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Primary and secondary dysmenorrhea: symptoms, risk factors, diagnosis, and treatment – review

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ABSTRACT

Dysmenorrhea, or painful uterine contractions during menstruation in women, is a common condition. It may affect up to 90% of patients in a doctor's office. Depending on the severity of symptoms, it may cause discomfort or prevent normal functioning in everyday life. Some women do not realize that this is not a normal symptom during menstruation. Unfortunately, lack of exercise, smoking, or drinking alcohol only increases the symptoms. A medical history and physical examination of the patient are important steps in finding the cause. Primary dysmenorrhea is primarily associated with the pathogenesis of prostaglandins and leukotrienes, which generate inflammation and pain. However, it has nothing to do with pelvic pathology. It usually first appears in young women during puberty, up to 24 months after their first period. If the history and physical examination are not clear about the primary cause of pain, a secondary cause should be considered. For this purpose, a transvaginal ultrasound examination should be performed. The most common secondary pathology is endometriosis. In the treatment of primary and secondary diseases, physical exercises and warm compresses are beneficial, which women are often unaware of. First-line pharmacological treatment may include NSAIDs or combined oral estrogen-progestogen hormonal therapy. The purpose of this review is to provide knowledge about the symptoms, risk factors, diagnosis, and treatment of dysmenorrhea.

KEY WORDS: primary dysmenorrhea, secondary dysmenorrhea, painful menstruation, dysmenorrhea risk, dysmenorrhea treatments, dysmenorrhea diagnosis

INTRODUCTION AND OBJECTIVE

Painful menstrual cramps of uterine origin are called dysmenorrhea [1]. It occurs in adolescent girls and young women during their reproductive years and affects as many as 50-90% [2,3]. The family doctor is often the first to report menstrual pain [4]. Dysmenorrhea may result in a negative impact on emotional, mental, and functional health [5]. Half of women miss school or work at least once and approximately 15% have frequent short-term absences [6]. This article aims to present:

- the symptoms of primary and secondary dysmenorrhea,
- the risk factors of primary and secondary dysmenorrhea,
- the diagnosis and possible treatments of these ailments to educate potential patients - adolescent and adult females for primary and secondary dysmenorrhea.

MATERIALS AND METHODS

To write this review article, 44 articles were analyzed containing keywords such as primary dysmenorrhea; secondary dysmenorrhea; painful menstruation; dysmenorrhea risk; dysmenorrhea treatments; and dysmenorrhea diagnosis in databases such as PubMed, Medline, Google Scholar, books, and other scientific articles.

CURRENT STATE OF KNOWLEDGE

Dysmenorrhea may be primary or secondary. Primary is not associated with diseases or pathology. It is characterized by lower abdominal pain that is repeated and happens during the menstrual cycle [7]. It is caused by an increase in prostaglandin levels and leukotriene levels [2,8]. Primary dysmenorrhea begins within about 24 months after menarche or when menstrual cycles become stable. Symptoms begin a few hours before or after the start of menstrual bleeding and resolve after 2 or 3 days [5,9]. They may correspond to hormonal disorders of the ovaries and consequently lead to future problems with menopause or fertility disorders in women of reproductive age [10].

Whereas secondary dysmenorrhea is associated with clinically recognizable pelvic pathology or medical condition [2]. Most often, the pain is caused by endometriosis, but there may also be other causes, such as adenomyosis, endometrial polyps, ovarian cyst, uterine polyps, uterine leiomyomas, congenital obstructive Müllerian, cervical stenosis [2,11].
Secondary dysmenorrhea symptoms can start to arise later in life or just after menarche [2]. The pain does not have to appear during menstruation [12] and is ordinarily detected in older females (>24 years) who have never had problems with painful periods before [13].

Clinical symptoms. Symptoms of primary dysmenorrhea begin up to two years after menarche and disappear after about 3 days [5,9]. In a study involving over 400 women with dysmenorrhea on a VAS (visual analogue scale) from 0 to 10: 47% of patients reported moderate pain and as many as 17% reported severe pain [14]. Pain in the lower abdomen may also be accompanied by other symptoms. They can be physical or mental. The physical symptoms of dysmenorrhea include:

- tender breasts,
- heavy lower abdomen,
- backache

- sleep difficulties,
- swollen legs,
- appetite disorders,
- constipation or diarrhea

Vomiting or nausea may also occur.

Mental symptoms during menstruation are not rare. Mood disorders such as nervousness, irritability, anxiety, and even depression may occur [5,11].

According to the study, depression and anxiety were more common in women with dysmenorrhea [13].

Females with secondary dysmenorrhea may often be distinguished from females with primary dysmenorrhea [11].

The pain associated with secondary dysmenorrhea may affect women at any time after menarche. It may start just after menarche or later in life [2]. Females experience constant or paroxysmal pain that does not have to be during menstruation [10]. Intensities of pain and times may vary [5]. The pain may be accompanied by symptoms such as a large uterus, dyspareunia, resistance to effective treatment [7,15], vaginal discharge - purulent-mucous or white-grayish discharge [4,5], menorrhagia, intermenstrual bleeding, friable cervix, dysuria, postcoital bleeding [5].

Risk factors. For many years, attempts have been made to find reasons explaining the occurrence of dysmenorrhea. According to current knowledge, they can be divided into general, biochemical, mental and social, gynecological, and obstetric [5,13]. General factors are age (before 30 years), higher or lower than normal body mass index, and low physical activity [4].

Mental and social factors are anxiety, depression, rape, disturbed childhood, psychosomatic symptoms, drug abuse, alcohol abuse, bad family relationship, smoking, low education [13].

Gynecological and obstetric factors are abnormal uterine position, abnormalities in length or the shape of the cervix, longer menstrual cycles, heavy menstrual flow, younger menarche age, nulliparity, previous cesarean section pelvic inflammatory disease, abortion or miscarriage, pelvic adhesions, varices, endometriosis, menopause [5,13].

Many studies show that biochemical factors such as prostaglandins and leukotrienes are the main cause of pain during menstruation [5,16]. A study that involved measuring the activity of prostaglandin F2a (PGF2α) in menstrual fluid that was contained in tampons was

carried out. Authors found that women who experience pain during menstruation had twice the level of PGF2α activity than women with amenorrhea [17]. The urine was also subjected to a detailed examination. High levels of leukotrienes were found in the urine of adolescent girls who suffered from period pain [18].

Secondary dysmenorrhea is caused by the pathology of the pelvis or by a specific disease (Figure 1.). The most frequent reason is endometriosis, as mentioned above [2]. Another important reason is adenomyosis [19].

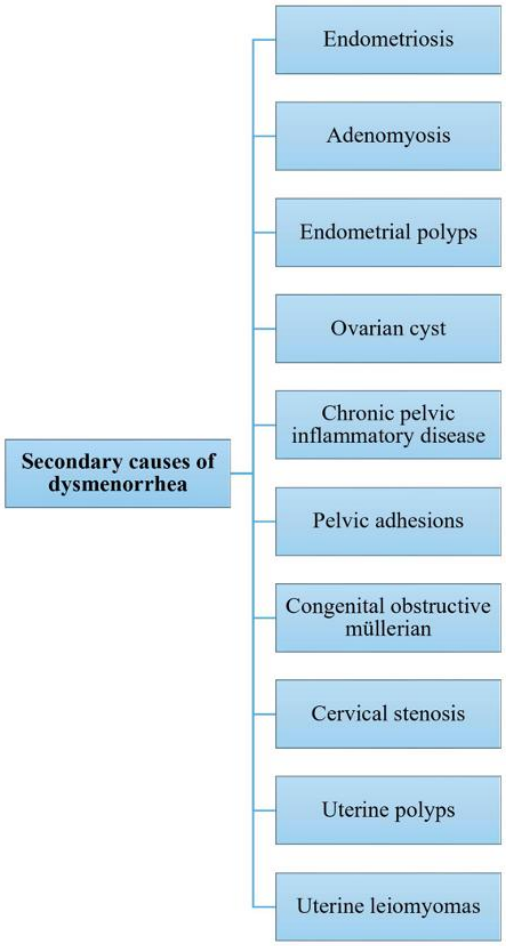

Figure 1. Secondary causes of dysmenorrhea.
Source: 2,6,11 i 12.

Diagnosis. To determine whether the patient's menstrual pain is primary or secondary a detailed history and a physical examination should be performed. The interview should

include menstrual, family, and surgical history [4]. The history should include the location of pain, whether pain coincides with menstruation, associated symptoms like fatigue, headache, diarrhea, tender breasts, nervousness, irritability, nausea, and vomiting, and which nonprescription therapies the patient has tried can help establish a diagnosis [2,20].

To diagnose primary dysmenorrhea, a typical interview is enough [9]. Pain begins within about 24 months after menarche or when your menstrual cycles become stable. It begins a few hours before or after the start of menstrual bleeding and resolves after 2 or 3 days. It is connected with lower abdominal pain which is cyclic and happens during the menstrual cycle [5,9]. Females with primary dysmenorrhea in physical examination are no deviation from the norm. Exam demonstrates that the uterus is normal-sized, painless, and mobile. Vaginal discharge is normal and the adnexa are free from any changes. This is a typical appearance in primary dysmenorrhea [21]. If the patient has a partner and is sexually active, pregnancy should be ruled out. Medical interviews should be carefully elicited because many patients think the pain is a normal part of the period. In a study of over 4,300 female patients with symptoms of pain that began around puberty, about two-thirds said it was normal [4]. Primary dysmenorrhea should be differentiated from pelvic pain syndrome (CPP), which is cyclical or non-cyclical pain in the lower abdomen that lasts for at least 3 to 6 months. It can appear during menstruation or occur independently. Up to 80% of patients with CPP are diagnosed with neurotic disorders [22].

When the reported symptoms do not match primary dysmenorrhea, the patient has a history of surgery, similarly, symptoms are in the family or a lack of response to treatment such as hormonal treatments or non-steroidal anti-inflammatories we must think about secondary [1,2,4,7].

In secondary dysmenorrhea, females have symptoms that we wrote above like dyspareunia, dysuria, intermenstrual bleeding, incorrect vaginal discharge, or postcoital bleeding [4,5,7,15]. In this case, we should perform a pelvic physical examination and ultrasonography (USG) to detect anatomic abnormalities or other pathology [2,15]. USG helps differentiate the cause of secondary dysmenorrhea like endometriosis, adenomyosis, leiomyomas, or Mullerian anomalies [5].

In the diagnosis of secondary pain origin, the following is also used:

- Endocervical swabs
- Vaginal swabs
- Urinary human chorionic gonadotropin pregnancy test

- Cervical cytology with/ without HPV testing
- Laparoscopy
- Doppler ultrasonography
- Magnetic resonance imaging (MRI)

Endocervical or vaginal swabs are useful in diagnosing sexually transmitted infections or pelvic inflammatory disease, cervical cytology or HPV testing rule out a suspected cervical malignancy. Laparoscopy, which until recently was intended for women who have problems conceiving and may suffer from endometriosis [5,15], is no longer the gold standard in diagnosing this condition, but it is still the technique of choice in surgical treatment [23]. Whereas Magnetic resonance imaging or Doppler ultrasonography is for patients with adenomyosis, torsion of the adnexa, or in suspected endometriosis when the ultrasound examination did not determine the cause (Table 1.) [5,15]. Non-invasive or minimally invasive diagnostic tests are also available for endometriosis diagnostics. They can be used to determine brain-derived neurotrophic factor from plasma, specific microRNA from saliva, or fucosyltransferase 4 expression [23].

SUSPECTED DIAGNOSIS	CLINICAL SYMPTOMS	DIAGNOSTIC METHOD
Primary dysmenorrhea	Cyclic, recurrent pain before or during menstruation, cramp, pain in the lower abdomen, nausea, vomiting, tender breasts, sleep difficulties, and swollen legs, appetite disorders, constipation or diarrhea, mood disorders	Diagnosis based on clinical symptoms. To rule out infection or pregnancy: Urinary human chorionic gonadotropin pregnancy test, Vaginal or endocervical swabs
Endometriosis	Cyclic or noncyclic pain during menstruation, infertility, dyspareunia, dysuria, dyschezia, pain during defecation	Transvaginal and pelvic ultrasonography Magnetic resonance imaging (MRI) (if inconclusive findings on the ultrasound, deep pelvic endometriosis)
Adenomyosis	Menorrhagia - heavy bleeding, may intermenstrual bleeding blood clots, dyspareunia	Transvaginal ultrasonography Magnetic resonance imaging (MRI)
Uterine leiomyomas	Cyclic pelvic pain, menorrhagia, prolonged periods sometimes dyspareunia may occur	Transvaginal ultrasonography
Ovarian cysts	Dull pain in the lower abdomen (usually), may cause heavy or irregular periods, spotting; Rupture of the cyst - sudden pain; Twisted cyst - sudden, severe, cramping pain of the lower abdomen on the twisted cyst side, vomiting, nausea, high pulse rate.	Transvaginal and pelvic ultrasonography
Pelvic inflammatory disease	Lower abdominal pain, dyspareunia, fever (more than 38C), abnormal vaginal mucopurulent discharge, bleeding after intercourse	Endocervical swabs Saline microscopy C-reaction protein, elevated erythrocyte sedimentation rate in the blood
Ectopic pregnancy	Amenorrhea, lower abdominal pain, abnormal uterine bleeding, cramping. If complications - e.g. hypotension, shock	Urinary human chorionic gonadotropin pregnancy test Transvaginal and pelvic ultrasonography
Congenital obstructive Müllerian malformations	Amenorrhea, infertility, miscarriage	Pelvic and transvaginal ultrasonography Magnetic resonance imaging (MRI) - preferred method

TABLE 1. Symptoms and diagnostic methods in suspected diagnosis.
Source: 2, 6, 24-27.

Treatment. Dysmenorrhea treatment begins similarly in each case. It aims to relieve pain so that patients can perform everyday activities without any problems. Methods of treating dysmenorrhea can be divided into pharmacological and non-pharmacological [5]. When the medical history matches the symptoms of the primary form of the disease, empiric treatment should be initiated. The problem occurs when symptoms do not respond to initial treatment,

then potential causes of secondary dysmenorrhea should be looked for [2,7]. However, initial actions should consist of educating women and reassuring them [5].

Non-pharmacological and non-invasive treatment. Non-pharmacological and non-invasive therapy is recommended as an adjunct to first-line treatment [4,28]. It can be also used as an alternative when first-line treatment is rejected or contraindicated for various reasons [4]. Non-pharmacological therapy works as a natural analgesic and antioxidant. It reduces uterine cramps caused by increased prostaglandins, increases beta-endorphin levels, and facilitates uterine circulation [29-32]. This type of therapy includes relaxation, heat treatments, exercises, acupuncture, acupressure, transcutaneous electrical nerve stimulation (TENS), behavioral interventions and pain management training, biofeedback, or manual therapy [28,29,33-35].

One of the basic methods that should be used first when dealing with menstrual pain is heat therapy in the lower abdominal area and exercises. Heat applied to the lower abdominal area is as effective as NSAIDs (Nonsteroidal anti-inflammatory drugs) and superior to acetaminophen, which is why most patients initially prefer these adjunctive therapy options [5].

Physical exercise reduces pain intensity and duration in primary dysmenorrhea. The review by Armor M et al. (2019) shows that exercising about 60 minutes a day three times a week can reduce the severity of pain but is not as effective as NSAIDs. Considering the benefits without the use of pharmaceuticals, it is worth recommending moderate exercise to patients [36,37].

One type of exercise worth considering is yoga. It lets you obtain a stabilization between body and mind. Performing 30 minutes of Nidra yoga twice a week allows you to regulate the level of thyroid, luteinizing, and follicle-stimulating hormones and relaxes the muscles, reducing menstrual pain [38].

Dietary supplements and alternative medicine, such as the use of herbs and plants, and Chinese medicine are also used in treatment. However, there is insufficient evidence to recommend the use of such therapy [5].

The next non-pharmacological and non-invasive is acupressure. Experimental studies have shown that it effectively provides sedative and analgesic effects [39]. Acupressure has no advantage over NSAIDs, but it may reduce pain intensity, the number of days with pain, and the amount of medication used [40,41]. Even though the effect of acupuncture is

confirmed in several studies, good comparisons and solid methodological techniques are lacking [5].

Transcutaneous electrical nerve stimulation (TENS) can be used as a non-pharmacological second-line treatment [9]. Studies in behavioral interventions, pain management training, and biofeedback were small and of poor methodological quality [4]. Manual therapy may be effective in relieving pain beyond both no treatment and NSAIDs. However, the low quality of randomized controlled trials necessitates more robust research [28].

Pharmacological treatment. First-line pharmacological treatment involves non-steroidal anti-inflammatory drugs (NSAIDs), which work by inhibiting cyclooxygenase enzymes, blocking the production of prostaglandins [5]. It has been proved that using NSAIDs 1-2 days before the onset of menstrual pain has a better effect than using NSAIDs as needed [21]. It is unclear whether any NSAID is safer or more effective than another. Each of them may cause side effects [5]. In approximately 20% of women with dysmenorrhea, taking these drugs does not bring any results and it is called NSAID-resistant dysmenorrhea [5,8].

Acetaminophen may be an alternative to NSAIDs. When taken with caffeine, it reduces pain but is not as effective as the previously mentioned drugs [5].

Hormonal therapy is also a first-line treatment for dysmenorrhea. It can be used as an alternative or added to NSAID therapy in females who are not planning to become pregnant soon [4]. This therapy may use progesterone-only or combined estrogen-progestin oral contraceptives [42]. Hormones are reducing cyclooxygenase-2 and prostaglandin production and thinning the endometrial lining [4]. In the menstrual fluid of women who take estrogen-progestin oral contraceptives, there are low levels of prostaglandins. Pills users experience significantly less dysmenorrhea and need less additional pain medication [5]. Some patients cannot take tablets due to an increased risk of venous thromboembolism [42].

Another type of oral contraception is continuous combined oral contraceptives. It has over 28 days of active hormone, so it may improve and more rapid pain relief, but it leads to more weight gain [4].

Progestin-only oral contraceptives including pills, implants, IUDs, or intramuscular injections [5]. They are an alternative for people who can't take estrogen therapy [4]. This type of contraceptive is particularly suitable for patients with secondary dysmenorrhea associated with endometriosis, but they cause irregular bleeding [5,42].

In endometriosis, a double-blind randomized controlled trial demonstrated the effectiveness of combined oral estrogen-progestin for the treatment of dysmenorrhea. Some studies confirmed the effectiveness of oral and depot medroxyprogesterone, the etonogestrel implant, and the levonorgestrel-releasing intrauterine system (LNG-IUS).[15] This last (LNG-IUS) is safe to use in nulliparous and adolescent patients for primary and secondary dysmenorrhea [42].

Gonadotropin-releasing hormone agonists and antagonists may be as second-line pharmacologic treatment. GnRH agonists include nafarelin, leuprolide acetate, and goserelin while antagonists include elagolix [5]. Some studies report a 75% reduction in dysmenorrhea symptoms in patients taking gonadotropin-releasing hormone for at least six months in combination with estrogen therapy for the treatment of surgically confirmed endometriosis [4].

Aromatase inhibitors may also be used to treat secondary dysmenorrhea. They cause amenorrhea but require additional estrogen therapy.

In the case of dysmenorrhea, alternative treatment may also include vasodilators (e.g. sildenafil), beta-2 adrenoceptor agonists, calcium channel blockers (e.g. nifedipine), vasopressin/oxytocin receptor agonists (e.g. atosiban and SR49059), antispasmodics (e.g. hyoscine butylbromide), magnesium. Their use is often limited by the side effects they cause [4,5].

There is an increasing talk of using cannabis to relieve menstrual pain. The two main ingredients of cannabis are cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC) [43]. They affect receptors found in muscle tissue, including the uterus: CB1 and CB2, acting as analgesics, and the vanilloid receptor (TRPV), which is involved in neuropathic pain signals [43,44]. Cannabis has promising effects in treating menstrual pain, but studies are needed to demonstrate full effectiveness and safety [43].

Surgical treatment. Surgical options are used in patients who do not improve with non-pharmacological, non-invasive, or pharmacological treatments. Laparoscopy is one of the surgical options. It is the preferred treatment of endometriosis [2]. Endometrial ablation can be used when pharmacology treatment has not achieved good results. It can be performed in patients who experience heavy menstrual bleeding.

When all other possible treatments have failed, hysterectomy may be used. This can be done without or with the removal of the ovaries. Each case should be assessed individually

depending on the etiology of dysmenorrhea and the patient's age. Another surgical methods are uterine nerve ablation and presacral neurectomy [5].

CONCLUSION

Dysmenorrhea is a common ailment that may disturb the everyday functioning of adolescent girls and mature women. Unfortunately, current lifestyle (e.g. smoking, alcohol) often increases the risk of pain during menstruation. Modern methods of diagnosing menstrual pain are so good that we can find the cause - primary or secondary. Therefore, patients should be made aware during visits to the doctor's office that such ailments are not normal and can be prevented, alleviated, and even cured.

Disclosures

Authors contributions

Conceptualization: Paulina Krzemińska and Joanna Kołodziej, Arkadiusz Biniewicz
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