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REVIEW ARTICLE

Dysmenorrhea and recent treatment options in adolescents and young adults

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ABSTRACT

Dysmenorrhea, or primary dysmenorrhea (PD), marked by menstrual cramps in the lower abdomen, is a common but often overlooked condition affecting a considerable number of women. The impact of dysmenorrhea extends beyond physical pain, often causing considerable disruption to daily activities, work, and social interactions. It significantly affects the quality of life, often causing absenteeism from school or work. Increased intrauterine prostaglandin secretion is linked to pelvic pain in PD. Diagnosis relies mainly on clinical assessment, considering symptoms and physical examination, with treatment aimed to enhance the quality of life. These menstrual cramps are frequently accompanied by other symptoms, such as headaches and nausea, which are believed to be due to prostaglandins released as the endometrium breaks down. A literature search using the keywords dysmenorrhea, menstrual pain, and hormonal contraceptives was done using the following databases: Google Scholar, ProQuest, ScienceDirect, Web of Science, Pubmed, and Scopus for articles published from 2015 to 2024. The literature study was done to find the connection of dysmenorrhea and menstrual pain with hormonal contraceptives. Common treatments include nonsteroidal anti-inflammatory drugs, hormonal contraceptives, and non-pharmacological interventions. This review provides an in-depth analysis of recent treatment advancements for dysmenorrhea, focusing on its pathophysiology, clinical diagnosis, and impact on women's quality of life. It evaluates current and emerging treatments, including pharmacological interventions, non-pharmacological therapies, surgical approaches, hormonal treatments, and investigational drugs, aiming to identify improvements in efficacy and side effects.

Keywords: Dysmenorrhea, primary dysmenorrhea, menstrual pain, treatment options, pathophysiology, hormonal contraceptives

INTRODUCTION

Dysmenorrhea, or menstrual pain, is a widespread issue affecting women worldwide.[1] However, its exact causes are not fully understood, complicating the treatment process, especially for those who do not find relief from standard medications such as non-steroidal anti-inflammatory drugs (NSAIDs).[2] This emphasizes the importance of further research into the underlying mechanisms of menstrual pain to enhance treatment options. Menstrual pain often occurs in a predictable cycle, with the most intense discomfort typically happening on the first day of menstruation and lasting as long as three days.[3] Despite being widespread and significantly affecting everyday life, it is frequently under-treated or dismissed. A considerable number of young women endure the pain quietly, choosing not to seek medical help.[4] This reluctance is largely driven by societal attitudes that view menstrual pain as something to be ashamed of, reinforcing the idea that it is a regular part of menstruation to be tolerated without complaint.[5] Dysmenorrhea has a substantial impact on quality of life and can result in missing school or work.[6] Primary dysmenorrhea (PD), marked by menstrual cramps in the lower abdomen, affects a considerable number of women, with prevalences ranging from 16% to 91.[7] These cramps are frequently accompanied by other symptoms, such as headaches and nausea, which are believed to be due to prostaglandins released as the endometrium breaks down. The good news is that symptoms often improve over time, with factors such as pregnancy, use of hormonal contraceptives, or effective stress management playing a role in this improvement.[8] Standard medical treatments, including NSAIDs to decrease prostaglandin production and hormonal contraceptives to reduce menstrual fluid volume, are typically effective, with success rates ranging from 64% to 100%.[9]

However, there are some drawbacks, such as certain medication contraindications and a group of women who do not respond to these treatments.[10] In such cases, alternative therapies can be useful, providing different options for those seeking a different approach.[11] Secondary dysmenorrhea (SD) is distinct from PD because it arises from specific medical conditions, including endometriosis, chronic pelvic inflammatory disease, adenomyosis, endometrial polyps, ovarian cysts, congenital abnormalities, or issues related to intrauterine contraceptive devices.[12] In contrast to PD, which is typically cyclical and linked to the menstrual cycle, SD often involves ongoing or widespread pain that does not necessarily coincide with menstruation.[13] It usually occurs in women over 24 years old who have not had previous issues with dysmenorrhea. Secondary dysmenorrhea is characterized by clinical signs such as an enlarged uterus, pain during intercourse, and resistance to typical treatments. Endometriosis, which involves endometrial tissue growing outside the uterus, is a frequent cause of SD.[14] As a result, diagnosing and treating SD involves identifying and managing the underlying causes, particularly endometriosis. Dysmenorrhea, commonly referred to as menstrual pain, is a prevalent condition affecting a significant proportion of menstruating individuals.[15] Primary dysmenorrhea, which occurs in the absence of pelvic pathology, is particularly common among adolescents and young adults. Secondary dysmenorrhea, on the other hand, is associated with underlying conditions such as endometriosis or fibroids. The impact of dysmenorrhea extends beyond physical pain, often causing considerable disruption to daily activities, work, and social interactions. Additionally, the emotional and psychological toll, including increased stress and anxiety, can further exacerbate the condition. Secondary dysmenorrhea involves other pathological mechanisms related to conditions such as endometriosis or pelvic inflammatory disease. Understanding the underlying pathophysiology aids in developing targeted treatment approaches. This knowledge is key to distinguish between different types of dysmenorrhea and choosing appropriate therapeutic pathways. Pharmacological treatment for dysmenorrhea generally focuses on managing pain and reducing inflammation. Nonsteroidal anti-inflammatory drugs (NSAIDs), other medications such as acetaminophen, and certain muscle relaxants can be used for pain relief. The choice of pharmacological treatment depends on individual patient needs, underlying conditions, and potential side effects. Understanding the pharmacological landscape is essential for providing effective and safe treatment options. Non-pharmacological treatments offer alternative or complementary approaches to managing dysmenorrhea. These may include lifestyle modifications, such as regular exercise, dietary changes, and stress reduction techniques such as yoga or meditation. Surgical interventions for dysmenorrhea are generally reserved for cases where other treatments have failed or when there

is an underlying condition such as endometriosis or fibroids. Procedures such as laparoscopic surgery, endometrial ablation, or hysterectomy are examples of surgical options. Hormonal treatments for dysmenorrhea aim to regulate or suppress menstrual cycles, thereby reducing pain. Oral contraceptives, hormonal IUDs, and other hormonal therapies are commonly used in this regard. These treatments can be effective for both primary and secondary dysmenorrhea, particularly when linked to hormonal imbalances or endometriosis. Emerging therapies and investigational drugs are being explored to improve the management of dysmenorrhea. These might include novel anti-inflammatory agents, targeted biological therapies, or other medications aimed at specific pathways involved in menstrual pain. This review article will discuss PD in a structured manner, beginning with its epidemiology, and outlining the prevalence and risk factors associated with PD. It will then explore the impact on quality of life, detailing how menstrual pain affects daily activities, work, and social interactions. Next, the pathophysiology will be examined, focusing on the role of prostaglandins and associated symptoms such as headaches and nausea. The article will proceed to discuss pharmacological treatment options, including NSAIDs and hormonal contraceptives, followed by non-pharmacological treatments such as heat therapy, exercise, and alternative therapies. Surgical interventions for severe cases will be covered, along with a deeper look into hormonal treatments aimed at managing PD. Finally, the review will discuss investigational drugs and emerging therapies, highlighting novel treatments aimed at improving efficacy and minimizing side effects. This structure provides a comprehensive background and analysis of current and future treatment strategies for PD.

Epidemiology

Dysmenorrhea, commonly known as menstrual pain, is a widespread condition impacting nearly half of women of reproductive age.[16] The introduction of NSAIDs in 1969 was a major advancement in pain management, and their over-the-counter availability since 1983 has offered an accessible solution for many women dealing with dysmenorrhea.[17] Primary dysmenorrhea, which is defined by painful menstrual cramps without an underlying pelvic disorder, is a widespread gynecological condition affecting many females of reproductive age globally. The reported prevalence of PD ranges from 45% to 95%, with severe pain observed in 2% to 29% of cases.[18] This wide variation in prevalence can be attributed to differences in study designs, demographic profiles, cultural practices, and individual pain thresholds. Research has shown that PD is more common among younger women, particularly those under 24 years old, with prevalence rates reaching as high as 70% to 90%.[19] This high rate among younger women might be related to factors such as hormonal changes, lifestyle influences, and stress, all of which can affect pain perception and pain tolerance.[20] The impact of PD extends beyond physical pain, affecting school performance, work productivity, and quality of life.[21] Despite the availability of effective treatments such as NSAIDs and hormonal contraceptives, some women still experience significant pain and disruptions to their everyday activities. This indicates the need for ongoing research to understand PD's underlying causes and to develop more personalized treatment approaches. [22]

Risk factors of PD

Primary dysmenorrhea has non-modifiable and behavioral risk factors. Family history of dysmenorrhea, age under 20 years (symptoms are more evident throughout adolescence), menarche prior to 12 years of age (owing to premature ovulatory cycles), menstrual flow lasting more than 7 days, and nulliparity are non-modifiable risk variables. Nulliparity, or never having given birth, is recognized as a significant risk factor for primary dysmenorrhea. Women who are nulliparous often experience more intense menstrual pain compared to those who have given birth. This may be attributed to hormonal factors and uterine contractions that are more pronounced in nulliparous women. The physiological differences in uterine response can lead to increased secretion of prostaglandins, which are linked to pain and cramping during menstruation. Understanding this association can help guide management strategies for dysmenorrhea. The correlation between multiparity and reduced dysmenorrhea risk can be indicated by several presumptions, including lesser endometrial prostaglandin release after term delivery, uterine neuronal degeneration, and decreased uterine norepinephrine in the third trimester.[23] These factors suggest that women who have given birth multiple times may experience less severe symptoms of dysmenorrhea compared to nulliparous women. Hormonal changes during pregnancy and childbirth may play a role in

reducing the risk of dysmenorrhea. Furthermore, the physiological changes in the uterus after multiple pregnancies may also contribute to a lower incidence of dysmenorrhea in multiparous women. Behavioral risk factors include body mass index (BMI) <20 kg/m^2 or >30 kg/m^2, poor omega-3 intake, tobacco (nicotine increases vasoconstriction), coffee usage, and psychosocial symptoms including despair and stress.[24] The risk factor of BMI lower than 20 kg/m^2 or higher than 30 kg/m^2 indicates potential underweight or obesity issues, while poor omega-3 fatty acid intake that is crucial for heart and brain health also contributes to these risks. Tobacco use, particularly nicotine, can increase vasoconstriction, leading to elevated blood pressure and reduced blood flow. High coffee consumption may exacerbate heart and anxiety issues. Finally, stressful parental relationships can lead to PD.[25] These behavioral elements can be treated, thus these must be identified. Stress decreases luteinizing and follicle-stimulating hormone discharge, impairing follicular growth and altering progesterone synthesis and release, that affects prostaglandin action. Stress chemicals such as adrenaline and cortisol affect prostaglandin production and myometrial binding. PD doubles the risk of irritable bowel syndrome in women. This syndrome may also worsen other illnesses due to pain sensitivity.

Symptoms of primary and secondary dysmenorrhea

The nature of patient and pain assessment approach affects dysmenorrhea incidence greatly. Dysmenorrhea should be diagnosed for patients with significant discomfort that limits activities or requires medical attention. Women, their families, and health services face serious health concerns with monthly hemorrhage and dysmenorrhea. Nulliparous women have more severe primary dysmenorrhea, whereas increased parity lowers frequency.

(a) Primary dysmenorrhea

In primary dysmenorrhea, excessive intrauterine pressure and myometrial activity produce discomfort during contraction. Uterine ischemia results from increased intrauterine pressure and reduced blood flow. Primary dysmenorrhea does not appear until ovulatory cycles (6–12 months after menarche), thus teenagers do not suffer discomfort in the initial cycles. Similarly, anovulatory women have no menstrual discomfort. The most likely cause of dysmenorrheic teenagers' condition is excessive prostaglandin F2α (PGF2α) and prostaglandin E2 (PGE2) levels in their menstrual fluid and endometrium, because PGF2α/PGE2 ratios are increased in primary dysmenorrhea.[26] Nearly 80% of dysmenorrheic women have significant pain relief by anti-PG drugs. Dysmenorrheic women have increased plasma vasopressin levels during menstruation, which promotes uterine activity and produces primary dysmenorrhea. Primary dysmenorrhea causes low midline, mild stomach pain or cramping during ovulatory menstruation.[27] Spasmodic and cyclic pain begins two days before menstruation and is strong (sometimes feels like labor on the first day. In contrast to the cramping that many women experience during menstruation, primary dysmenorrhea requires therapy since the female patient is unable to do routine tasks. Common symptoms include nausea, vomiting, diarrhea, headache, and vertigo. Nervousness, melancholy, irritability, and sleeplessness are further dysmenorrhea symptoms. Organic pelvic lesions such as endometriosis and pelvic inflammatory disease (PID), and intrauterine devices cause secondary dysmenorrhea. This form of dysmenorrhea usually happens years post menarche and may begin 1 or 2 days before menses.

(b) Secondary dysmenorrhea:

Secondary dysmenorrhea is a pelvic pathology-related menstrual discomfort. Chronic pelvic discomfort before and during menstruation is frequent. Because of tissue development, endometriosis and adenomyosis may cause significant cramping and pain. Pelvic inflammatory illness may cause lower abdominal discomfort and soreness.[28] Uterine fibroids and endometrial polyps may cause heavy menstruation and discomfort. Dysmenorrhea may be exacerbated by Müllerian duct malformations, fixed uterine retroversion, tiny ovarian cysts, IUDs, cervical stenosis, and pelvic varicocele, causing severe suffering and daily life disturbance. Pelvic examination could identify discomfort, adnexal lump, or uterine myomas. Endometriosis discomfort rises two to three days before menses and is worse on days with heavy menstrual flow. Dyspareunia, infertility, severe menstrual bleeding, and dysmenorrhea indicate organic illness. Cultures from the cervix and vagina, pelvic or vaginal ultrasound, hysterosalpingography, hysteroscopy, and other laboratory testing may help diagnose secondary dysmenorrhea. Table 1 lists symptoms suggestive of PD and SD.

Table 1. Differentiating symptoms of PD and SD [29,30]

Symptoms	Primary dysmenorrhea	Secondary dysmenorrhea
Onset	Occurs after ovulatory cycles (6–12 months post-menarche)	Usually develops years after menarche
Pain Characteristics	Low midline, mild cramping; spasmodic and cyclic pain	Chronic pelvic pain before and during menstruation
Timing of pain	Begins 1-2 days before menstruation; strongest on the first day	Increases 2-3 days before menses; worsens with heavy flow
Duration of pain	Typically lasts 8-72 hours	Can last longer, depending on the underlying condition
Intensity of pain	Ranges from mild to severe; can feel like labor pains	Often severe and debilitating; can limit daily activities
Associated symptoms	Nausea, vomiting, diarrhea, headache, vertigo	Dyspareunia, infertility, severe menstrual bleeding, bloating
Psychological symptoms	Nervousness, melancholy, irritability, sleeplessness	May include anxiety, depression, and mood disturbances
Causes	Excessive PGF2α and PGE2 levels; increased plasma vasopressin	Endometriosis, adenomyosis, PID, uterine fibroids, endometrial polyps, malformations of Müllerian ducts, fixed retroversion, ovarian cysts, IUDs, cervical stenosis, pelvic varicocele
Pathophysiology	Involves increased uterine contractions and ischemia	Linked to various pelvic pathologies affecting reproductive organs
Management options	Relieved by anti-PG drugs, NSAIDs, hormonal contraceptives	Treatment focuses on addressing underlying conditions, may involve medication, surgery, or other interventions
Diagnosis	Diagnosed through medical history, physical examination	May involve pelvic examination, imaging (ultrasound, hysterosalpingography), and laboratory testing (cultures, blood tests)
Impact on daily life	Can cause significant disruption to daily activities	Often leads to missed work/school and decreased quality of life
Complications	Rarely leads to serious complications	May lead to fertility issues or chronic pelvic pain syndromes

Pathophysiology

Dysmenorrhea's exact cause is not entirely understood, but studies suggest it involves an increased release of prostaglandin F2α and prostaglandin E2 in the uterus during menstruation.[31] These prostaglandins lead to stronger contractions of the uterine muscles and reduced blood flow, resulting in uterine ischemia and the production of anaerobic metabolites, causing pain. Prostaglandins are synthesized through the arachidonic acid pathway, which involves cyclooxygenase enzymes and is influenced by progesterone levels,[32] which peak in the mid-luteal phase. However, if pregnancy does not occur, the corpus luteum breaks down, resulting in a steep drop in progesterone levels, triggering endometrial shedding and menstrual bleeding.[33] The release of lysosomal enzymes, prompted by this process, contributes to the arachidonic acid cascade, increasing prostaglandin production.[34] Research has shown that women with dysmenorrhea have higher prostaglandin levels than those without, correlating with stronger menstrual cramps, more intense pain, and other related symptoms.[35] Prostaglandin overproduction and release can cause intense contractions of the uterine muscle, leading to reduced blood flow, oxygen deprivation, and severe uterine pain.[36] These effects, commonly seen in primary dysmenorrhea, resemble those caused by contractions during labor or miscarriage.[37] Cyclooxygenase (COX) inhibitors reduce prostaglandin production and can help alleviate menstrual pain.[38] Arachidonic acid, a key precursor to prostaglandins, is a long-chain polyunsaturated fatty acid found in cell membranes.[39] The production of prostaglandins relies on the presence of this fatty acid, which is regulated by cyclic adenosine monophosphate.[40] Several factors, including hormonal changes, mechanical stress, and tissue injury, can stimulate the cAMP pathway and increase prostaglandin production.[41] Phospholipase A2, an enzyme regulated by progesterone, releases arachidonic acid from membrane phospholipids.[42] When progesterone levels drop during the late luteal

phase, phospholipase A2 becomes more active, increasing arachidonic acid release and boosting prostaglandin production during menstruation.[43] This surge in prostaglandin activity, combined with cell death and tissue damage, contributes to the severity of menstrual pain. Dysmenorrhea is restricted to ovulatory cycles, and increased prostaglandin levels are associated with more intense menstrual pain, inflammation, and other related symptoms.[44] Characteristics of dysmenorrhea include strong uterine contractions, high resting tone, elevated intrauterine pressure, and irregular muscle activity, all of which can lead to decreased uterine blood flow and exacerbated pain.[45]

Pharmacological treatment options for menstrual pain

First-line therapy for primary dysmenorrhea typically includes NSAIDs and hormonal contraceptives**.** Nonsteroidal anti-inflammatory drugs , such as ibuprofen and naproxen, are the most commonly prescribed medications for dysmenorrhea or menstrual cramps, because they reduce the production of prostaglandins, which are responsible for uterine contractions and menstrual pain. Hormonal contraceptives, including oral contraceptives, patches, and intrauterine devices (IUDs), help regulate or suppress ovulation and reduce menstrual flow, easing pain. Both treatments are effective for many women, though individual responses may vary, and side effects should be considered when selecting an option. A Cochrane review of NSAIDs in dysmenorrhea randomized controlled trials (RCTs) demonstrated strong evidence to support NSAIDs as the first-line treatment for PD. In these trials, NSAIDs, particularly COX-2-specific inhibitors, effectively reduced menstrual pain in primary dysmenorrhea by inhibiting prostaglandin production while minimizing side effects.[46] NSAIDs are a common treatment for dysmenorrhea, or menstrual cramps.[47] Prostaglandins are chemicals that cause uterine contractions, leading to pain during menstruation.[48] By reducing prostaglandin production, NSAIDs help ease these contractions and provide relief from pain.[49] Popular NSAIDs include ibuprofen, naproxen, diclofenac potassium, and meclofenamate.[5] These medications block both COX-1 and COX-2 enzymes. To achieve the best results, it is suggested that NSAIDs be taken 1–2 days before menstruation begins.[51] However, these drugs may not be effective for everyone, with about 20%–25% of users experiencing little to no relief or encountering side effects.[52] These side effects can vary from mild ones, such as nausea or dizziness, to more severe ones, such as gastrointestinal ulcers. NSAIDs can pose risks to the liver or kidneys, as well as cause issues with blood circulation. Despite these risks, NSAIDs are generally more effective than placebos for managing dysmenorrhea.[53] Serious adverse effects are relatively uncommon due to the short duration of treatment, typically 2–3 days.[54] However, it is essential to be aware of the potential side effects and consult a healthcare provider for any concerns.[55] Ex-vivo tests, which analyze tissue samples outside the body, have shown that aspirin resistance may be linked to genetic differences, absorption challenges, or other factors affecting how the drug is processed. [56]

Non-pharmacological treatment options

Alternative methods have shown promise in relieving dysmenorrhea and include heat therapy, herbal treatments, transcutaneous electrical nerve stimulation, acupuncture, and yoga.[57] Although these approaches appear beneficial, there needs to be more evidence to establish them as standard treatments. Physical exercise also helps alleviate dysmenorrhea by boosting pelvic blood flow and triggering the release of beta-endorphins, which serve as natural painkillers.[58] In young adult women, a low-fat vegetarian diet may lead to a shorter and less severe duration of dysmenorrhea.[59] Omega-3 fatty acids could ease adolescent dysmenorrhea.[60] This outcome might be because omega-3 fatty acids produce less intense prostaglandins and leukotrienes, which play a role in menstrual pain and inflammation.[61] Arachidonic acid is a precursor to prostaglandins, which can play a role in dysmenorrhea.[62] Adjusting a person's diet to include fewer high-fat foods and more beans, seeds, fruits, and vegetables could help lower arachidonic acid levels, potentially easing dysmenorrhea.[63] Exercising regularly, ideally for 45 to 60 minutes at least three times a week, might also help relieve dysmenorrhea symptoms, especially for women under 25 years of age.[64] While dietary supplements are sometimes used to manage dysmenorrhea, there needs to be more evidence to prove their effectiveness, and their safety is still being determined.[65] Acupuncture, which stimulates nerve fibers and interacts with endorphins and serotonin, might be another option for treating dysmenorrhea.[66] Although initial studies suggest it could help, more research is needed to confirm its benefits.

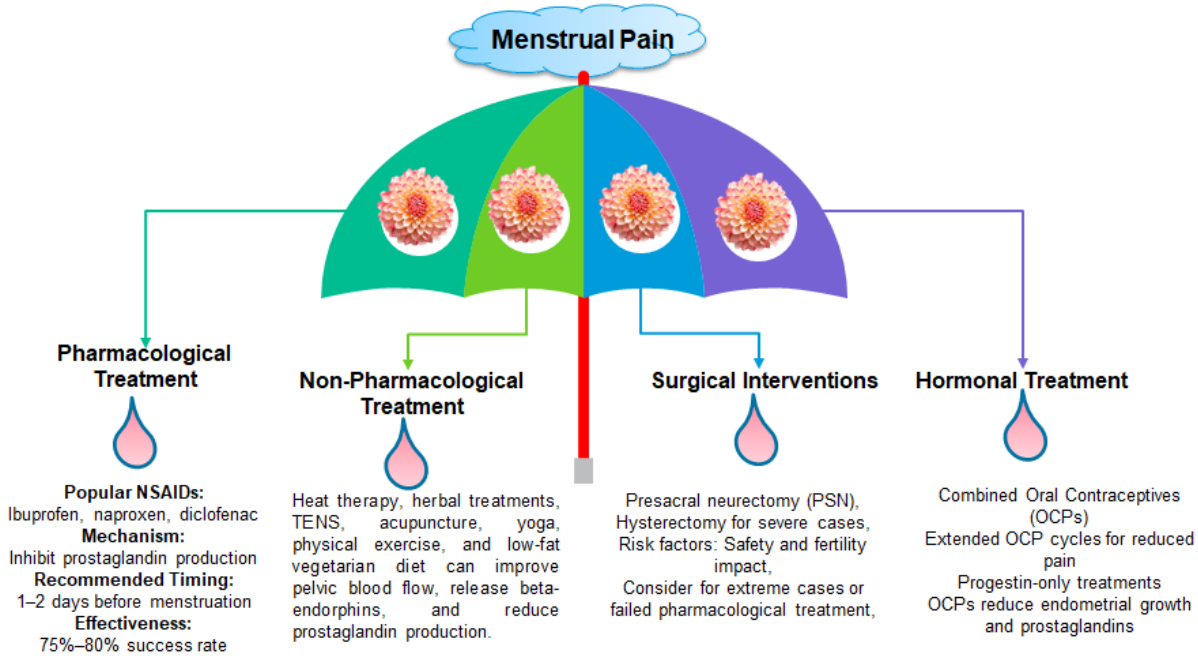

Figure 1. Treatment modalities for dysmenorrhea

Surgical interventions

Surgical treatment is typically an option only for severe cases of dysmenorrhea that do not respond to other methods (Fig.1). These surgical procedures can include laparoscopic uterosacral nerve ablation (LUNA), presacral neurectomy (PSN), or hysterectomy in the most severe cases. LUNA and PSN are designed to cut nerve fibers in the pelvis, reducing pain signals from the cervix. However, the safety and effectiveness of these procedures for primary dysmenorrhea are not well-established. Hysterectomy is usually a last resort for extreme cases that have not improved with other treatments. Still, it is generally avoided for teenagers, young women, and those who may wish to have children due to its irreversible impact on fertility. Because weak evidence supports their effectiveness, surgical approaches are usually not advised for managing PD. These are typically reserved for extreme cases where other treatments have failed. Physicians should weigh considerations such as a patient's age, their interest in future fertility, and the severity of symptoms before recommending surgery. It is vital to have detailed conversations with patients regarding the risks, benefits, and alternative surgery options, ensuring they can make informed choices. Surgical removal of endometriosis is a common treatment for relieving symptoms, but other surgical methods might be helpful for patients with SD who do not have obvious anatomical causes. Laparoscopic PSN and LUNA are surgical techniques that have been used to treat severe cases of dysmenorrhea. However, the popularity of LUNA has waned following a major randomized controlled trial by Kushwah et al.,[67] which found that LUNA did not substantially reduce menstrual pain. This study, however, did not consider LUNA or PSN in situations where NSAIDs were ineffective in patients without endometriosis or persistent pelvic pain. Additional research has explored the role of these surgical approaches in treating primary dysmenorrhea. In one randomized double-blind study, half of the women with primary dysmenorrhea experienced pain relief after undergoing LUNA.[68] Another study found that 73% of participants reported improvement with a combination of LUNA and PSN, while 69% experienced pain relief following LUNA alone. [69] Another study reported that PSN is an effective surgical procedure to control primary dysmenorrhea. Our preliminary results revealed that the degree of pain relief in cases of severe midline dysmenorrhea. [70] It is not always clear whether these patients had previously tried NSAIDs or if surgery was chosen because NSAIDs were not an option. Further research is needed to assess the effectiveness of LUNA and PSN, particularly for cases of NSAID-resistant dysmenorrhea in individuals without endometriosis or chronic pelvic pain. For those with SD with no obvious anatomical causes, other surgical options might be explored beyond the typical interventions for endometriosis.

Hormonal treatment

If NSAID does not work, hormonal therapy should be tried for at least three menstrual cycles while continuing with NSAIDs.[71] Hormonal therapy is a common choice for sexually active women with dysmenorrhea, especially if they also want birth control. The most commonly used hormonal therapy is combined oral contraceptives (OCPs), which might also help reduce acne in adolescents.[72] Oral contraceptives work by reducing endometrial growth and decreasing the amount of endometrial tissue available to produce prostaglandins and leukotrienes. They also prevent ovulation and lower progesterone levels.[73] Oral contraceptives can lower the amount of prostaglandins and leukotrienes in menstrual fluid, indicating that their production in the uterus is decreased, which might contribute to less pain during menstruation. For women taking OCPs who still have symptoms during the pill-free interval, extending the hormone phase beyond the usual 21 days might be beneficial. A recent study on a 91-day extended OCP cycle with 150 mcg levonorgestrel and 30 mcg ethinyl estradiol for 84 days, followed by 7 days of 10 mcg ethinyl estradiol, found that it was used over four years with no cases of venous thromboembolism and minor changes in cholesterol levels.[74] Hormonal treatments, such as cyclic regimens, are commonly used to alleviate dysmenorrhea, though studies often do not differentiate among various hormone combinations. Hormone-based therapy is also considered for women with secondary dysmenorrhea who do not respond to NSAIDs and prefer to avoid surgery. A randomized placebo-controlled study showed that OCPs are effective in managing secondary dysmenorrhea related to endometriosis.[75] Continuous OCP regimens seem more effective than cyclical ones following endometriosis surgery. Despite these concerns, current guidelines continue to recommend hormonal suppression as a treatment for dysmenorrhea.[76] The primary treatment for endometriosis in adolescents and young adults typically involves continuous combined estrogen and progestin hormone therapy. This approach aims to stop the growth of endometrial tissue and reduce bleeding from endometrial implants, which can cause pain, scarring, and infertility. While this treatment can be effective, further research is needed to confirm its long-term benefits. According to the Cochrane Database, additional studies are required to evaluate the extended use of combined OCPs approved by the FDA for this age group.[77] Extended regimens using the vaginal ring or transdermal patch can help reduce endometriosis-related pain. The vaginal ring often works better than the patch, especially for those with rectovaginal lesions. However, both options can lead to irregular bleeding when used continuously. If patients do not find relief with noncyclic OCPs, treatment may involve gonadotropin-releasing hormone (GnRH) agonists such as nafarelin or leuprolide, typically given for six months. These drugs suppress the hypothalamic-pituitary axis, reducing estrogen levels and eventually easing endometriosis symptoms. Initially, GnRH agonists can cause a surge in pituitary hormones such as follicle-stimulating hormone and luteinizing hormone, which may lead to temporary pain from ovarian stimulation. Eventually, these agonists induce an estrogen-deficient state. GnRH antagonists work differently by blocking pituitary GnRH receptors, leading to an immediate and reversible reduction in hormone levels. Unlike GnRH agonists, they do not cause a surge in gonadotropins but still achieve a similar hypoestrogenic effect. Studies are ongoing to test the safety and effectiveness of an oral GnRH antagonist called elagolix for treating endometriosis, including its potential use in adolescents.[78] Progestin-only treatments are another option for managing endometriosis. They suppress the hypothalamic-pituitary-ovarian axis, causing anovulation and reducing estrogen levels, which leads to the shrinkage of endometrial tissue and endometriotic lesions. Injectable DMPA, the levonorgestrel intrauterine system (LNGIUS), and the etonogestrel subdermal implant have positively reduced endometriosis symptoms. Danazol, which was once used to treat endometriosis-related pain, is now less popular because of its side effects, including weight gain, swelling, muscle pain, acne, and excessive hair growth (Figure 2).

Table 2 provides detailed information about various NSAIDs, including their dosage, common brand names, and pharmacological uses along with potential adverse reactions. Each NSAID is highlighted for its specific applications, such as pain relief, menstrual cramps, and gastrointestinal risks. The table serves as a quick reference guide for healthcare professionals and patients to understand the usage and side effects of common NSAIDs. Complementary therapies for NSAIDs in managing dysmenorrhea include heat therapy, which helps relax muscles and improve blood flow, and dietary supplements such as magnesium, omega-3 fatty acids, and vitamin E to reduce inflammation and pain. Herbal remedies such as

ginger**,** fennel, and chamomile tea are known for their anti-inflammatory and muscle-relaxing properties. Acupuncture stimulates nerves and releases endorphins, while exercise and yoga improve circulation and reduce cramps. Transcutaneous electrical nerve stimulation (TENS) and cognitive behavioral therapy (CBT) also offer effective pain relief by managing both physical discomfort and emotional stress. These methods complement NSAIDs and enhance overall pain management.

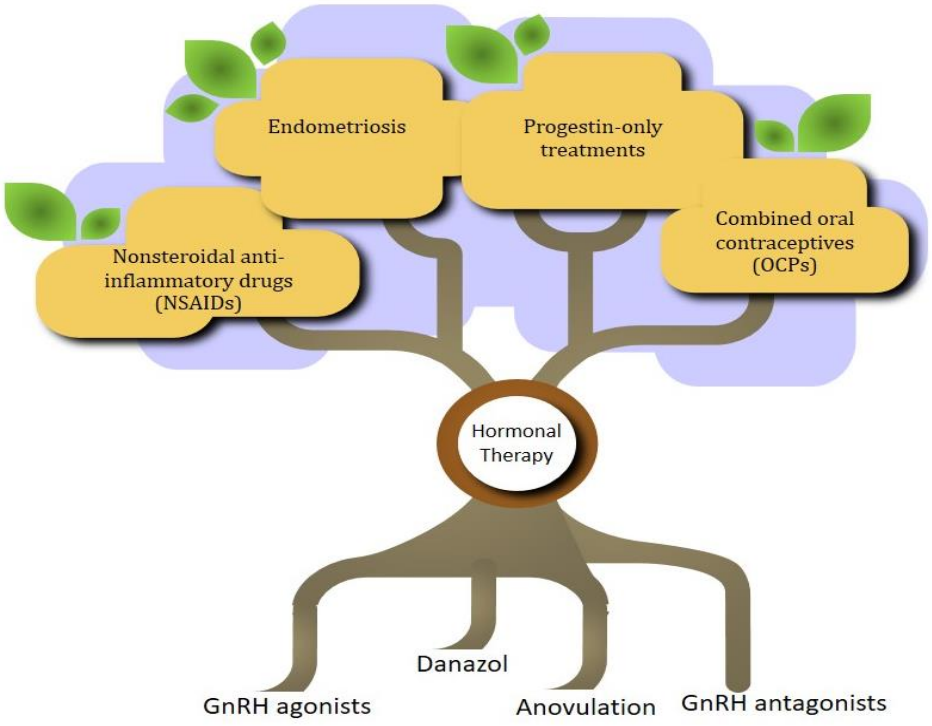

Figure 2. Dysmenorrhea and endometriosis treatment

Table 2. NSAIDs used during menstruation in the treatment of primary dysmenorrhea in adolescents and young adults.[79]

NSAID	Dosage information	Common brand names	Pharmacological use and adverse reactions
Ibuprofen	200-400 mg every 4-6 hours	Advil, Motrin	Commonly used for pain relief, it can cause gastrointestinal upset in some individuals.
Naproxen	220-440 mg every 8-12 hours	Aleve	Longer-acting than ibuprofen; may require less frequent dosing. Considered effective for menstrual cramps.
Ketoprofen	25-50 mg every 6-8 hours	Orudis	Less commonly used; higher risk of gastrointestinal side effects; consult a healthcare professional.
Aspirin	325-650 mg every 4-6 hours	Bufferin (Bayer)	Less commonly used for primary dysmenorrhea due to bleeding risk; should not be used in adolescents with viral infections (Reye's syndrome risk).
Diclofenac	50-100 mg every 6-8 hours	Voltaren, Cataflam	Available in oral and topical forms; can be more potent.
Mefenamic Acid	250 mg every 6 hours	Ponstel	Often prescribed for menstrual pain, it can cause gastrointestinal upset and may require a prescription in some regions.
Etodolac	200-400 mg every 6-8 hours	Lodine	Used for menstrual pain

Investigational drugs

Aromatase is an enzyme that converts C19 androgens into estrogen and has become a focus for treating endometriosis. Aromatase inhibitors (AIs) are known to reduce endometriotic lesions and relieve pelvic pain.[80] However, these medications can cause a decrease in bone mineral density, therefore taking calcium and vitamin D supplements is recommended to mitigate this risk.[81] Reversible aromatase inhibitors, such as letrozole (Femara) and anastrozole (Arimidex), can suppress aromatase by 97-99% with 1-5 mg/day doses.[82]Exemestane (Aromasin), which is irreversible, achieves similar inhibition at 25 mg/day. Letrozole is often seen as the most potent of the three. However, despite their effectiveness, the use of aromatase inhibitors for treating endometriosis is not approved by the U.S. Food and Drug Administration, making their use in this context experimental. There is limited data on their safety for adolescents. More studies are needed to explore whether early treatment with AIs could slow the progression of endometriosis and reduce infertility risk.

CONCLUSION

Primary dysmenorrhea is a common condition in women of reproductive age that is often overlooked and inadequately treated. It can significantly affect the quality of life, leading to absences from work or school. Treatment typically aims to manage pain using both pharmaceutical and alternative methods. This overview highlights the need for prompt diagnosis and effective management of PD to enhance women's quality of life. Ongoing research is crucial to validate treatment effectiveness and understand more about the causes of dysmenorrhea.

Author Contributions

VIRR and BD were responsible for the conception and design of the study. PMP contributed to the acquisition of data. MNL and PMP were involved in the analysis and interpretation of data, as well as drafting the article. Critical revisions were made by VIR and BD. All authors have read and approved the final manuscript.

Ethical Statement & Informed Consent

Not applicable.

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Data Availability Statement

There were no new data generated, data sharing is not applicable.

Conflict of Interest

The authors declare that no conflicts exist.

Financial Disclosure

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Declaration the Use of AI in Scientific Writing

Nothing to declare.

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