Details of the pattern have been well described. Of particular interest and relevance to the pathogenesis of primary dysmenorrhea is the uterine contraction pattern during menstruation when the symptoms of dysmenorrhea occur. During menstruation in normal women, the uterine basal tone is minimal (less than 10 mm Hg), there are 3–4 contractions during each 10-minute interval with active pressures at the peak of a contraction reaching up to 120 mmHg (comparable to the intrauterine pressure during the second stage of labor with pushing), and the contractions are synchronous and rhythmical. In patients with primary dysmenorrhea, four contraction abnormalities alone or in combination have been reported. They include elevated basal tone (more than 10 mm Hg), which is frequently seen, elevated active pressures (more than 120 mmHg, often more than 150–180 mmHg), increased number of contractions per 10 minutes (more than 4 or 5), and nonrhythmic or incoordinate uterine contractions. These abnormalities lead to poor uterine reperfusion and oxygenation, thus giving rise to pain. If more than one contraction abnormality is present, they synergize with each other so that the pain threshold is exceeded with much smaller changes in each parameter than if only one anomaly were present.

Uterine Blood Flow
Studies to determine uterine blood flow in women have been difficult because of the highly invasive methods and technically challenging requirements involving hydrogen clearance, nitrous oxide, electromagnetic flowmeters, and the microsphere methods.

Fig. 3. The arachidonic acid cascade showing the cyclooxygenase (COX) pathway, the biosynthesis of cyclic endoperoxides PGG and PGH, and the final products: prostacyclin, prostaglandins F (PGF) and E (PGE), and thromboxane A2 (TXA2). The enzymes are shown in italics. Thus, COX inhibitors block early in the COX pathway. Prostaglandin F, PGE, and TXA induce smooth muscle contractions (uterine contractility, vasoconstriction) and hypersensitization of pain nerve fibers.

Thermoelectric blood flow recordings based on thermodilution have been used for assessing changes in uterine pressure and variations in blood flow. In eumenorrheic women the uterine contractions do not affect uterine blood flow. By contrast, the strong and abnormal uterine contractions in dysmenorrheic women reduce uterine blood flow and cause myometrial ischemia, resulting in pain. Such changes can be produced with pharmacologically induced uterine contractions which, if excessive, will reduce blood flow and produce cramp-like pains. Administration of an uterolytic, such as a calcium channel blocker or NSAID, abrogates the hypercontractility and restores blood flow to normal.

These earlier studies are now supported by Doppler flow studies. The pulsatility index and resistance index of both uterine arteries and the arcuate artery were significantly higher on the first day of menstruation in women with primary dysmenorrhea, suggesting increased blood flow impedance and indicating uterine vasoconstriction as a cause of the pain.

**MANAGEMENT**

There are three approaches to the management of primary dysmenorrhea: pharmacological, nonpharmacological, and surgical. By far, the pharmacological approach has been better documented for efficacy, whereas the other approaches have more variable evidence.

In evaluating treatment efficacy, it is critically important to consider not only the relief of pain but also the powerful placebo effect in up to 35–40% of dysmenorrheic subjects, the primary outcome index (is it pain or something else) being evaluated, the time to relief of pain (rapidity of onset) and onset of peak pain relief, the duration of pain relief, and secondary outcome indices (such as relief of associated symptoms, functionality as measured by reduction in absenteeism, and qualitative improvement in performance). These have been discussed by us elsewhere in detail. Only patients with primary dysmenorrhea should be included, and the criteria for such a diagnosis should be adhered to, but laparoscopy is not essential. Patients using an intrauterine device or oral contraceptives should be excluded, although a few trials have included them.

In primary dysmenorrhea, all trials should be prospective, double-blind, and placebo-controlled, involving several cycles, with each treatment given for 2–3 cycles. After ibuprofen was shown to be effective, it is now the gold standard against which new drugs or treatment modalities are evaluated. Because of intra-cycle-to-cycle variability of dysmenorrhea symptoms, it is preferable to use a parallel rather than a crossover study design for trials using only a limited number of cycles (2–3 cycles). There is little or no crossover effect because primary dysmenorrhea is confined to only 3 days or less, over which time the pathophysiology (vide supra) occurs and clears off. A crossover (blinded and random) from one treatment or placebo to another is the optimum study design because patients can act as their own controls or treatment comparisons and the menstrual fluid prostaglandins can be reliably compared.

**Pharmacological Agents**

**Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)**

In women with dysmenorrhoea, NSAIDs are significantly more effective for pain relief than placebo (odds ratio [OR] 7.91, 95% confidence interval [CI] 5.65–11.09). Overall adverse effects were also significantly more common (OR 1.52, 95% CI 1.09–2.12). There was insufficient power to detect differences between different NSAIDs because most individual comparisons were based on a few small trials unsuitable for meta-analysis. Thus there is insufficient evidence to determine which (if any) individual NSAID is the most safe and effective for treatment of dysmenorrhoea. My personal preference is to select an NSAID that has been around for a long time, is currently available as a generic and therefore is relatively inexpensive, and has and many randomized double-blinded clinical trials with data on time to onset of relief with the first dose, in addition to overall efficacy. Such NSAIDs are ibuprofen, sodium naproxen, or ketoprofen. Thus far, trials have shown ibuprofen, naproxen, ketoprofen, mefenamic acid, and nimesulide to be significantly better than placebo or comparably as effective as ibuprofen or naproxen sodium. In our study, naproxen 400 mg provides greater pain relief than placebo and acetaminophen within 30 minutes and is maintained at 6 hours after administration. Ketoprofen (100 mg) was reported more effective at 45 minutes, continuing for up to 2 hours, than 500 mg naproxen, using visual analog scale scores to assess pain. In a multicenter, randomized, double-blind, crossover study, we found 12.5 and 25 mg ketoprofen and 200 mg ibuprofen were significantly better than placebo, with a similar sum of the pain intensity differences and total pain relief scores at 4 hours for the two NSAIDs. This does not mean that other NSAIDs, including the COX-II specific inhibitors, should not be considered. Never-
The conversion of arachidonic acid into cyclic endoperoxides involves catalytic conversion by the enzyme cyclooxygenase (COX). There are two forms of COX: I and II. Cyclooxygenase I is secreted basally whereas COX II is secreted in response to a variety of stimuli. Nonsteroidal anti-inflammatory drugs inhibit both COX I and COX II. Because COX II responds to stimuli, the COX II inhibitors are deemed more specific and, therefore, unlikely to induce gastrointestinal ulcers. More specific COX II inhibitors are now available, but concerns about their adverse effects have recently attracted attention. Rofecoxib,49 valdecoxib,50,51 and lumiracoxib52 are effective for treating primary dysmenorrhea. Thus far, COX II inhibitors are equally effective but not better than naproxen sodium.49,50,52 Given the above considerations, concerns about safety of COX II inhibitors, the short duration of therapy for relieving primary dysmenorrhea, and the low costs of OTC NSAIDs such as ibuprofen and naproxen, it is prudent to recommend established NSAIDs with track records of long-term safety as the preferred pharmacologic agent.

A Cochrane analysis found two trials on NSAID for endometriosis but analyzed only one involving 24 patients.53 There is no evidence that NSAIDs are effective for pain in endometriosis.53 Earlier smaller studies gave conflicting conclusions.54,55

**Oral Contraceptive**

A Cochrane analysis in 2001 concluded from four randomized controlled trials that combined oral contraceptive pills (OCPs) with medium-dose estrogen and first-/second-generation progestogens are more effective than placebo for relief of primary dysmenorrhea.56 We have shown that such OCPs (estrogen and progestin) reduce menstrual fluid volume and prostaglandins to within, or even below, normal range,4,12,13 with concomitant clinical relief during that cycle. The relief and the reduction in prostaglandins are confined only to that particular cycle, with no carry-over effect after stopping the OCP.4,12,13 Oral contraceptive pills may also lower the elevated plasma vasopressin levels found in dysmenorrheic women and lead to attenuation of the excessive uterine activity.57 Monophasic and triphasic OCPs are equally effective because there is no significant difference in the prevalence rate of dysmenorrhea between users of these preparations,58 but the observations are indirect. A recent randomized, double-blind, placebo-controlled trial of adolescents confirmed that low-dose (20 μg ethinyl estradiol) OCP is also clinically effective in relieving primary dysmenorrhea,59 albeit the Moos Menstrual Distress Questionnaire, which does not assess pain, was used. Analyses of extended-use OCP found that few studies reported on menstrual pain, but the regimen fared slightly better than cyclic use.60 There is insufficient information about long-acting gestational contraceptives and primary dysmenorrhea.

**Glyceryl Trinitrate**

Diminished levels of nitric oxide induce myometrial contractions while nitric oxide causes uterine relaxation. Thus glyceryl trinitrate as a source of nitric oxide can be expected to relax the exaggerated myometrial contractions in primary dysmenorrhea. A recent review concluded that nitroglycerin signifi-
cantly reduces the pain in primary dysmenorrhea. A pilot uncontrolled study found that satisfactory-to-excellent relief was obtained in 90% of patients with primary dysmenorrhea. In a multinational, double-blind, placebo-controlled, randomized crossover study, transdermal glyceryl trinitrate 0.1 mg/h was found to be significantly more effective during the first 6 hours of treatment and demonstrated greater overall efficacy than placebo. A comparison of transdermal glyceryl trinitrate with diclofenac sodium in an open, randomized, crossover trial found both treatments to be effective during the first 2 hours after medication but with slightly, but not significantly, reduced efficacy for glyceryl trinitrate. In all the studies, there is low tolerability for glyceryl trinitrate because of headache occurring in 20–26% of patients. The doses of glyceryl trinitrate patches used were from 0.1 to 0.2 mg/h.

**Magnesium**

A Cochrane data analysis in 2001 found three small trials comparing magnesium with placebo for relief of primary dysmenorrhea. Magnesium was more effective, but the dose and regime were widely variable. Magnesium has been given as magnesium pidolate. In one study, magnesium reduced menstrual fluid PGF₂α to 45% of its pretreatment levels, which provides a mechanistic rationale for this therapy. Currently, it is not clear what dose, preparation, and regime to use for magnesium in treating primary dysmenorrhea. Further studies are needed.

**Calcium Antagonists**

Nifedipine, a calcium channel blocker, inhibits myometrial contractility, thereby relieving primary dysmenorrhea. By blocking calcium entry into smooth muscle cell, intracellular free calcium is reduced, the muscle relaxes, contractions are reduced, vasodilatation is promoted, and ionic stimulation of prostanooids release is decreased. Adverse effects reported from the studies include transient facial flush, increased pulse rate, palpitations, and headache.

**Vitamin B**

One small trial found vitamin B6 was more effective at reducing menstrual pain than placebo or a combination of magnesium and vitamin B6. A combination of magnesium and vitamin B6 was no different from placebo. One large trial found that 100 mg vitamin B1 daily was more effective than placebo.

**Vitamin E**

Treatment of primary dysmenorrhea with vitamin E was reported in 1995, but evidence for its efficacy is limited. In a recent randomized, double-blind, placebo-controlled trial, 500 international units vitamin E and placebo were effective with more marked effects for vitamin E, suggesting a potentially large placebo effect. Recently, the same investigators found 100 mg vitamin E given for 5 days around menstruation significantly reduced the severity and duration of menstrual pain and blood loss than placebo. More definitive trials are needed.

Vitamin E relieves primary dysmenorrhea, probably through prostaglandin biosynthesis, but there is no data on menstrual fluid PGF₂α and uterine contractility. In vitro and in vivo studies in mice suggest that prostaglandin production is affected. Vitamin E increases the production of vasodilator prostacyclin and prostaglandin E₂ (PGΕ₂), as well as a dose-dependent upregulation of phospholipase A₂ and arachidonic acid release, but inhibits COX posttranslational activity. In macrophages, vitamin E abrogates peroxynitrite induction of COX and significantly suppresses arachidonic acid metabolism and prostaglandin production through inhibition of PLA₂ and COX. In short, vitamin E and its analogues suppress phospholipase A₂ and COX activities to inhibit prostaglandin production but promote vasodilator and uterine muscle relaxing prostanooids such as prostacyclin.

**Herbs**

Adolescents who drank rose tea (n=70) perceived less menstrual pain and distress at 1, 3, and 6 months, compared with controls (n=60). Other herbs, such as extracts of sweet fennel seeds (Foeniculum vulgare), are less potent than naproxen for relief of primary dysmenorrhea. A Cochrane analysis concluded that a small trial showed fish oil (mega-3 fatty acids) to be more effective than placebo. Krill oil significantly reduces the number of analgesics used for dysmenorrhea. Currently there is insufficient evidence to recommend the use of herbal and dietary therapies for dysmenorrhea.

**Nonpharmacologic Approaches**

**Transcutaneous Electrical Nerve Stimulation (TENS)**

A recent Cochrane review analyzed seven randomized controlled trials of transcutaneous electrical nerve stimulation (TENS) compared with placebo or no treatment. Overall, high-frequency TENS is more effective for pain relief in primary dysmenorr-
rhea than placebo TENS. Low-frequency TENS is no more effective than placebo TENS. Our own double-blind, randomized, placebo-controlled studies using high frequency TENS found it to be significantly better than placebo TENS. Thirty percent of severe dysmenorrheic cycles can be effectively relieved by TENS without need for pain medication. The amount of back-up NSAID required in the remaining 70% of cycles was significantly less than without TENS. Transcutaneous electrical nerve stimulation is a noninvasive and effective method for relief of primary dysmenorrhea and empowers the woman to control her treatment because she can regulate the intensity and duration of TENS applied.

Transcutaneous electrical nerve stimulation confers relief of pain through two potential mechanisms. By sending a volley of afferent impulses through the large diameter A sensory fibers of the same nerve root, TENS raises the threshold for pain signals by lowering the “gate,” thus blocking signal reception along the same root from the uterine hypoxia and hypercontractility. Thus, the uterine signals are less perceived or appreciated. Transcutaneous electrical nerve stimulation also stimulates release of endorphins from the peripheral nerves and the spinal cord, thus providing another avenue of partial pain attenuation. The opiate antagonist naloxone can neutralize this effect.

**Acupuncture and Acupressure**

Both acupuncture and acupressure have been tried for relief of primary dysmenorrhea. However, the limited trials and variable techniques and designs used render systematic analysis difficult. A Cochrane analysis and review found one small trial showing acupuncture to be significantly more effective for pain relief than placebo acupuncture and two no-treatment control groups. Given weekly for three menstrual cycles, acupuncture reduced analgesic medication by 41% compared with placebo acupuncture in women with primary dysmenorrhea. In a recent study, acupuncture was successful in primary dysmenorrhea (defined as no recurrence of symptoms for 2 years or more and no need for medication) in 93% of patients, compared with only 3.7% in the placebo group. In an uncontrolled international pilot study, acupuncture point injection with vitamin K alleviated primary dysmenorrhea with extension of relief into nontreatment follow-up cycles. Thus, there is some suggestive evidence that acupuncture may play a role in the nonpharmacologic relief of primary dysmenorrhea. However, well-designed, controlled, larger, and more definitive trials are needed.

The therapeutic efficacy of acupressure was considered similar to that of ibuprofen in relief of dysmenorrhea. Acupressure (both administered and self-applied) at Sanyinjiao significantly reduced menstrual pain. Acupressure is a relatively effective, cost-free method of self-care if the patient is not interested in taking medications.

**Other Nonmedication Self-Help Therapy**

Continuous, low-level, heat-wrap therapy applied to the suprapubic region is significantly superior to acetaminophen throughout the first 8 hours of application for relief of primary dysmenorrhea. This can be used by patients or as an adjunct to other better evidence-based therapies. A randomized, placebo-controlled study found significant relief of primary dysmenorrhea pain with magnet (2,500 gauss) compared with placebo magnet–treated cycles.

**Surgical or Manipulative Approaches**

**Nerve Ablation**

Observational studies support the use of uterosacral nerve ablation and presacral neurectomy for primary dysmenorrhea. Both surgical procedures interrupt the cervical sensory pain fibers in the pelvic area. A Cochrane meta-analysis of 8 of 11 trials (2 did not meet criteria) included five for laparoscopic uterosacral nerve ablation, two for laparoscopic presacral neurectomy, and two for open presacral neurectomy. There was some evidence for efficacy of laparoscopic uterosacral nerve ablation-resection over placebo or no treatment, and long-term presacral neurectomy was significantly better than laparoscopic uterosacral nerve ablation. However, there is insufficient evidence to recommend surgical nerve interruption for the management of primary dysmenorrhea. Adverse events were more common with presacral neurectomy. Because uterosacral nerve ablation essentially transects postganglionic sensory fibers, they are likely to regenerate with time and the pain returns. Sufficiently powered, future, randomized controlled trials are needed.

**Spinal Manipulation**

A Cochrane analysis and its follow-up found no evidence to suggest that spinal manipulation is effective for treatment of primary dysmenorrhea. Four trials of high-velocity, low-amplitude manipulation suggest that it was no more effective than sham manipulation for the treatment of dysmenorrhoea.
Three of the smaller trials favored high-velocity, low-amplitude manipulation, but one trial with an adequate sample size found no difference. The Toftness technique was shown to be more effective than sham treatment by one small trial.

**Management Algorithm**

A simplified algorithmic approach has been developed by me for the management of dysmenorrhea. I have used it for more than 20 years of practice, and it has seldom let me down. We employ the rule of two, which is easy to remember, with each step of the algorithm having only two choices to select from. When a patient presents with chronic pelvic pain, it is important to distinguish between pain associated with menstruation and pain that occurs at other times. If it is associated with menstruation, it is dysmenorrhea, which then has to be separated into primary dysmenorrhea and secondary dysmenorrhea. The typical history of primary dysmenorrhea and the normal pelvic examination findings would sort out primary from secondary dysmenorrhea. However, in some cases of endometriosis presenting during the teenage years and with no pelvic abnormalities, there can be a striking similarity with primary dysmenorrhea.

Once the diagnosis of primary dysmenorrhea is arrived at, the most effective treatment of choice remains between an NSAID and the combined estrogen-progestin oral contraceptive (Fig. 4). If the patient wants to use oral contraceptive as a method of birth control, a combined oral contraceptive is prescribed for her birth control needs, and she can be expected to obtain relief of her primary dysmenorrhea (vide supra—oral contraceptive). The choice of 3 months can be construed as arbitrary, but sufficient time must be given to test efficacy of the medication because

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**Fig. 4.** Pathway for the selection of prostaglandin synthetase inhibitor compared with oral contraceptive in the management of primary dysmenorrhea.


**Fig. 5.** Algorithm for managing primary dysmenorrhea with oral contraceptive.

intensity of primary dysmenorrhea can fluctuate from cycle to cycle. On the other hand, waiting for even more cycles of trying with the medication is unnecessary and subjects the women to a trial of endurance. If dysmenorrhea is not adequately relieved by oral contraceptives after three cycles, consider adding an appropriate NSAID during the menstrual phase (Fig. 5). Thereafter, the management is similar to that of the patient initially given an NSAID. With birth control pills, 80–90% or more of women can be satisfactorily relieved of primary dysmenorrhea if the diagnosis is correct.

If contraception is not desired or if the patient prefers other nonoral contraception, the medication of choice for relief of her primary dysmenorrhea is a NSAID. Patients with gastroduodenal ulcer or who are allergic to NSAIDs should be recommended to use an oral contraceptive and not given NSAID (Fig. 6). To obtain maximum and continuous relief from painful menstrual cramping and to avoid exposing a potential very early pregnancy, NSAIDs should be taken with the onset of menstruation and continually for the first 2–3 days of menstrual flow so as to inhibit prostaglandin production, rather than on an as-needed basis. Table 1 summarizes the types of NSAIDs, their doses, and clinical efficacy in the relief of primary dysmenorrhea. Nonsteroidal anti-inflammatory drugs given at the time of menstruation do not appear to affect the development of the endometrium but inhibit COX activity and reduce prostaglandin

Table 1. Clinical Efficacy of Prostaglandin Synthetase Inhibitors and Doses Used for Treatment of Primary Dysmenorrhea

<table>
<thead>
<tr>
<th>Prostaglandin Synthetase Inhibitor Group</th>
<th>Medication</th>
<th>Dose (Times per Day)</th>
<th>Clinical Relief (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indole acetic acid derivatives</td>
<td>Indomethacin</td>
<td>25 mg (3–6)</td>
<td>73–90</td>
</tr>
<tr>
<td></td>
<td>Flufenamic acid</td>
<td>100–200 mg (3)</td>
<td>77–82</td>
</tr>
<tr>
<td></td>
<td>Mefenamic acid</td>
<td>250–500 mg (4)</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>Toltenamic acid</td>
<td>133 mg (3)</td>
<td>88</td>
</tr>
<tr>
<td>Fenamates</td>
<td>Ibuprofen</td>
<td>400 mg (4)</td>
<td>66–100</td>
</tr>
<tr>
<td></td>
<td>Naproxen sodium</td>
<td>275 mg (4)</td>
<td>79–90</td>
</tr>
<tr>
<td></td>
<td>Ketoprofen</td>
<td>50 mg (3)</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>12.5–2.5 mg (4)</td>
<td></td>
<td>87–88</td>
</tr>
<tr>
<td>Arylpropionic acid derivatives</td>
<td>Suprofen</td>
<td>200 mg (4)</td>
<td>60–80</td>
</tr>
<tr>
<td></td>
<td>Piroxicam</td>
<td>10–20 mg (1–2)</td>
<td>70–80</td>
</tr>
<tr>
<td></td>
<td>Nimesulide</td>
<td>50–100 mg (1–2)</td>
<td>78–83</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Rofecoxib</td>
<td>25 mg (2)</td>
<td>Not available</td>
</tr>
<tr>
<td></td>
<td>Valdecoxib</td>
<td>20–40 mg (2)</td>
<td>Not available</td>
</tr>
<tr>
<td></td>
<td>Lumiracoxib</td>
<td>400 mg (1)</td>
<td>Not available</td>
</tr>
</tbody>
</table>

* Percentage of women obtaining relief.
† Also available as over-the-counter medication in United States.
‡ Withdrawn from the market.
§ Effective compared with naproxen.
production and release. Thus, the menstrual fluid volume remains relatively unchanged, but the menstrual fluid prostaglandins are markedly reduced to the level obtained in a normal pain-free menstrual cycle or even below normal levels.4,11,14,16,18,20

If relief is inadequate, combination oral contraception can be tried for up to another three cycles. Because NSAIDs provide relief in as many as 80–85% of dysmenorrheic patients if judiciously used, laparoscopy becomes necessary only in a small group of women who have a history suggesting primary dysmenorrhea (Fig. 6). Patients with endometriosis are not relieved by NSAIDs (vide supra–COX II inhibitor).53 There is no published evidence to support relief of endometriosis with monthly cyclic use of oral contraceptive. If pelvic disease causing the dysmenorrhea is found at laparoscopy, appropriate therapy is directed to the underlying pathology so that relief of the secondary dysmenorrhea may be attained. If no pelvic pathology is found, multimodal therapy, using some of the partially evidence-supported or less well-established therapies discussed above, may be tried.

Cervical dilation and hysteroscopy are recommended at the time of laparoscopy to ensure completeness of excluding secondary dysmenorrhea and for any temporary relief that dilation may confer on some patients by widening the cervical canal and promoting menstrual flow and thereby reducing menstrual fluid prostaglandin contact with the myometrium. Additionally, cervical dilation may induce paracervical neuriapraxia or partial disruption of the paracervical innervations. However, there is no published evidence about the efficacy of cervical dilation, even for the short term.

REFERENCES


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