Primary Dysmenorrhea: Recognizing Menstrual Pain as a Significant Health Issue with Lasting Impacts and Strategies for Improvement.

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BACKGROUND: The pain associated with menstruation is called as dysmenorrhea can be primary and secondary. Primary dysmenorrhea is pain which comes from having a menstrual period or "menstrual cramps." Usually, it is caused by natural chemicals called prostaglandins that are produced in the lining of uterus. Primary dysmenorrhea is also called as idiopathic or true dysmenorrhea without any identifiable cause in contrast to secondary type which has an underlying pathology. Most menses are accompanied by cyclic discomfort during the menstrual cycle, which is perpetual. Both the local and systemic symptoms are apparently as a result of increased level of prostaglandins (F2α) in the menstrual fluid. This results in uterine cramping, nausea, vomiting, backache, diarrhea, giddiness, syncope and fainting. It's normal to have some pain during menstruation and about 60% of menstruating women have mild cramps during their period especially in the reproductive age. About 5% to 15% of women report period pain that's so severe which affects their daily activities. However, this number is likely higher, as healthcare providers believe many people don't report menstrual pain. It has a detrimental effect on young women's quality of life (QOL) and is the primary cause of their absence from work or school. Various treatment options are available to counter this problem such as the administration of nonsteroidal anti-inflammatory drugs, hormonal contraceptives, and/or the use of non-pharmacological aids (e.g. application topical heat, exercise etc.). The primary goal of treatment is to reduce pain and improve the quality of life in patients suffering from dysmenorrhea.

Key words: Primary dysmenorrhea, prostaglandins, reproductive age, nonsteroidal anti-inflammatory drugs.

INTRODUCTION

Dysmenorrhea is a Greek word, Dys means ''difficult,'' ''painful,'' or ''abnormal.'' Meno is ''month'', and rrheais''flow,'' meaning difficult monthly flow. [1,2] It means cramping pain accompanying menstruation. [3] The main mechanism thought to underlie dysmenorrhea, regardless of concurrent presence of endometriosis/adenomyosis, is uterine myometrial hyper contractility and vasoconstriction-either within the uterus itself or in menstrual fluid or peripheral blood are attributed to alterations in uterine physiology.[4] Menstruation is considered as a landmark of homeostatic condition of reproductive system. As it is observed in cases of dysmenorrhea, the same physiological condition of menstruation creates an awful situation if it is accompanied by excruciating pain. Though dysmenorrhea literally means painful menstruation, a more realistic and practical definition includes painful menstruation of sufficient magnitude so as to incapacitate day to day activities.[5] The term primary dysmenorrhea (PD) is described as cyclic menstrual pain without any identifiable associated pathology, whereas secondary dysmenorrhea frequently complicate endometriosis, leiomyomas, PID, adenomyosis, endometrial polyp and menstrual outlet obstruction, [6] and typically starts soon after menarche.[7] Characteristic symptom in PD are cramps, colicky spasms of pain in the suprapubic area, occurring within 8–72 hours of menstruation and peaking within the first few days as menstrual flow increases. Many women with primary dysmenorrhea also suffer from headaches, diarrhoea, nausea, vomiting, and back and thigh pain in addition to excruciating cramps.Excess production and release of prostaglandins during menstruation by the endometrium cause hyper contractility of the uterus leading to uterine hypoxia and ischemia, which are believed to cause pain and cramps.[8] It has been demonstrated that secretory endometrium contains more prostaglandins than proliferative endometrium. Increased level of prostaglandins E_2 are seen in these patients and may increase the sensitivity of the nerve

endings to pain.[9] Both the local and systemic symptoms are apparently as a result of increased level of prostaglandins (F2α) in the menstrual fluid. This results in nausea, vomiting, backache, diarrhea, giddiness, syncope and fainting in addition to cramping.[10]

Historical background: The term "dysmenorrhea" was first used by the Greeks, who described it as "painful menstrual flow." 11. Although the term "dysmenorrhea" only entered the English language around 1810, it has been used throughout history and is as old as medicine. The Kahun Papyrus (1850 B.C) is probably the first textbook of Gynaecology, deals lower abdominal pain with swelling and offers their treatment. In Ebers Papyrus, a condition is mentioned that sounds like dysmenorrhea.[12] The Kahun Papyrus of about 1900 B.C. suggested that for relief bandaging of the abdomen with a mixture of crushed onion and pine sawdust was helpful. The Ebers Papyrus of a somewhat later date contained a prescription for alleviating menstrual pain. The nineteenth century saw the beginnings of clinical investigation. Most likely, the idea that dysmenorrhea was caused by mechanical obstruction was first put forth by McIntosh in 1832. Marion Sims established the adage, "Null, dysmenorrhea nisi obstructive". In 1903 Schultz presented his hypoplasia theory. He hypothesised that the impaction of blood in the uterine sinuses, followed by pressure pain due to a lack of muscles to push the blood out, was the source of the pain. The inadequate musculature was a sign of an infantile uterus and incomplete development. This launched a wave of therapy by oestrogens for all patients, no matter the size, shape, or position of' their uteri. Since that time there has been a trend toward the explanation of' dysmenorrhea in terms of' mechanisms rather than nomenclatures. The data available, however, make it possible to outline a scheme showing how a number of factors may contribute the development of' dysmenorrhea.[13] According to Hippocrates, *usre al-tamth* occurs due to stagnation of menstrual blood secondary to cervical obstruction and causes painful menstrual period. Abu Ali Husain bin Abdullah bin Sina claims that *usre al-tamth* is caused by a blockage in the menstrual blood flow. He also described that if the menstrual blood is balanced in quality and quantity, the cycle is regular.[2]

Prevalence: Statements in the literature on the prevalence of dysmenorrhea differ notably. With estimates ranging from 67% to 90% for those aged 17–24, a higher prevalence was generally seen in young women. Menstrual pain was reported by a higher percentage of teenagers (93%), according to a recent Australian study of girls in their senior year of high school. With prevalence rates ranging from 15% to 75%, studies on adult women are less reliable in describing the condition's prevalence and frequently concentrate on a particular demography. Severe pain sufficient to limit daily activities is considerably less common, affecting approximately 7%–15% of women although a study of adolescents and young adults aged 26 years or less reported that 41% of the participants had limitations in their daily activities due to dysmenorrhea. [14] Of all women, 10% to 15% are unable to function because of pain; 90% have discomfort with at least one cycle. [6] The prevalence of dysmenorrhea was reported to be 65% in India (Kumbhar et al., 2011), 76% in Malaysia (Wong, 2011), and 60% in Canada (Burnett et al., 2005). Menstrual issues are very common in teenage girls, according to a study done on students in Dammam, Saudi Arabia (Rafique, Al-Sheikh, 2018).[15] Because of the different definitions and the methods of assessment, studies conducted in menstruating women have shown that the prevalence of PD varies from 45% to 95%.[16]A systematic review conducted by the World Health Organization (WHO) in 2006 found the prevalence of menstrual pain in reproductive-aged women to be between 17% and 81%.[17]

Etiology: The etiology of primary dysmenorrhea has been the source of considerable debate. Until quite recently, many medical and gynaecological texts ascribed the source of primary dysmenorrhea as emotional or psychological problems. Dysmenorrhea was attributed to a variety of causes such as anxiety, emotional instability, a faulty outlook on sex and menstruation, or imitation of the mother's feelings about menstruation (Jeffcoate 1975). Psychoanalytic concepts like rejecting the feminine role or not being able to conceive leading to a frustrated "crying" uterus have also been linked to it (Ylikorkala 1978). Vasopressin, a hormone that also promotes the contraction of muscle tissue, and uterine prostaglandins, which are linked to uterine contractions (Rosenwaks 1980), are two physiological causes of dysmenorrhea that have been found through experimental and clinical research (Stromberg 1984). [18]

Etiological factors:

The Psychic Factor: The majority of women are less physically efficient and more emotionally unstable just before and during their periods, which alone lowers their pain threshold. Dysmenorrhea may even be an excuse to avoid doing something which is disliked. The expectation of pain may be fostered by over anxious parents and by curtailment of normal activities during menstruation. [19] "Every visceral function is subjected to influences exerted by the psyche and emotional states through the autonomic and endocrine systems" (Kunz 1934). Novak and Harnik (1929) categorically state that all occurrences of dysmenorrhea can be explained by psychogenic factors. Their investigations indicate that psychic trauma, usually sexual, always lies at the bottom of the first attack of dysmenorrhea, and that the recurrent monthly attacks are a result of anxiety and fear. In a study of the menstrual function in psychotic patients, Allen (1935) found that specific types of menstrual disorders are associated with the various psychoses, and that psychoneurotics invariably showed severe dysmenorrhea.[13]

Constitution, threshold, exercise and posture: Miller (1934) found that women whose menses were painless were on the average taller and showed more pronounced breast development than dysmenorrheic group. Menstruation is generally more painful in the asthenic type, according to Kapur (1940). According to Goldwasser (1938), a significant fraction of the dysmenorrhea group consisted of constitutional inferiors. Julius Bauer (1942) wrote dogmatically that primary dysmenorrhea is almost invariably a symptom of a neuropathic constitution, usually associated with signs of infantilism and asthenia. The association of faulty posture, poor muscle tone, and painful menstruation has been stressed by many authors. (Clo1927; Flulman, 1939J Goldwasser, 1938; Mazer, 1~40; Miller, 1930.) This relationship has led to many attempts towards the alleviation of dysmenorrhea by posture correction and exercise. Fluhman (1940) pointed out that the attention to rules of rest and hygiene is probably the significant factor. With improvement of general health through proper rest, sleep, and diet as well as exercise, there will undoubtedly be better posture, muscle tone, as well as increased resistance to pain.[13]

Obstruction and contraction: The similarity of menstrual cramps to labor pains has been responsible for a generalized assumption that uterine contractions were responsible for both. Kolisher wrote in 1909 that by bimanual examination he could feel colonic contractions of the uterus in patients with dysmenorrhea. He maintained that in these patients, blood could be seen coming out of the cervix in jets, unlike the continuous flow in normal women.

The endocrine picture: Several factors must be considered in answering this question. Obviously the musculature must be strong enough to produce the high tension. Lack of muscular tone is probably one reason why the stretched muscles of multipara do not frequently produce dysmenorrhea. The relationships of the endocrine glands, and the ratios of their secretions are of undoubted significance in the production of uterine contractions. The relief of dysmenorrhea by many different hormone preparations can be explained based on these facts.[13,19] Primary dysmenorrhea cases have been linked to uterine myometrial hyperactivity and higher concentrations of platelet activating factor (PAF.) Leukotrienes and PAFs are vasoconstrictors and stimulate myometrial contractions.[20]

Cytokines and other pro-inflammatory factors as inflammatory mediators in primary dysmenorrhea: Activated macrophages produce proinflammatory cytokines TNFα, IL1, IL6, etc. responsible for upregulating inflammatory responses. IL6 is a pleiotropic cytokine with multi-directional effects on the cells of the innate and acquired immunity system. A pleiotropic cytokine, IL6 affects both innate and acquired immune system cells in several ways. IL6's primary functions include triggering and controlling the acute inflammatory response as well as aiding in the formation and targeting of the acquired response. There is limited research that suggests VEGF plays a role in endometriosis-related dysmenorrhea in patients. The most potent factor known to affect ovarian endometriomas, the menstrual cycle, and embryonic development is VEGF.

C - reactive protein (CRP) in the menstrual cycle; CRP is a clinically recognized acute phase protein. It is thought that a healthy person's normal CRP concentration shouldn't be higher than 3 mg/L. Research on adult females has demonstrated that elevated CRP levels varied greatly during the menstrual cycle. CRP peaked during the menstrual cycle, dropped during the follicular phase, peaked on the day of expected ovulation, and increased during the luteal phase.[21]

Risk factors: When other factors are removed, primary dysmenorrhea equally affects women

regardless of race and socioeconomic status. However, increased pain duration or severity is positively associated with earlier age at menarche, long menstrual periods, smoking, and increased body mass index (BMI). In contrast, parity appears to improve symptoms. [7] Numerous studies in the current body of literature have demonstrated that PD may be associated with a variety of risk factors, such as biological, psychological, social, and lifestyle factors. A family history of dysmenorrhea, a younger age at menarche, and a heavier menstrual flow are examples of biological factors while as stress, anxiety, and depression are examples of psychological factors. A lower level of social support and lifestyle factors include cigarette smoking and irregular diet. [16] Age younger than 30 years, body mass index less than 20 kg/m^2, earlier menarche (younger than 12 years), longer cycles, heavy menstrual flow and history of sexual abuse increase the risk of primary dysmenorrhea. Nulliparity and premenstrual syndrome are also associated with the disorder.[22]

These risk factors for primary dysmenorrhea can be divided in two categories;

- Non-modifiable risk factors include:
- Family history of dysmenorrhea
- Less than 20 years old (symptoms worsen in adolescence)
- Menarche prior to age 12 years (because ovulatory cycles begin early)
- More than seven days of menstrual bleeding
- Nuliparity: The association between multiparity and decreased risk of dysmenorrhea can be explained by several assumptions such as, lower release of prostaglandins by the endometrium after a child birth, decreased uterine norepinephrine during the 3rd trimester of pregnancy, as well as neuronal degeneration that takes place in the uterus following a term delivery.[23]
- Behavioral or modifiable risk factors include:
- < 20 or > 30 Body mass index
- Low intake of omega 3 (fish) fatty acids
- Smoking (nicotine induces vasoconstriction)
- Caffeine consumption (also induces vasoconstriction)
- Primary dysmenorrhea can favourably be impacted by psychosocial symptoms like anxiety, depression, and a tense relationship with parents.[23]

Pathophysiology of pain: As a defence mechanism that our body has permanently incorporated into its system, pain has been thought of as a sensation that we experience in response to environmental stimuli that put us in danger. Pain is a human primate instinct and can be defined as a distressing sensation, as well as an emotional experience that is linked to actual or potential tissue damage, with the sole intention to alert the body's defence system to respond to a stimulus in order to prevent additional tissue damage. Three fundamental processes take place in the basic pain mechanism when noxious stimuli are present: transduction, transmission, and modulation. Transduction, for example, proceeds in the following order along the nociceptive pathway: (1) Chemical tissue events are derived from stimulus events, (2) chemical tissue and synaptic cleft events are subsequently changed into electrical events in the neurons and (3) electrical events in the neurons are transduced as chemical events at the synapse.[24] Pathophysiologically, prostaglandins are implicated in dysmenorrhea. With the commencement of menstruation, endometrial sloughing takes place triggering the endometrial cells to release prostaglandins. Prostaglandins stimulate myometrial contractions and ischemia. Women with more severe dysmenorrhea have higher levels of prostaglandins in menstrual fluid, and these levels are highest during the first 2 days of menstruation. Prostaglandins are also implicated in secondary dysmenorrhea. However, anatomic mechanisms are also suspected, depending on the type of accompanying pelvic disease. [7] Increased production of prostaglandin F2α (PGF 2α) resulting in increased uterine contractions (dysrhythmic) and markedly elevated intrauterine pressures (up to 400 mm Hg); possible increased sensitivity to PGF2α as well.[6] Prostaglandins might contribute to the synthesis of additional growth factors and chemokines that are involved in the inflammatory response or in the menstrual cycle's healing process. Neutrophils and leukocytes may migrate into the endometrium more readily when prostaglandins are present. The myometrium produces PGF2α and PGE2, which are involved in the synthesis of numerous other proteins, including cytokines. The pituitary gland secretes the hormone vasopressin, which is triggered by periodic fluctuations in the amount of estradiol in the body. Vasopressin levels are lower during the follicular phase and rise during ovulation. Vasopressin has the potential to cause ischaemia and dysmenorrhea by increasing uterine contractile activity and decreasing

blood flow through the uterus. [21] These compounds are found in higher concentrations in secretory endometrium than in proliferative endometrium. Late luteal phase progesterone decline causes lytic enzymatic action, which releases phospholipids and activates the cyclooxygenase (COX) pathway while generating arachidonic acid. Dysmenorrhea is caused by high-amplitude contractions and a higher uterine tone in women who have primary dysmenorrhea due to increased prostanoids synthesis. It is theorized that women suffering from dysmenorrhea have upregulated COX enzyme activity and prostanoid synthase activity. This leads to the therapeutic use of nonsteroidal anti-inflammatory drugs (NSAIDs), which act as COX enzyme inhibitors. [24]

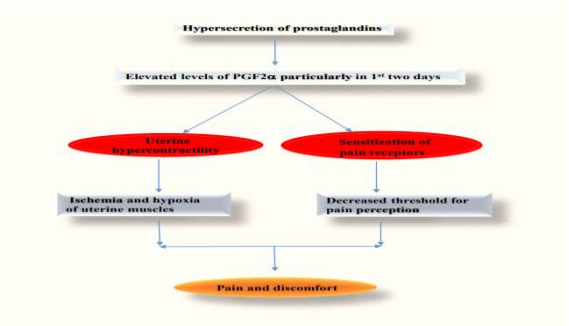

Fig5: Pathology of primary dysmenorrhea [26]

Progesterone levels stabilise cellular lysosomes during ovulation, but they decrease at the end of the luteal phase, causing lysosome damage and the release of phospholipase A2 (PLA2). PLA2 initiates the cyclooxygenase pathway with resultant prostanoid production. This clarifies the correlation between the onset of pain of dysmenorrhea and only in ovulatory cycles. [27]

Significant changes in brain connectivity and structure have been observed in women with primary dysmenorrhea (PDM) in recent studies. Dysmenorrheic women had larger grey matter volumes in areas linked to endocrine regulation and pain modulation, while smaller volumes were found in areas linked to pain transmission and sensory processing, according to a 2010 study by Tu et al. [28,29]. The orbitofrontal cortex and insula were among the brain regions where Liu et al. (2016) observed increased cortical thickness; however, the amygdala, thalamus, and caudate showed decreased volumes.[28,30] Additionally, PDM patients showed reduced grey matter density in the left anterior insula, suggesting more profound structural alterations.[28] These structural changes correlate with the severity of menstrual pain, underscoring the complex interplay between brain structure and function in PDM.[28,30] The connection between pain perception and the anterior cingulate cortex (ACC) in women with primary dysmenorrhea (PDM) reveals significant abnormalities in brain connectivity. Research identifies three main subdivisions of the default mode network (DMN): the ventral medial prefrontal cortex (mPFC), dorsal mPFC, and posterior cingulate cortex, which are crucial for sensory modulation and pain regulation. PDM patients exhibit dynamic changes in regional brain activity throughout the menstrual cycle. Notably, during the periovulatory phase, there is decreased homogeneity in the DMN's ventromedial prefrontal cortex, alongside hyperconnectivity within both the DMN-salience and DMN-executive control networks. This suggests a shift from pain severity to cognitive modulation in PDM women as their menstrual cycle progresses. Additionally, altered connectivity patterns are observed: reduced precuneus connectivity with the left dmPFC and right ACC, contrasted by increased connectivity with the left thalamus. A positive correlation exists between the amplitude of low-frequency fluctuations (ALFF) in the left dmPFC and PDM duration. Further findings indicate adaptive hyperconnectivity in the periaqueductal grey (PAG) during painful menstruation, while hypoconnectivity occurs in the dorsolateral prefrontal cortex and DMN during both menstruation and periovulatory phases. This maladaptive pain modulation may increase vulnerability to other disorders later in life. Young women with PDM also show heightened theta oscillations in various brain regions during different menstrual phases, highlighting complex neurophysiological changes.[29]

Clinical features: In general primary dysmenorrhea appears 6–12 months after the menarche when ovulatory cycles begin to become established. The early cycles after the menarche are usually an ovular and tend to be painless. Backache and lower abdomen cramps are the most common forms of the discomfort, while vomiting and diarrhoea may be related gastrointestinal issues. The first two days of menstruation are when symptoms are most common.[1,20] Some women may notice water retention, changes in sex drive, fatigue, breast tenderness. Swelling and discomfort of the breast, known as mastalgia may also be caused by water retention during menstruation. Some women experience emotional disturbances starting one or just a few days prior to their period and stopping soon

after the period has started. [31] The pain is similar to labour, with suprapubic cramping, and may be accompanied by lumbosacral backache, pain radiating down the anterior thigh and rarely syncopal episodes. The pain of dysmenorrhea is colicky in nature and, unlike abdominal pain that is due to chemical or infectious peritonitis, is relieved by abdominal massage, counter-pressure or movement of the body.[25]

Classic symptoms of primary dysmenorrhea:

1. Within a few months or two years of menarche, menstrual pain started.
2. Pain starts right before menstruation or at onset of menstruation
3. Pain is lower abdominal and can radiate to back, inner thighs, or both
4. Pain rarely lasts longer than 72 hours.
5. Pain is episodic and crampy in nature
6. Pain is similar from one menstrual cycle to the next
7. Additional symptoms: fatigue, headaches, dizziness, and sleep disturbances.[32]

Diagnosis of primary dysmenorrhea: In order to evaluate a menstrual pain subject properly, a thorough clinical history and physical examination is recommended. Pelvic disease should also be ruled out. The menstrual history (age at menarche, regularity, duration of cycles, amount of flow, time between menarche and onset of dysmenorrhea), the family history of dysmenorrhea, sexual history, pain characterization (type, location, irradiation, associated symptoms, chronology), and system review (gastrointestinal, genitourinary, musculoskeletal, and psychosocial) should all be included in the clinical history. Adolescents who are sexually active, women who have severe pain or limited activity, and those whose conditions do not improve with first- or second-line therapy should all have pelvic exams. While an abdominal examination, to exclude other diseases, is recommended in adolescents who are not sexually active and do not have a history of systemic disease but are typical of primary dysmenorrhea, a pelvic examination is not required.[23]

Other conditions simulating dysmenorrhea:

Menstrual pain of ovarian origin (corpus luteum hematoma); A comparatively rare and isolated accident is haemorrhage into and from the corpus luteum. This can happen on its own, but it can also be triggered by physical activity, abrupt cooling of the body surface, and direct injury that might occur during coitus.

Ovulation Pain: Mid-cycle pain (Mittelschmerz) is present from time to time during the menstrual life of almost 50% of women, although it is often not recognized for what it is. The discomfort appears between the l0th and 15th days, is experienced in the hypogastrium or in one or other iliac fossa, and is occasionally referred to the rectum. It varies in severity but rarely lasts longer than 12-24 hours. It is sometimes accompanied by ovulation bleeding and may be present in 1 month and not in another.

Orthopedic conditions simulating dysmenorrhea: Many women alleged to have dysmenorrhea indicate (if asked) that their pain takes the form of a low backache during the premenstrual phase. This symptom often dates from pregnancy. Yet careful inquiry reveals that the pain commenced during pregnancy, or that it dates from an injury or strain during the puerperium.[19]

Other causes of lower abdominal pain:

Gynecologic; PID, Tubo-ovarian abscess, ectopic pregnancy, incomplete abortion, prolapsing leiomyoma, mittelschmerz, ovarian mass, ovarian torsion, obstructed outflow tract

Gastrointestinal; Gastroenteritis, colitis, appendicitis, diverticulitis, constipation, inflammatory bowel disease, irritable bowel disease, obstructed small bowel, mesenteric ischemia, malignancy

Urologic; Cystitis, pyelonephritis, urinary tract stone, perinephric abscess.

Musculoskeletal; Hernia, abdominal wall trauma

Miscellaneous; Peritonitis, diabetic ketoacidosis, herpes zoster, opiate withdrawal, sickle cell crisis, vasculitis, abdominal aortic aneurysm rupture.[7]

Impact of dysmenorrhea: Pain costs the healthcare system a lot of investments because it requires ongoing rehabilitation for patients who experience unpleasant pain, which may lower their quality of life and decrease their productivity at work, slowing down the growth of our economy.[24] Females form the backbone of the society and particularly doctors hold enormous responsibilities. Dysmenorrhea which is a common problem that ails the females every month cyclically with pain in the lower abdomen and pelvis,

affective and somatic features often limit their output and result in their absence from educational institutions. Current central Government's main thrust is to improve the economy of the country and there is an effort to tap the potential of young population and their skill development. Female population receives the maximum attention in this regard. Govt. has come up with many policies like "Beti Padao" to generate more employment for females.[33] Quality of life is imminently reduced in primary dysmenorrhea. It affects social interactions, friendships, family ties, and athletic endeavours. It also frequently results in decreased academic achievements and causes absenteeism from work, school, or university. A negative impact of primary dysmenorrhea is observed on many aspects of academic performance which include class attendance, homework, writing, exam passing and grades, but according to some studies, concentration in class is most affected.[34]

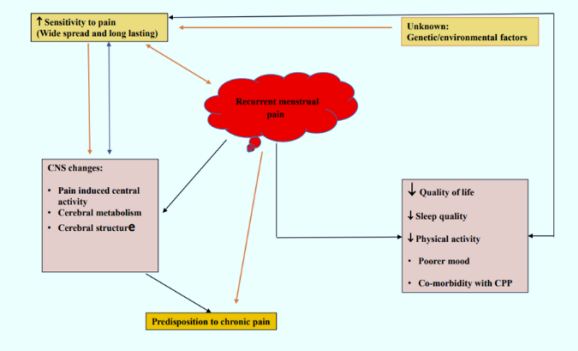

Fig6: Schematic representation of the proposed (red lines) and known (black lines) effects of recurrent dysmenorrheic pain, as well as the interrelationships of these effects.[35]

According to an Indian study, 31.67% of female medical students with dysmenorrhea and 8.68% of them missed a lot of classes and college. [36] Dysmenorrhea puts a significant financial and social strain on families, communities, and the world at large when it is left untreated. [37] According to estimates, dysmenorrhea costs the US economy two billion dollars, or 600 million work hours. The total cost of healthcare for patients with primary dysmenorrhea in Japan is 2.2 times greater than the total cost of healthcare for female patients without dysmenorrhea after adjusting for baseline characteristics.[38,39]

Secondary dysmenorrhea: Menstrual discomfort resulting from an underlying pathological condition, or structural deformity inside or outside the uterus is known as secondary dysmenorrhea.[40]

Table4: Differentiating features of primary and secondary dysmenorrhea.[3]

Differentiating features	Primary	Secondary
Onset	Within 2 years of menarche	20-30 years, may be pre and post-menopausal
Description	Cramping-hypogastrium, back, inner thigs	Variable dull ache
Symptomatology	Nausea, vomiting, diarrhoea, headache, fatigue	Dyspareunia, infertility, menstrual disorders
Pelvic findings	Normal	Variable depending on cause
Etiology	Excessive myometrial contractions and prostaglandin production, ischemia	Endometriosis, PID, adenomyosis, fibroids, pelvic vein congestion
Management	Reassurance, analgesics, NSAIDs, antispasmodics, OC pills, surgery (rarely).	Treatment directed as per the cause

Differential diagnosis between primary and secondary dysmenorrhea:

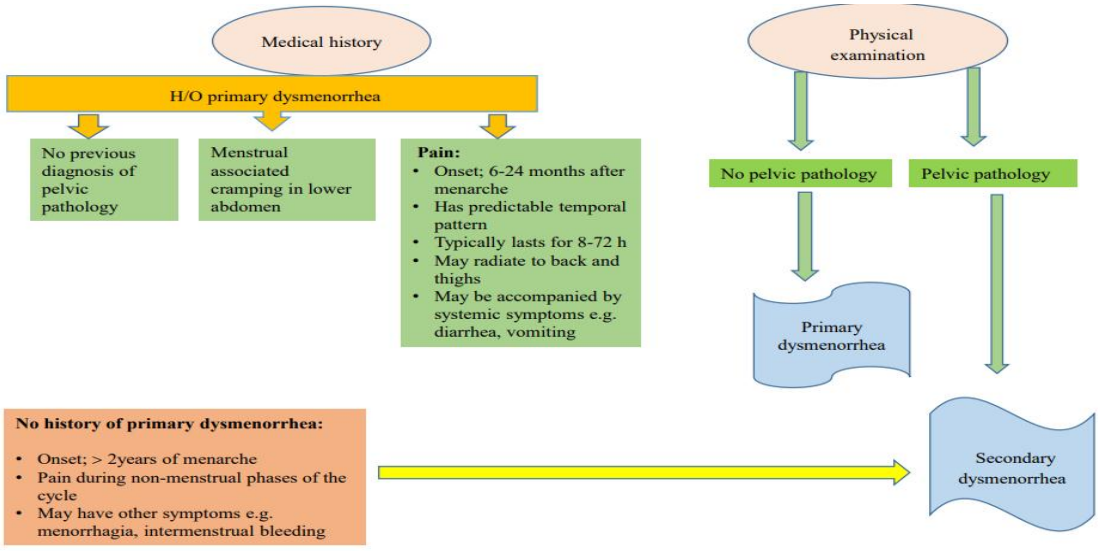

Fig9: A diagnostic flow diagram for the differential diagnosis of primary and secondary dysmenorrhea.[35]

Management options for primary dysmenorrhea: [41,42]
The foremost targeted goal in the management of primary dysmenorrhea is the reduction of reported pain and relief from the associated systemic symptoms, as well as improved function by way of minimizing the absence from school, work and extracurricular activities. [17]
Primary dysmenorrhea can be managed in three ways:

- Pharmacological
- Non- pharmacological
- Surgical

Pharmacological: The pharmacological approach to treatment has been more thoroughly documented for its efficacy compared to other methods, which show more inconsistent evidence. In evaluating treatment efficacy, it is critically important to consider not only the relief of pain but also the primary outcome index (is it pain or something else) being evaluated, the duration of pain relief, rapidity of onset of pain relief, the point at which pain relief peaks, and secondary outcome indices (like the relief of related symptoms, functionality as measured by reduction in absenteeism, and qualitative improvement in performance.) [41]

NSAIDS; Non-steroidal anti-inflammatory drugs (NSAIDs) are considered the first line treatment. They work by inhibiting the activity of cyclooxygenase (COX) enzymes which results in decreased prostaglandin production, decreased prostaglandin concentration in menstrual fluid, decreased uterine contractility and menstrual volume.[27] Therefore, NSAIDs are recommended as the first line therapy in females who prefer using analgesics or when contraceptives are contraindicate. There is no targeted superiority of one NSAID formulation over the other, but few of them have comparable efficacy and safety in managing PD. The effectiveness of any NSAID is predicted when it is administered. NSAIDs should be started one to two in anticipation of menstruation, taken with meals to minimize negative gastrointestinal effects, and for the best possible treatment efficacy and safety with a regular dosing regimen, and continued throughout the first 2 to 3 days of bleeding. [43]

Selective COX-2 inhibitors; It is said that the therapeutic efficacy of NSAIDs is primarily the result of cyclooxygenase-2 (COX-2) inhibition, whereas their well-recognized gastrointestinal toxicity and disruption of platelet function is obtained by suppressing the activity of cyclooxygenase-1 (COX-1). Therefore, COX-3 inhibitors have better tolerability compared with non-selective COX inhibitors. Hence, this class of medicines are the first-line treatment for the relief of pain (Evidence levelI-A.) [44] Rofecoxib and valdecoxib have been withdrawn from the market because of cardiovascular concerns (rofecoxib, valdecoxib) and potentially life threatening skin reactions (valdecoxib.)[45] Despite a decreased incidence of GI side effects with COX-2 inhibitors, their use by patients with active GI ulcers, infection with Helicobacter pylori, or inflammatory bowel disease has not been adequately studied. Contraindications for COX 2 inhibitors include aspirin-sensitive

asthma, ulcers, significant renal impairment, or inflammatory bowel disease.[46]

Hormonal suppression; Combined oral contraceptive pills have been shown to be effective in relieving primary dysmenorrhea by high quality evidence in a Cochrane review as well as being recommended by RCOG and SOGC (Society of Obstetricians and Gynaecologists of Canada). The low dose OCP preparations with doses less than 35 mcg should be the preferred preparation since there is no benefit to one generation or higher dose pills. COCs with 20 mg of ethinylestradiol are less recommended since they increase the risk of unexpected bleeding. Because ovarian suppression causes endometrial thinning, the volume of menstrual fluid and prostaglandin levels are lowered. This result reduces myometrial contractions during menses. Ovarian suppression to treat dysmenorrhea can be trialed for 3-6 months in women with cyclical pain. Progesterone-only medications like desogestrel 75 mcg, depo provera, nexplanon subdermal implant, and levonorgestrel-releasing intrauterine system (LNG-IUS, Mirena) can also be used to suppress hormones. Desogestrel 75 mcg can induce amenorrhea in 10% of its users, more than other progesterone only pills, and can reduce dysmenorrhea.[47]

OCPs are commonly used to treat heavy menstrual bleeding and irregular bleeding besides being used as contraceptives. Regardless of how they are taken, oral contraceptives work well to treat dysmenorrhea because they prevent ovulation, which lowers the amount of prostaglandins produced by the endometrial glands. Because anovulatory cycles have lower levels of prostaglandin, oral contraceptives (OCs) have been used to suppress ovulation and ease menstrual pain. Hormonal therapies should be offered to females who are not currently planning pregnancy unless contraindications exist. OCPs have the dual benefits of treating the comorbid menstrual disorder and reducing menstrual pain when taken continuously by patients with primary dysmenorrhea. [46]

Glyceryl trinitrate; Because nitric oxide produces smooth muscle relaxation, medications that increase levels of nitric oxide may reduce the pathologic uterine contractions responsible for dysmenorrhea. In addition, there is reduced nitric oxide production when progesterone levels decrease. However, up to a quarter of patients treated with glyceryl trinitrate experienced treatment limiting headaches, so this medication is typically not a first-line treatment option for menstrual pain. [32]

Magnesium; Magnesium, like calcium, is important for the membrane fixation mechanism and can influence synapses via mechanisms that rely on calcium. Reductions in magnesium levels increase synaptic transmission, resulting in myometric muscle contractions and, consequently, dysmenorrhea. By lowering prostaglandin synthesis and the spasticity of small muscles and vessels, foods high in magnesium can lessen the severity of dysmenorrhea. As eggs contain calcium and magnesium, they can help prevent dysmenorrhea.[48] several studies have shown that magnesium provides pain relief superior to placebo, but formulations and dosages varied widely among the studies. Inadequate information is currently available to solely recommend magnesium therapy. [32]

Vitamin D; Vitamin D receptors (VDRs) are distributed in the ovary and uterus, so vitamin D has an active role in female reproductive system. Additionally, its receptor is important for controlling steroid hormones in the female reproductive system. According to studies, ovarian function and menstrual cycle regulation are positively impacted by a sufficient serum level of vitamin D. Vitamin D may benefit dysmenorrhea through a number of different mechanisms. In the endometrium, 1,25-dihydroxyvitamin D (1,25[OH]2D), the bioactive form of vitamin D, decreases prostaglandin synthesis by suppressing expression of cyclooxygenase-2, and increases prostaglandin inactivation by upregulating 15-hydroxyprostaglandin dehydrogenase. In addition, 1, 25(OH) 2D down-regulates prostaglandin receptor expression. 1, 25(OH) 2D may also exert anti-inflammatory effects through other pathways.[49]

Vitamin E; The antioxidant vitamin E prevents the peroxidation of phospholipids, the release of arachidonic acid and hence its conversion to prostaglandin, as suppression of prostaglandin synthesis has become the main treatment of primary dysmenorrhea.[50]

Effect of diet; Nutritional deficiencies are the most important factors that disrupt the hypothalamic-pituitary-ovarian axis. The nutritional status influences sexual steroids and hormone levels are altered because of less energy from inadequate nutrition. This discovery aligns with the outcomes of

contemporary research that suggests the impact of fish oil on primary dysmenorrhea. Fish oil inhibits the prostaglandins synthesis through its main mechanism of action. Increased consumption of dietary omega-3 fatty acids allows them to pass through the phospholipid membrane. Omega-3 and omega-6 fatty acids compete with one another during menstruation to produce leukotriene and prostaglandins. The synthesis of prostaglandin is a result of arachidonic acid found in animal fats, particularly meat. Less powerful prostaglandins derived from omega-3 fatty acids can lessen the myometrial and vascular contraction. Fruits and vegetables are abundant containing sources of vitamins and antioxidants. Consequently, it was established by combining these data with research on vitamin plasma levels that women experiencing dysmenorrhea consumed fewer fruits and vegetables and had lower vitamin plasma levels. Dietary antioxidants include vitamins, minerals, zinc, and beta-carotene. Instead of using non-steroidal anti-inflammatory drugs during the painful periods, women are advised to use natural antioxidants such as vitamin E, vitamin C, and β-carotenoids for the reduction of pain.[48]

Herbs; Herbs with *musakkin* (analgesic), *dafi'-i-tashannuj* (antispasmodic), *mudirr-i-hayd wa mudirr-i-bawl* (emmenagogue and diuretic) properties are useful for pain relief and to increase the menstrual flow. *Mudirr-i-hayd* drugs have *harr*, *mulattif*, and *mufatteh* properties, and fluidizes blood to induce smooth blood flow, dilates the uterine blood vessel, and increases blood circulation in uterine vessels, rectifies the functional defect of the uterus, and consequently makes the blood flow easily through vessels and induces increased menstrual flow and relieves the pain. Some herbs such as *zanjabeel (Zingiber officinale* Roscoe), *saunf (Foeniculum vulgare* Mill), *gul surk (Rosa damascena* Herrm), *zeera safaid (Cuminum cyminum* Linn), *baboona (Matricaria chamomilla* L), *satar farsi (Thymus vulgaris* L), *Noni (Morinda citrifolia* L), *sowa (Anethum graveolens* L), *hulba (Trigonella foenum-graecum* L), combination of *anisoon* or *saunf*, *zafran*, *chaturbeeja* (*Trigonella Foenum-graceum* L, *Lepidium sativum, Nigella sativa* L, *Trachyspermum ammi*), *hilteet (Ferula assafoetida* L), are proven for their efficacy in dysmenorrhea.[51]

Non-pharmacologic: [42]

Behavioral Interventions: The behavioral approach assumes that psychological and environmental factors interact with and influence physiological processes. Research has demonstrated that life stress can influence dysmenorrhea, which lends some evidence to the behavioral approach for this type of disorder (Marini 1978; Siegel 1979). A variety of interventions are labelled as behavioral, and it is difficult to provide a single definition. Behavioral interventions are primarily aimed at modifying an individual's behavior but can also be aimed at modifying thoughts or cognitions to subsequently change behavior. Behavioral interventions for dysmenorrhea may include both physical and cognitive procedures such as biofeedback, desensitization-based procedures, Lamaze exercises, hypnotherapy, and relaxation training (Denny 1981; Lewis 1983). These kinds of interventions do not alter any underlying organic pathology; instead, they concentrate on psychological and physical coping mechanisms for dysmenorrhea symptoms.[18]

Exercise: Exercise increases the endorphins and serotonin (natural painkillers) levels. Exercise during menstruation to get rid of menstrual pain.

- Cure menstrual cramps with simple and not too heavy exercises as the uterus is weak during menstruation.
- Doing mild exercises like stretching, walking, or biking- exercise may improve blood flow and reduce pelvic pain.
- Walking for 30 minutes every day increases the endorphins level which provides relief.
- Slow running can help get rid of menstrual pain. Running three times in a week.
- Abdominal crunch exercise helps reduce menstrual cramps. Lie flat on the floor with hands on sides and lift the legs up few inches from the ground and then bend the knees. Now bring the knees and chin close to the chest and hold the position for 10 seconds. Relax and repeat 5 times.
- Butterfly stretching helps cure menstrual cramps. Sit on the floor with knees bent and spread on two sides and the soles joined together. Move the legs up and down in the same speed for a minute and then relax. Repeat for 2-3 minutes in the beginning.[5]

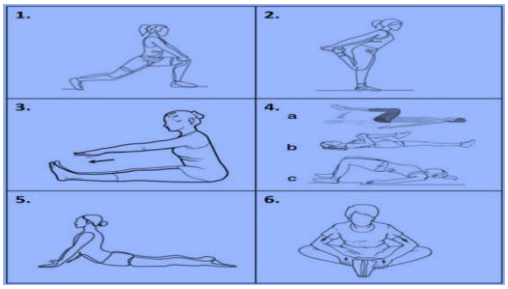

Fig11: Therapeutic procedures of stretching exercises
1. Iliopsoas stretch 2. Rectus femoris stretch 3. Hamstring stretch 4. Lower back muscle stretch (a) Lower back rotation stretch (b) Knee to chest (c) Bridge exercise 5. Lower abd. Muscle stretches 6. Abductor muscles stretch.[52]

Acupuncture treatment of primary dysmenorrhea: It is unclear exactly how acupuncture works to relieve menstrual pain. Three potential, non-exclusive mechanisms are supported by the available experimental data for its long-term effects on primary dysmenorrhea:
1) Descending pain modulation,
2) An increase in uterine blood flow via ovarian sympathetic nerve reflex
3) A change in prostaglandin levels.

Nonetheless, a great deal of research has been done to determine the mechanisms through which acupuncture may reduce pain, and the most recent findings indicate that endogenous opioids, dopaminergic neurotransmitter modulation, and anti-inflammatory effects mediated via the hypothalamus–pituitary–adrenal (HPA) axis may all play a role.[53]

Acupressure; Benefits of acupressure
- Relieving pain
- Balancing the body
- Maintaining good health
- The body can deeply relax through the acupressure's healing touch, which also improves circulation and lowers tension.
- By relieving stress, acupressure strengthens resistance to disease and promotes wellness.[54]

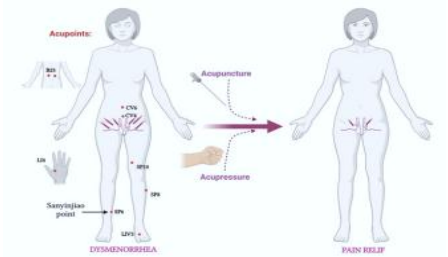

Fig. Common accupoints used in acupuncture and acupressure in relieving dysmenorrhic pain.[55]

Transcutaneous electrical nerve stimulation: Those women who suffer severely during the menstrual period and who do not want to take medication or who cannot take medication due to side effects, might benefit from the use of the non-pharmacological device, the TENS. In addition the TENS can serve as an adjuvant mode of treatment to the pharmacological agents in dysmenorrhea. The analgesia that is induced by the TENS can be explained by one of the three theories;
A) The gate control theory
B) The endorphin mediated pain relief theory
C) The diffuse noxious inhibitory controls theory

According to the gate control theory large diameter ‘A’ nerve fibers are being stimulated in specific dermatomes, a blockade or gating effect is established at the dorsal horn level of the spinal cord blocking the transmission of pain impulse further to the upper nervous system.

The endorphin mediated pain relief theory is based upon the fact that stimulus outside the CNS (like pain, physical effort) can increase the level of endogenous endorphins resulting in a potent analgesic effect. In the diffuse noxious inhibitory control theory, response of a small diameter afferent fiber groups, evoked through continuous pain input to convergent dorsal horn neurons, are suppressed effectively by noxious or intense cutaneous stimulation such a with TENS, but not by noxious stimuli.[56]

Topical heat: Superficial heat that ranges from 40–45 °C treats the application site to a depth of about 1 cm. Historically, menstrual pain has been reduced by applying superficial heat in a variety of ways (such as hot water bottles, towels, or bags). Deep heat induces vascular and metabolic alterations in deeper tissues and organs, even though deep heat techniques, like shortwave diathermy and microwave diathermy, target deeper structures at depths of 2-4 cm. Applying local heat to the affected area helps ease muscle tension and relax the abdominal muscles in women experiencing dysmenorrhea, thereby reducing pain from spasms. Heat can also increase pelvic blood circulation to eliminate local blood and body fluid retention and diminish congestion and swelling, thereby enabling a reduction in pain caused by nerve compression.[57]

Surgical or manipulative approaches: Surgery for primary dysmenorrhea is considered only when the pain is so severe as to be incapacitating, when medical treatment has failed, and when a significant psychological or pathological basis is excluded. Surgical or manipulative treatments are rare indications in PD and barely before the age of 18 years. Impending marriage and childbearing as well as the hazards, poor results of surgery, justify procrastination.[19]

Nerve ablation: Observational studies support the use of uterosacral nerve ablation and presacral neurectomy for primary dysmenorrhea. The cervical sensory pain fibers in the pelvic region are cut off by both surgical techniques. Laparoscopic uterosacral nerve ablation-resection was shown to be somewhat more effective than a placebo or no treatment at all, and long-term presacral neurectomy outperformed laparoscopic uterosacral nerve ablation by a significant margin.

Spinal manipulation: There is no evidence, according to a Cochrane analysis and its follow-up, that spinal manipulation is a useful treatment for primary dysmenorrhea. In four trials, manipulation at high velocity and low amplitude was found to be no more effective in treating dysmenorrhea than sham manipulation.[41]

Laparoscopy: If the patient has received adequate medical therapy over 4-6 cycles and has not shown satisfactory response, a diagnostic laparoscopy should be considered to rule out an pelvic lesions causing secondary dysmenorrhea and simultaneous treatment can be given if present.

Dilatation of the cervix: The objective of this operation is to stretch the fibromuscular tissue at the level of the internal os to such an extent as to render it hypotonic. Some believe that the adjacent nerve fibers are also damaged. Usually, a good deal of resistance is encountered during dilatation; if this is absent it means that case has been ill chosen and that a cure is unlikely. The dilatation proceeds gradually all the way to Hegar 10. The procedure can be extremely challenging and carries a genuine risk of cervix injury, which could lead to recurrent abortions in the future. Dilatation is rarely justified but may be done along with laparoscopy.

Presacral neurectomy: The suggested goals of this procedure are to enhance the uterine vascularity, block motor impulses that could be causing uterine spasm, and interrupt the sensory pathways from the uterus. The last is probably the main effect. Presacral neurectomy is never justifiable unless all the simpler procedures have failed.[19]

Hysterectomy: Hysterectomy may offer permanent relief who has pain confined to her menses, and therefore there is good evidence for excellent patient satisfaction following hysterectomy Pelvic pain should be carefully investigated prior to considering a hysterectomy. A hysterectomy may be necessary if the patient had completed the family and there is evidence of an underlying illness that can be treated with one.[7]

Other treatments in PD: Physiotherapeutic treatments, being supported by clinical trial data, could be a very useful treatment alternative for women with PD, particularly those who are not eligible pharmaceutical treatment, as the studies that were examined indicate that physiotherapy has no negative effects. Physiotherapy techniques in the treatment of PD include isometric exercises, massage therapy, yoga, electrotherapy, connective tissue manipulation, stretching, kinesio tape, progressive relaxation exercises and aerobic dance.[58]

Cupping therapy: Cupping therapy is a multifaceted therapy with multiple benefits for a range of conditions, such as pain management, paralysis, acne, and herpes zoster. In Egypt and other Arabic countries, cupping therapy is known as *'Al-Hijamal.*[2]

Discussion: A common condition in women throughout their adult lives, primary dysmenorrhea usually starts in adolescence and is remarkably frequently severe. Historically, the importance of dysmenorrhea has been downplayed by societal and clinical attitudes towards menstruation, which may have contributed to our current lack of knowledge about its mechanisms and limited treatment options. Menstruation as a "taboo" and a "curse" seem to be fading, thankfully, as more people realize that menstrual disorders in general, especially in teenagers should not be disregarded. In fact, new research shows that dysmenorrhea is a real and serious chronic pain disorder that can co-occur with other familiar chronic pains and is just as incapacitating. In fact, the etiology of those other unpleasant conditions and the related psychological, physiological, and quality-of-life dysfunctions that are more common in women may be largely attributed to dysmenorrhea. Usually, the pain is mild,

but for some women, the pain is so severe that it keeps them from doing their normal activities for several days a month. While its diagnosis is based on patients' history, symptoms, and physical examination, its treatment aims to improve the QOL through the administration of nonsteroidal anti-inflammatory drugs, hormonal contraceptives, and/or the use of non-pharmacological aids (e.g., topical heat application and exercise). Patients must be monitored to measure their response to treatment, assess their adherence, observe potential side effects, and perform further investigations, if needed. Medical and procedural treatments should be used appropriately to allow affected patients to perform their day-to-day activities without missing significant amounts of school or work. Patients should be counseled to follow up with their healthcare provider when dysmenorrheic symptoms are bothersome and not well-controlled. It is important to educate and create awareness among young patients regarding the importance of properly balanced and healthy nutrition for reducing the pain of dysmenorrhea. Some vitamins and healthy dietary modifications have been associated with reduced menstrual pain. Regular physical activity is effective in reducing dysmenorrhea. Exercise acts as a nonspecific analgesic by improving pelvic circulation and stimulating the release of β-endorphins.

CONCLUSION

Even though dysmenorrhea is a cyclical disorder and a recurring health issue, most women who suffer from it can avoid frequent absences from work or school if treatment strategies are implemented appropriately and at the right time.

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