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Volume XV, Issue 8 November 2007

Dysmenorrhea: Contemporary Perspectives

Painful menses or dysmenorrhea affects 40–90% of women. Despite its high prevalence, understanding of its pathophysiology and its relation to other pain syndromes in women is still limited. Dysmenorrhea has been historically categorized into two distinct types: primary and secondary. Primary dysmenorrhea is menstrual pain without pelvic pathology, with onset typically just after menarche. Pain in primary dysmenorrhea occurs during menses and lasts 2–3 days. Secondary dysmenorrhea describes menstrual pain when underlying pathology is identified (such as uterine or ovarian lesions); its onset may be years after menarche. Pain may start 1–2 weeks before menses and persist beyond, lasting several days. On the other hand, population-based studies in Italy have not found an association between the presence of leiomyoma (benign tumors) and higher rates of dysmenorrhea.[1] Although the distinction between primary and secondary dysmenorrhea may be useful in terms of treatment approach, there seems little difference in pain experience or sensitivity between the two groups.

Dysmenorrhea often presents in conjunction with related somatic complaints and with mood or behavioral changes. Premenstrual syndrome (PMS) has been used to refer to somatic complaints, and premenstrual dysphoric disorder (PMDD) is used to characterize emotional disturbance prior to menses that hinders social function; both sets of symptoms overlap in typical sufferers.[2] Notably, antidepressants are effective in treating many of the associated mood symptoms.[3]

For many women, the symptoms of dysmenorrhea have a significant impact on quality of life for at least a portion of each month. A Swedish study analyzing absenteeism due to dysmenorrhea in young women found that one-third to one-half missed school or work at least once, and 5–14% were absent more frequently.[4] A community-based survey of women in the United Kingdom found dysmenorrhea to be closely related to chronic daily pain, with 80% of women with chronic pelvic pain reporting dysmenorrhea.[5]

Epidemiology

Dysmenorrhea is often classified as mild, moderate, or severe based on relative pain intensity, impact on working ability, and requirements for analgesics. Primary dysmenorrhea is most common in the early 20s, with 80% of Caucasian women reporting some degree of menstrual pain; the prevalence decreases steadily after age 20.[6] Variation across cultures clearly exists—for example, the majority of women in Western cultures report pain during menses, compared to only a quarter of rural Mayan women.[7] This discrepancy may reflect cultural influences in the way menstruation is perceived and the subsequent reporting of dysmenorrhea. For instance, Islamic law may forbid menstruating women from praying, fasting during Ramadan, or having sex. Similarly, Hindu followers may also consider a menstruating woman's touch to be impure. These taboos may lead to the underreporting of pain, underestimation of the prevalence of dysmenorrhea among certain populations, and ultimately failure to treat appropriately.[8]

Supported by an educational grant from **Endo Pharmaceuticals, Inc., USA**

The interface between cultural and ethnic influences on dysmenorrhea symptoms is not clear-cut. Older data collected in the U.S. National Health Examination Survey III during 1966–1970 found that African-American and Caucasian adolescents (aged 12–17) had similar rates of dysmenorrhea nationwide, but the former had nearly double the rate of absenteeism attributable to menstrual cramping, even after adjusting for socioeconomic status.[9] Even more strikingly, one study of Hispanic teenaged girls attending a Texas high school in the late 1990s found a rate of severe dysmenorrhea three times higher (42%) than that previously reported for African Americans and Caucasians (14%), with nearly 20% missing school days due to dysmenorrhea.[10] These two studies may define absenteeism rates differently and are separated by a wide temporal gap, which is critical because nonsteroidal inflammatory drugs (NSAIDs) were not used in the late 1960s to manage dysmenorrhea. Further demonstrating the complex influence of ethnicity on dysmenorrhea, Goldstein-Ferber and Granot characterized dysmenorrhea among three cultural subgroups of Israeli Arab adolescents (Muslim, Christian and Druze). While the actual prevalence and pain intensity of dysmenorrhea did not differ across these groups, somatization tendencies and self-efficacy, which are mediators of pain experience, did show differences.[11] These studies suggest that the expression of pain as dysmenorrhea may need to be explored with attention to both ethnicity and cognitive factors.

Associated Risk Factors

A systematic review of risk factors for dysmenorrhea conducted by Latthe et al. identified several candidates: younger age, low body mass index, smoking, early menarche, prolonged or aberrant menstrual flow, related perimenstrual somatic complaints, pelvic infections, previous sterilization, somatization, psychological disturbance, and a history of sexual assault. Higher parity, a stable relationship, physical exercise, fish intake, and use of oral contraceptives were protective.[12]

Psychosocial factors have not been studied extensively in relation to dysmenorrhea, in contrast to other chronic pain syndromes, but many of the same factors seen with general pain problems such as high somatization, emotional disturbance, and psychological symptoms were found in small studies to be associated with higher rates of dysmenorrhea. In a population-based study of menstrual health encompassing over 2,000 Indian women in Goa (published after Latthe's systematic review), dysmenorrhea intensity increased with severity of depression, anxiety, and somatic complaints. The authors proposed that dysmenorrhea should be considered as part of the spectrum of medically unexplained syndromes and viewed as a multifactorial disorder.[13] Indeed, primary dysmenorrhea has numerous associated somatic comorbidities such as nausea and vomiting, diarrhea, tiredness, and feelings of irritability. In addition, many idiopathic pain disorders such as irritable bowel syndrome, painful bladder syndrome, and fibromyalgia frequently coexist with primary dysmenorrhea.[14-16]

Presentation

The pain of dysmenorrhea is often described as a crampy or colicky pain in the suprapubic region that may radiate to the lumbosacral region or the anterior thigh. In primary dysmenorrhea, pain starts with the onset of menstrual flow with a typical duration of 2–3 days. In secondary dysmenorrhea, pain may start weeks before menstrual flow and persist beyond the cessation of bleeding.

Pelvic examination generally reveals prominent uterine tenderness during menstruation, although in patients with secondary dysmenorrhea, the uterus may be painful outside of menses. Physical examination findings in dysmenorrhea differ distinctively from pelvic inflammatory disease; palpation of the cervix or adnexal structures are not typically excessively painful in dysmenorrhea patients. With endometriosis, adnexal masses or rectovaginal nodules may be present when there is extensive inflammation, and ectopic tissue growth has occurred inside the peritoneal cavity.

Pathophysiology

Aberrations in the local inflammatory environment of the menstruating uterus have been viewed as the primary mechanism for dysmenorrhea, but sensitization in the central nervous system, such as that described in the case of fibromyalgia and migraine headache, may also play a role. The relative contribution of peripheral and central dysfunction in accounting for the menstrual pain experience is unknown.

Primary Dysmenorrhea

Primary dysmenorrhea occurs with the establishment of ovulatory cycles. Recent research suggests that declining uterine progesterone levels in the late luteal phase during endometrial sloughing removes inhibition of production of arachidonic acid, which is subsequently metabolized by the cyclooxygenase (COX)-2 pathway into eicosanoids (including leukotrienes and prostanoids).[17,18] Studies of eicosanoids suggest that elevated levels of these biologically active lipids are a key cause of dysmenorrhea, mediating hyperalgesia and inflammatory pain while lowering the pain threshold during menstruation; levels decrease in response to treatment with NSAIDs.[17,19,20] Clinically recognized for their use in labor settings and abortion, prostaglandins E_2 (PGE_2) and PGF_2 mediate vasoconstriction, ischemia, and uterine hypoxia, leading to hyperactive myometrial contractions accompanied by diarrhea, nausea, and vomiting.[19,20]

Elevated levels of eicosanoids may be a key cause of dysmenorrhea

Vasopressin is another potential factor in the pathogenesis of dysmenorrhea. In vitro and in vivo infusion of vasopressin stimulates uterine muscle activity, yet evidence is conflicting as to whether circulating vasopressin levels are elevated in women with primary dysmenorrhea.[21,22] Similarly, only one of two different experimental vasopressin receptor antagonists has shown potential efficacy for menstrual-related pain.[22,23]

A small experimental study assessing pain perception in Jewish college students found that those with dysmenorrhea had enhanced perception (visual analogue pain intensity scores) and response (evoked potential latencies) when heat stimuli were applied to the hand.[24] Similarly, Brinkert and colleagues described enhanced pain perception in dysmenorrheic subjects for both detection and tolerance of experimental colonic distension (a model used to assess visceral pain sensitivity in irritable bowel syndrome).[25] Further studies are needed to fully elucidate the role of central neurological adaptations in dysmenorrhea.

Secondary Dysmenorrhea

When dysmenorrhea presents later in life, it is often associated with specific pelvic abnormalities, including chronic pelvic pain, dyspareunia, metrorrhagia, pelvic inflammatory disease, adenomyosis, leiomyomas, malformation of mullerian ducts, ovarian cysts, intrauterine polyps or adhesions, contraceptive intrauterine devices (IUDs), and most commonly endometriosis. There may also be neural or hormonal causes for secondary dysmenorrheic pain, including a possible positive feedback loop in endometriosis between aberrant estrogen and PGE_2.[26] Other studies on prostaglandin production induced by an IUD have been inconclusive, and there is conflicting evidence regarding elevations in COX-2 expression in endometrial lesions.[27-29]

Treatment

Nonsteroidal Anti-inflammatory Drugs

In the 1980s, NSAIDs came into popularity as the most common treatment for dysmenorrhea, providing relief of pain by blocking COX pathways and reducing levels of peripheral prostaglandins, particularly PGE_2. They also potentially influence pain transduction in the spinal cord.[30] Large randomized, controlled trials have found that NSAIDs such as naproxen, ibuprofen, and mefenamic acid provide fast relief of dysmenorrhea when compared to placebo, even at over-the-counter doses. Generally, 80–85% of women will experience relief of symptoms following therapy.[19] Few studies have attempted to demonstrate the superiority of one particular NSAID.[31]

Combined oral contraceptives and NSAIDs are considered first-line therapy

NSAIDs ideally should be administered 24–48 hours prior to the expected onset of menses in order to inhibit prostaglandin production, and then continued through the usual 3 to 5 days of menses. Common side effects of NSAIDs used intermittently include nausea, vomiting, and diarrhea, and may include effects on the nervous system such as headache, drowsiness, dizziness, and dryness of the mouth. Caution should be exercised in using these medications in patients with existing cardiovascular or renal issues or with difficulty handling intravascular volume, as they may worsen or lead to the onset of hypertension. Cardiovascular risks are uncommon for the typical young woman using these medications for dysmenorrhea, but older patients and those with existing cardiovascular conditions or elevated risk of thrombosis appear to face higher risks of myocardial infarction and stroke. Prolonged administration of NSAIDs (i.e., outside the menstrual phase) should be limited to avoid the well-recognized risks of gastric ulceration following loss of COX-1-mediated cytoprotection, which may occur in 15–30% of regular users.[32]

Hormonal Treatments

Induction of anovulation using hormonal treatments is commonly used to treat dysmenorrhea. Combined oral contraceptive pills (COCs) comprising estrogen and progestin attenuate hyperactive myometrial activity by inhibiting ovulation, reducing menstrual fluid volume, lowering endometrial COX-2 levels throughout menstruation, and keeping prostaglandin production in check.[33] Despite widespread use of COCs, few randomized controlled trials have been conducted to demonstrate their efficacy versus placebo.[34] Use of this strategy for treating dysmenorrhea is based on the demonstrated clinical efficacy of COCs when used as contraceptives. Combined oral contraceptives and NSAIDs are considered first-line therapy for women with primary or secondary dysmenorrhea. Possible adverse effects associated with COC use include nausea, vomiting, headaches, breast tenderness, and the rare risks (4/10,000) of venous thrombosis leading to pulmonary embolism or myocardial infarction associated with estrogen use.[35]

For women preferring not to take a daily pill, the levonorgestrel-releasing intrauterine system (LNG-IUS) is an alternative hormonal treatment that releases a progestin derivative (20 µg/day) directly on the endometrium. Prevention of endometrial growth leads to reduced menstrual flow or amenorrhea. Small studies have shown that this IUS subsequently reduces menstrual pain and treats secondary dysmenorrhea due to endometriosis.[36,37] The LNG-IUS has the added benefits of preventing pregnancy, the convenience of being durable for up to 5 years, ease of insertion and removal, while only posing rare side effects that include uterine infection or uterine perforation during insertion. Oral progestins (medroxyprogesterone acetate, norethindrone) may also be used to induce anovulation; however, the use of oral progestins to treat dysmenorrhea is not well studied. The injectable contraceptive depot medroxyprogesterone acetate (DMPA) given every 3 months can also induce anovulation for 7–9 months after intramuscular injection and can significantly relieve dysmenorrhea symptoms. When using a progestin-only conceptive such as DMPA, caution must be given to prevent estrogen deficiencies and loss of bone mineral density.

Surgery

Surgical approaches including pelvic nerve transection and extirpative surgery for endometriosis or leiomyomas may be considered after failure of medical management. The published literature is limited, however, and a Cochrane meta-analysis of controlled trials assessing nerve transection surgery finds that evidence is insufficient to conclusively demonstrate significant pain relief from these procedures (Proctor et al. 2005). Two neurolytic procedures have been used to block afferent input from cervical sensory neurons, including presacral neurectomy (PSN), which transects the presacral nerves lying within the boundaries of the interiliac triangle, and uterosacral nerve ablation, which transects the pelvic splanchnic nerves within the uterosacral ligaments at their cervical insertion.[38] Zullo et al. found PSN to be superior to laparoscopic endometriosis excision at 2-year follow-up (83.3% vs. 53.3%).[39] Johnson and colleagues similarly found uterosacral nerve ablation superior to diagnostic laparoscopy in providing dysmenorrhea relief at 1-year follow-up.[40] Uterosacral nerve ablation carries a risk of ureteral injury if not performed properly, and PSN is associated with visceral side effects, including constipation, urinary urgency, and major vessel injury.[41]

Alternative Therapies

Many patients turn to complementary medicine as a "natural" solution to dysmenorrhea. The published experience with vitamin and mineral supplements suggests some benefit for both magnesium and vitamin B1 through possible interference with prostaglandin production, although a Cochrane review suggests that more research is needed to confirm their efficacy.[42] These supplements pose minimal risk at recommended doses. A small study also suggests that omega-3 fatty acids

from fish oil decrease menstrual pain intensity, although the side effects may include nausea and acne exacerbation.[43]

Both transcutaneous electrical nerve stimulation (TENS) and acupuncture are noninvasive forms of local nerve stimulation used to relieve dysmenorrheic pain. The mechanism of action for TENS is thought to be through elevation of the pain threshold and stimulation of endorphin release. TENS does not appear to affect uterine contractile pressures; rather, it seems to act by increasing uterine blood flow and reducing myometrial ischemia.[44] Acupuncture has been used for thousands of years in Eastern civilizations; by exciting nerve fibers, it appears to work in concert with serotonin and endorphin mediators to inhibit pain sensitivity. Several clinical trials demonstrate efficacy for high-frequency TENS versus sham TENS for treating dysmenorrhea. However, a Cochrane review of randomized controlled trials of stimulation techniques overall only identified one small, albeit well-designed, trial suggesting that acupuncture may be effective.[45-48]

With increased attention to dysregulation of the peripheral inflammatory pathways in dysmenorrhea, few recent studies have been published on the efficacy of behavioral interventions. With increased recognition of central alterations in pain perception among dysmenorrhea sufferers, these options are also important to consider. Therapeutic strategies in this category include relaxation, biofeedback, and pain management counseling, identical to strategies used for chronic pain syndromes. A recent Cochrane review found only older studies with significant methodological weaknesses and limited efficacy, but the authors strongly urged that updated studies be conducted.[49]

Conclusion

Dysmenorrhea appears to be a significantly underutilized model for understanding visceral pain pathophysiology. Is it possible that because it is a near universal symptom in Western women, its significance in the etiology of idiopathic pain conditions has been largely overlooked? A clear need exists to unify research which has separately focused on observed exaggeration in peripheral inflammation and aberrant central processing of pain. Although most women will achieve effective pain relief through safe pharmaceutical options, treatment-resistant women may represent a high-risk cohort for developing other pain syndromes. Behavioral and complementary treatments clearly need further study, as indicated by recent Cochrane reviews, particularly as surgical treatments for dysmenorrhea pose serious, though rare risks. A validated, unified classification system and disease-specific outcomes instrument would be valuable in accelerating the pace of research in this field.

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