EXPERT OPINION

From Diagnosis to Optimal Prescription:
A Modern Pathway for Managing Primary Dysmenorrhea

Reviewed by:

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Overview of Primary Dysmenorrhea

Primary dysmenorrhea (PD) is defined as painful, cramping pain in the lower abdomen during menstruation without any identifiable pelvic pathology. The pain usually begins before or at the onset of menses and follows a cyclic pattern, being most severe on the first day and lasting up to 72 hours.[1,2] PD is characterized by recurrent, spasmodic lower abdominal pain that may radiate to the back and thighs and is often accompanied by symptoms such as nausea, vomiting, diarrhea, weakness, lightheadedness, and headache.[3] The condition is primarily caused by excessive production of prostaglandins during menstruation. A decline in progesterone before menses leads to endometrial shedding and increased prostaglandin synthesis, resulting in uterine vasoconstriction and painful contractions. These prostaglandin-induced effects explain the gastrointestinal symptoms such as nausea and diarrhea often experienced during dysmenorrhea.[4]

PD commonly affects young women and typically begins within 6 to 24 months after menarche, once ovulatory cycles are established.[2] The worldwide prevalence of dysmenorrhea ranges from 45% to 95% among women of reproductive age, with 2% to 29% reporting severe pain.[1,3] Despite its high prevalence, PD remains underdiagnosed and inadequately treated, often due to social taboos and the perception that menstrual pain is normal.[2] It is the most common gynecological problem among women of all races and ages and remains poorly understood and overlooked in women's health monitoring.[5]

Burden and Impact on Quality of Life

PD significantly impacts the physical, emotional, and social well-being of women. It is a major cause of absenteeism from school and work, accounting for an estimated 600 million lost hours and approximately $2 billion in annual economic losses in the United States. Studies report school absenteeism rates between 14% and 51% among females with PD, with class attendance decreasing by 29% to 50% during menstruation. Research from Palestine found that over half of university students with dysmenorrhea missed classes due to painful menses, while studies in Hong Kong and Turkey reported significantly lower quality of life (QOL) scores among affected women.[6] Dysmenorrhea leads to absenteeism (20.1%), reduced concentration and academic performance (40.6%), and decreased participation in school activities (29.6%). Women with dysmenorrhea incur higher healthcare costs compared to the general female population, with increased prevalence of depression, anxiety, and stress-related disorders. Primary dysmenorrhea, in particular, raises the likelihood of major depressive disorder by more than 70%.[2]

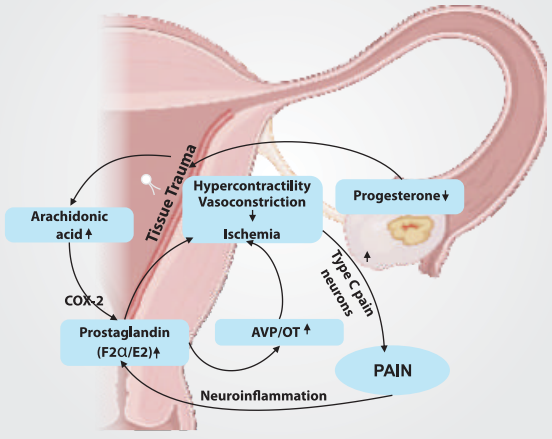
Pathophysiology

The exact pathophysiology of dysmenorrhea is not completely understood; however, prostaglandins play a central role in its development. During menstruation, endometrial sloughing triggers the release of prostaglandins, primarily prostaglandin F2α (PGF2α) and prostaglandin E2 (PGE2), which stimulate myometrial contractions and vasoconstriction. This leads to uterine ischemia, accumulation of anaerobic metabolites, and hypersensitization of nociceptive fibers, resulting in pelvic pain.[1,6]

Prostaglandins are synthesized through the arachidonic acid cascade mediated by the cyclooxygenase (COX) pathway. Arachidonic acid synthesis is regulated by

progesterone via the lysosomal enzyme phospholipase A2. During the luteal phase, progesterone levels peak, but if conception does not occur, the corpus luteum degenerates, leading to a rapid decline in progesterone. This decline causes endometrial breakdown and the release of lysosomal enzymes, generating arachidonic acid and subsequently prostaglandins (Fig. 1).[6]

Figure 1: Pathophysiology of PD[7]



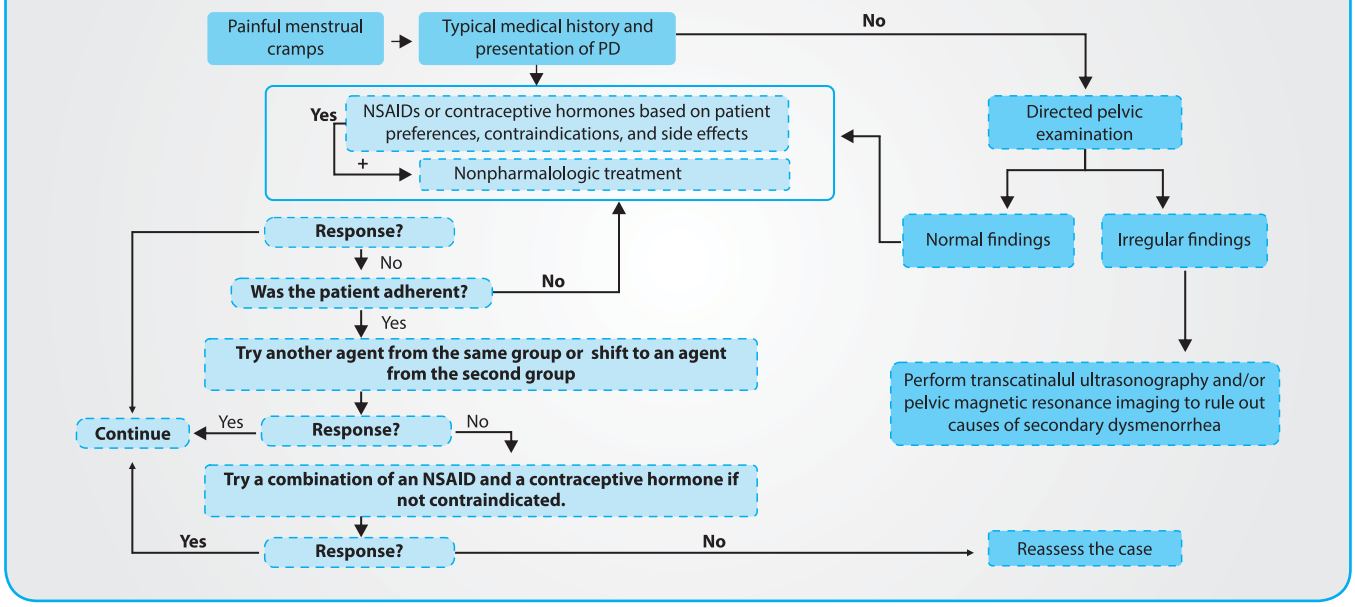
Women with dysmenorrhea have been shown to exhibit higher concentrations of PGE2 and PGF2α in menstrual fluid compared to those without the condition. Additionally, uterine artery Doppler studies demonstrate elevated resistance blood flow during menses in women with dysmenorrhea, likely reflecting increased vascular constriction associated with prostaglandin activity.[1]

Diagnosis

The diagnosis of primary dysmenorrhea (PD) is primarily based on a detailed medical history and physical examination to rule out pelvic pathology. The evaluation includes assessing menstrual, gynecological, and sexual history, such as age at menarche, menstrual regularity and duration, abnormal discharge, pain characteristics, and associated systemic symptoms. Inquiry about sexual activity and sexually transmitted infections is also essential (Fig. 2).

In cases with typical PD symptoms, diagnosis can be made from medical history alone, and empiric treatment with NSAIDs or oral contraceptives may be initiated. A pelvic examination is recommended for sexually active women or those with suspected pelvic inflammatory disease, sexually transmitted infections, or severe symptoms.[6]

Figure 2: Algorithm of the diagnosis and treatment of PD[6]



Treatment

The primary goal of treating PD is to relieve pain, improve quality of life, and reduce absenteeism from work or school. Both pharmacological and non-pharmacological therapies are effective options. The first-line treatments include nonsteroidal anti-inflammatory drugs (NSAIDs) and hormonal contraceptives, as both reduce prostaglandin production, which is directly linked to menstrual pain.[6]

Pharmacological Treatment

NSAIDs

NSAIDs are cost-effective analgesics and anti-inflammatory agents regarded as the cornerstone of PD management. They act by inhibiting the cyclooxygenase (COX) enzyme, thereby reducing prostaglandin synthesis. NSAIDs are recommended as first-line therapy for patients preferring analgesics or when hormonal contraceptives are contraindicated.[4,6]

Hormonal Contraceptives

Hormonal contraceptives are also first-line therapy, particularly for women requiring contraception or those intolerant or unresponsive to NSAIDs. They suppress ovulation and endometrial proliferation, thereby reducing prostaglandin production. Effective options include combined oral contraceptives, contraceptive patches, vaginal rings, levonorgestrel intrauterine systems, and depot medroxyprogesterone acetate.[6]

Acetaminophen (Paracetamol)

Acetaminophen is suitable for patients unable to tolerate NSAIDs or who do not wish to use hormonal contraceptives. It has a mild COX inhibitory effect, reduces prostaglandin production, and is considered safe with minimal gastrointestinal side effects.[6]

Role of Drotaverine in the Management of Dysmenorrhea

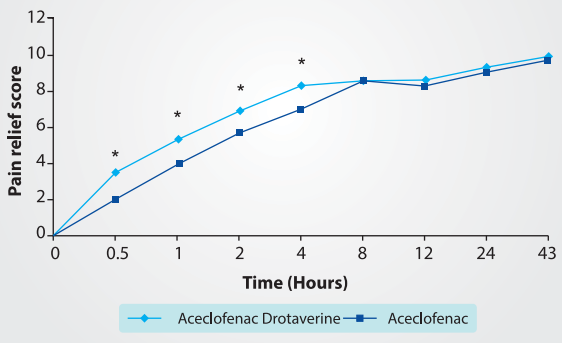
Drotaverine, an isoquinoline derivative, is a potent and effective oral antispasmodic widely used for relieving smooth muscle spasms in various conditions, including dysmenorrhea. It acts directly on smooth muscles by selectively inhibiting phosphodiesterase isoenzyme IV and exerting a mild calcium channel–blocking effect without anticholinergic action. The absence of anticholinergic side effects makes it suitable for sensitive patient groups. Moreover, drotaverine does not mask symptoms of acute abdomen, ensuring accurate diagnosis, and lacks opioid-like effects, thus avoiding the risk of addiction. Clinically validated for over 35 years, drotaverine is commonly combined with analgesics in practice to enhance its spasmolytic and pain-relieving efficacy.[8]

Combination Therapy of Drotaverine and Aceclofenac

Aceclofenac, a proven analgesic and anti-inflammatory agent, has demonstrated efficacy across multiple conditions, while drotaverine, a smooth muscle relaxant, alleviates uterine contractions and enhances uterine blood flow, thereby reducing hypoxia. Together, the combination of aceclofenac and drotaverine offers a synergistic effect, making it an effective option for relieving pain associated with dysmenorrhea.

A double-blind, double-dummy, randomized, multicentric study involving 200 women aged 18–35 years with primary dysmenorrhea evaluated the efficacy and safety of a fixed-dose combination of aceclofenac (100 mg) and drotaverine (80 mg) administered twice daily compared to aceclofenac (100 mg) alone for up to 3 days. The combination therapy demonstrated significantly superior pain relief, as reflected by higher TOPAR/4 (24.0 *vs* 18.54; $p = 0.000$) and TOPAR/8 (40.3 *vs* 35.2; $p = 0.003$) scores (Fig. 3), greater SPID/4 (17.9 *vs* 13.88; $p = 0.000$) and SPID/8 (31.06 *vs* 26.8; $p = 0.001$), and higher peak PID/4 (6.60 *vs* 5.75; $p = 0.001$) and peak PR/4 (8.26 *vs* 7.10; $p = 0.000$) compared to aceclofenac alone. Although peak PID/8 and peak PR/8 were comparable between groups ($p > 0.05$), patients receiving the combination required fewer doses (150 *vs* 168) and reported better global efficacy evaluations by both patients ($p = 0.002$) and investigators ($p = 0.001$). Both regimens were well tolerated. These findings confirm that the aceclofenac–drotaverine combination provides faster, more effective, and well-tolerated relief from primary dysmenorrhea compared to aceclofenac monotherapy.[9]

Figure 3: Pain-relief scores at each time points for both study treatments. (♦) Aceclofenac–drotaverine; (■) aceclofenac; (*) p < 0.059



Comparative Study: Drotaverine *vs.* Ibuprofen

The efficacy and tolerability of drotaverine 80 mg versus ibuprofen 400 mg in primary dysmenorrhea (DOROTA study) was evaluated. Pain intensity differences over six hours (SPID-6) showed comparable baseline scores, but greater pain reduction occurred with ibuprofen, achieving complete relief at 3 hours compared to 4 hours with drotaverine. Drug efficacy was rated as excellent or good by 41.8% of drotaverine-treated and 68.6% of ibuprofen-treated patients. Tolerability was also significantly higher with ibuprofen (86.8%) than drotaverine (78.4%) ($p = 0.02$).10

Non-pharmacological Treatment

Maintaining an active lifestyle and a balanced diet rich in vitamins and minerals is generally advised for better health and may help relieve dysmenorrhea symptoms. Regular moderate exercise, particularly in obese women, can reduce menstrual pain, although evidence is insufficient to define specific types or durations of activity. Heat therapy is also a simple, well-tolerated option that effectively alleviates pain without the side effects associated with NSAIDs.[4]

Table 1: Non-pharmacologic Treatment for PD[1]

Consistent Evidence Supporting Use	
Physical Exercise	Releases anti-inflammatory cytokines and cortisol levels, decreasing prostaglandin release.
Heat Therapy	Relaxation of abdominal muscles and increasing pelvic blood circulation
Mixed Data	
Acupuncture	Unclear mechanism, possibly through the interaction with peripheral nervous system
Neuromodulation (High-frequency TENS and Sacral neuromodulation)	Activating large-diameter afferent nerve fibers interact with inhibitory neurons in the central nervous system
Supplements	Hypothesized mechanism of action differs per supplementation used
Cannabinoids	Activation of the cannabinoid receptor leads to sedative and analgesia effects

Conclusion

PD is a prevalent condition primarily driven by excessive prostaglandin production leading to uterine contractions and pain. Effective management focuses on symptom relief and improving quality of life through pharmacological and non-pharmacological interventions. Drotaverine, a selective phosphodiesterase IV inhibitor, offers significant spasmolytic and analgesic benefits without anticholinergic or opioid-related effects. The drotaverine–aceclofenac combination provides superior, faster, and well-tolerated pain relief compared to aceclofenac alone. Overall, drotaverine remains a safe and effective therapeutic option in the optimal management of PD

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