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A REVIEW ON EVALUATION, MANAGEMENT AND PATHOPHISIOLOGY OF DYSMENORRHEA

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ABSTRACT

Menstrual cramps are throbbing or cramping pains in the lower abdomen. Many women experience menstrual cramps just before and during their menstrual periods. For some women, the discomfort is annoying can be severe enough to interfere with everyday activities for a few days every month. Dysmenorrhea is the most common gynecologic complaint among adolescent and young adult females. Dysmenorrhea in adolescents and young adults is usually primary (functional), and is associated with normal ovulatory cycles and with no pelvic pathology. In approximately 10% of adolescents and young adults with severe dysmenorrhea symptoms, pelvic abnormalities such as endometriosis or uterine anomalies may be found. Potent prostaglandins and potent leukotrienes play an important role in generating dysmenorrhea symptoms. Nonsteroidal anti-inflammatory drugs (NSAID) are the most common pharmacologic treatment for dysmenorrhea. Adolescents and young adults with symptoms that do not respond to treatment with NSAIDs for 3 menstrual periods should be offered combined estrogen/progestin oral contraceptive pills for 3 menstrual cycles. Adolescents and young adults with dysmenorrhea who do not respond to this treatment should be evaluated for secondary causes of dysmenorrhea. The care provider's role is to explain about pathophysiology of dysmenorrhea to every adolescent and young adult female, address any concern that the patient has about her menstrual period, and review effective treatment options for dysmenorrhea with the patient.

KEYWORDS: Primary dismenorrhoea, Age of menarche, daily activity steroidal anti-inflammatory drugs (NSIDS).

INTRODUCTION

Dysmenorrhea is a word derived from the Greek language dys (difficult, painful or abnormal), meno (month and rrhea (flow) it means a painful.

Menstrual cramps are throbbing or cramping pains in the lower abdomen. Many women experience menstrual cramps just before and during their menstrual periods. For some women, the discomfort is annoying can be severe enough to interfere with everyday activities for a few days every month.[1]

Dysmenorrhoea is defined as painful menstrual cramps of uterine origin. It is common gynecological condition that can affect as many as 50% of women 1. 10% of these women suffer severely enough to render them incapacitated for one to three days each menstrual cycle.[2] This situation not only has a significant effect on quality of life and personal health but also has a global economic impact.[3]

It has been proposed that the release of prostaglandins in the menstrual fluid leads to uterine contractions that give rise to the pain of dysmenorrhoea.[1,4] Being a common and significantly bothersome health problem, particularly affecting young women, dysmenorrhoea is a significant problem and worthy of study.

Two categories of dysmenorrhoea are defined, primary and secondary.

Primary is a menstrual pain without any organic pathology.[5] The initial onset of primary dysmenorrhoea is usually at or shortly after menarche, when ovulatory cycles are established. When the pelvic pain is associated with an identifiable pathological condition, such as endometriosis, ovarian cysts, pelvic inflammation, myomas or intrauterine devices it is considered to be secondary dysmenorrhoea. This category is more likely to occur years after the onset of menarche and can occur premenstrually as well as during menstruation.

Secondary dysmenorrhoea is a painful period due to an underlying condition. Secondary dysmenorrhea can be caused by[9]: from project.

- Endometriosis
- Ovarian cysts
- Pelvic inflammatory disease
- Infection of the female reproductive organs

- Uterine fibroids (noncancerous growths in the uterus)
- Intrauterine device
- Tumors
- Inflammatory bowel disease
- Scars inside the abdomen from previous surgery
- Tumors
- Inflammatory bowel disease

The prevalence of dysmenorrhea: The prevalence of dysmenorrhoea among young women varies widely from country to country. Studies of university students showed its prevalence to be 64% in Nigeria[6] and Mexico,[7] 84% in Thailand,[8] 88% in Turkey,[9] and 93% in Taiwan.[10] Studies of high school students also revealed diverse dysmenorrhoea prevalence rates, being 48% in Mexico,[11] 72% in Ethiopia,[12] and 93% in Australia.[13] In a local study on secondary school girls, its prevalence was 69%.[14]

Dysmenorrhea Symptoms and Risk Factors

While lower abdominal cramping is the most common dysmenorrhea symptom, many adolescents suffer from other menstruation-associated symptoms, such as headaches and vomiting (Fig. 1). Symptoms typically accompany the start of menstrual flow or occur within a few hours before or after onset, and last for the first 24e48 hours. Severity of dysmenorrhea symptoms positively correlates with early menarche and with increased duration and amount of menstrual flow.[15, 16] Low fish consumption correlated with dysmenorrhea severity in two studies.[16, 17] In addition, cigarette smoking may increase duration of dysmenorrhea, presumably because of nicotine induced vasoconstriction.[13] Premenstrual symptoms, which are more common starting in the third decade of life, are less common in adolescent girls and are often alleviated by adequate treatment of dysmenorrheal. The symptoms are

Cramps

Nausea

Vomiting

Loss of appetite

Headaches

Backaches

Legaches

Weakness

Dizziness

Diarrhea

Facial blemishes

Abdominal pain

Pathophysiology of dysmenorrhe

Advances in the last three decades and current understanding suggest that in primary dysmenorrhea there is abnormal and increased prostanoid and possibly eicosanoid secretion, which in turn induces abnormal uterine contractions. The contractions reduceuterine blood flow, leading to uterine hypoxia.That increased vasoactive prostanoid secretion is responsible for the etiology of primary dysmenorrhea is supported by 1) the striking similarity between the clinical symptoms of primary dysmenorrhea and the uterine contractions and adverse effects observed in prostaglandin-induced abortion and labor, 2) substantial evidence demonstrating and correlating the amount of menstrual prostanoids in women withprimary dysmenorrhea compared with eumenorrheic women, and 3) many clinical trials demonstrating the efficacy of cyclooxygenase (COX) inhibitors in relieving the pain of primary dysmenorrhea through prostaglandin suppression and quantitative decrease of menstrual fluid prostaglandins. The majority of dysmenorrhea in adolescents and young adults is primary (or functional), is associated with a normal ovulatory cycle and with no pelvic pathology, and has a clear physiologic etiology.[18, 19] After ovulation there is a buildup of fatty acids in the phospholipids of the cell membranes. The high intake of omega-6 fatty acids in the western diet results in a predominance of the omega-6 fatty acids in the cell wall phospholipids.[20] After the onset of progesterone withdrawal before menstruation, these omega-6 fatty acids, particularly arachidonic acid, are released, and a cascade of prostaglandins (PG) and leukotrienes (LT) is initiated in the uterus (Fig. 2). The inflammatory response, which is mediated by these PG and LT, produces both cramps and systemic symptoms such as nausea, vomiting, bloating, and headaches. In particular, the prostaglandin F2a, cyclooxygenase (COX) metabolite of arachidonic acid, causes potent vasoconstriction and myometrial contractions, leading to ischemia and pain.[19] Secondary dysmenorrhea refers to painful menstruation associated with pelvic abnormalities, which may be seen in about 10% of adolescents and young adults with dysmenorrhea. Secondary dysmenorrhea is more likely to be associated with chronic pelvic pain, midcycle pain, dyspareunia, and metrorrhagia.

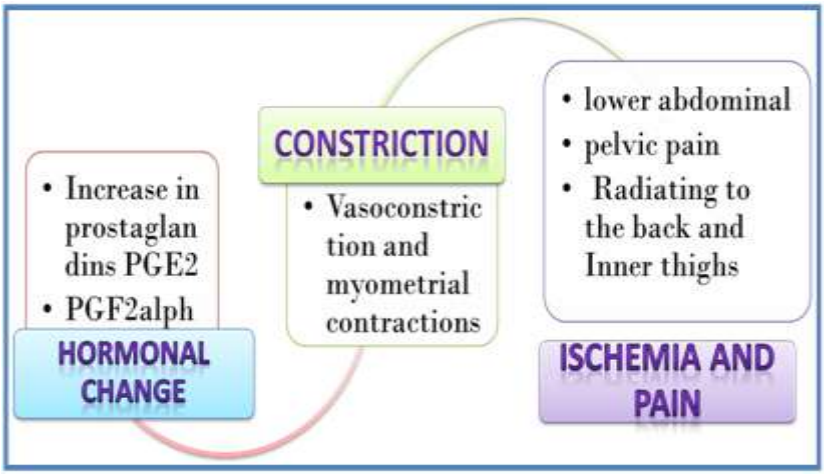

Figure (1): Pathophysology of dysmenorrhea

Endometriosis: Endometriosis is an estrogen-dependent disorder. Immunohistochemical studies have located estrogen receptor expression and increased expression of aromatase in epithelial and stromal cells of endometriotic tissues and peritoneum.[21, 22] Thus, while aromatase activity is not detectable in normal endometrium, it is expressed inappropriately in endometriosis, leading to a rise in local biosynthesis of estrogen. This acquisition of steroidogenic capacity may permit theectopic endometrial tissues to survive despite the lack of ovarian steroids during menstruation. In addition, aberrant expression of cytokines such as interleukin-1 and tumor necrosis factor-alpha may influence the establishment and proliferation of these ectopic endometrial implants.[23] Endometriosis is the most common cause of secondary dysmenorrhea in adolescents and young adults. It is defined as the presence and growth of uterine glands and stroma outside the uterine cavity.

The majority of endometriosis implants are located in the pelvis, with the ovaries being the most common site. The severity of pain from endometriosis involves several factors. These include the location of the lesion, depth of invasion, and stretching or scarring of tissue. In particular, women with deep implants tend to have more active disease and more severe pain.33 However, the presence of symptoms does not always predict the extent of endometriosis.[24]

Management: There are three approaches to the management of primary dysmenorrhea: pharmacological, nonpharmacological, and surgical. By far, the pharmacological approach has been better documented for efficacy, whereas the other approaches have more variable evidence.

Non-pharmacological Approach

Interventions such as herbal preparations,[25] transcutaneous nerve stimulation,[26] acupuncture,[27] exercise,[28] and topical heat therapy[29] have been reported to improve dysmenorrhea in some studies. A low-fat vegetarian diet was associated with a decrease in dysmenorrhea duration and intensity in young adult women.[30] Dietary supplementation with omega-3 fatty acids had a beneficial effect on dysmenorrhea symptoms in adolescents in one study.[31] Increasing dietary omega-3 fatty acids intake leads to production of less potent prostaglandins and less potent leukotrienes, which may have accounted for the reduction in menstrual symptoms observed in adolescent girls in that study.

Pharmacological Agents

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

In women with dysmenorrhoea, NSAIDs are significantly more effective for pain relief than placebo (odds ratio [OR] 7.91, 95% confidence interval [CI] 5.65–11.09).[32] Overall adverse effects were also significantly more common (OR 1.52, 95% CI 1.09 –2.12). There was insufficient power to detect differences between different NSAIDs because most individual comparisons were based on a few small trials unsuitable for meta-analysis. Thus there is insufficient evidence to determine which (if any) individual NSAID is the most safe and effective for treatment of dysmenorrhoea. My personal preference is to select an NSAID that has been around for a long time, is currently available as a generic and therefore is relatively inexpensive, and has many randomized double-blinded clinical trials with data on time to onset of relief with the first dose, in addition to overall efficacy. Such NSAIDs are ibuprofen, sodium naproxen, or ketoprofen. Thus far, trials have shown ibuprofen, naproxen, ketoprofen, mefenamic acid, and nimesulide to be significantly better than placebo or comparably as effective as ibuprofen or naproxen sodium. In our study, naproxen 400 mg provides greater pain relief than placebo and acetaminophen within 30 minutes and is maintained at 6 hours after administration.[33] Ketoprofen (100 mg) was reported more effective at 45 minutes, continuing for up to 2 hours, than 500 mg naproxen, using visual analog scale scores to assess pain.[34] In a multicenter, randomized, double-blind, crossover study, we found 12.5 and 25 mg ketoprofen and 200 mg ibuprofen were significantly better than placebo, with a similar sum of the pain intensity differences and total pain relief scores at 4 hours for the two NSAIDs.[35] This does not mean that other NSAIDs, including the COX-II specific inhibitors, should not be considered. Never- theless, cost considerations, lack of superiority, and concerns about the adverse effects of COX-II inhibitors do not support

them as a first-line NSAID for treatment of primary dysmenorrhea. Several NSAIDs have been approved and are available as OTC medications, including ibuprofen, naproxen sodium,45 and ketoprofen.[35,36]

Not all adolescents and young adults with dysmenorrhea respond to NSAIDs, and some of those who do respond report only partial relief.[51,55] One possible explanation is that most NSAIDs inhibit only cyclooxygenase and do not affect the production of other inflammatory mediators such as leukotrienes. However, in a recent study, treatment with the leukotriene receptor antagonist montelukast (Singulair_), in the FDA approved dose (for asthma) and commencing immediately before the menstrual period, failed to improve dysmenorrhea symptoms in adolescents.[56] Occasionally, adolescents who do not respond to NSAIDs may have psychogenic causes of dysmenorrhea. Most important, adolescents who do not respond to NSAIDs may have secondary organic causes of dysmenorrhea.

Oral Contraceptive

Oral contraceptive pills (OCP) are considered the second-line treatment for dysmenorrhea. By decreasing endometrial growth, OCPs limit the production of PGs. Lower levels of PGs have been reported in the menstrual fluid of women taking OCPs compared to those not taking OCPs.3 In a recent double-blind, randomized, controlled trial by Davis et al comparing adolescents taking 28-day pack OCPs (ethinyl estradiol 20 mcg and levonorgestrel 100 mcg) to those taking placebo, OCP users were found to have significantly less dysmenorrhea and required less additional pain medication.[40] For patients who show a favorable, but incomplete, response to OCPs taken cyclically, OCPs may be taken continuously to reduce the number of painful menses in a year. Furthermore, for those patients showing an inadequate response to combination therapy with NSAIDS and OCPs, consideration of common causes of secondary dysmenorrhea and investigation with ultrasound or laparoscopy may be warranted.

Many studies have reported an association between OCP use and decreased dysmenorrhea. While one study suggested that OCPs consisting of a potent progestin (such as levonorgestrel) might be more beneficial in treatment of dysmenorrhea,[41] other studies showed OCPs with less potent progestins to be beneficial as well.[42,43] Overall, the consistency of OCPs effect across populations and with different pill formulations[42-46] supports the use of OCPs in the treatment of dysmenorrhea.

Injectable long-acting hormonal contraceptives

The injectable contraceptive depot medroxyprogesterone acetate (DMPA) is a progestin-only, long-acting, effective, and convenient contraceptive method. About two thirds (64%) of adolescents reported less dysmenorrhea symptoms while using DMPA (Depo-Provera_) as a contraceptive method.[47] Since the use of this progestin-only contraceptive may lead to relative estrogen deficiency, there is a concern regarding its effect on bone mineral density (BMD), particularly when used during adolescence, a critical period for BMD accrual.

Herbs help to relive dysmenorrhea / Nontraditional or Alternative Treatments

❖ **Fennel**

Fennel essential oil (FEO). FEO is a fruit essence derived from the Foeniculum vulgare plant that has been used as an antispasmodic for pediatric colic and respiratory disorders.[48] Fennel significantly reduces symptoms of primary dysmenorrhea. Fennel essential oil found to inhibit uterine contractions caused by prostaglandins E2 and Oxytocin.

Helps to regulate the menstrual cycle, may help reduce hormone fluctuation. It is also aids in reducing muscle spasm.

Figure (7): Fennel

Fennel also contains small amounts of coumarins that could affect coagulation and bleeding.[49]

❖ **Sweet Marjoram**

This is best oil for menstrual cramps. Reduces pain on all levels. Great to use with a hot compress on the abdomen when experiencing menstrual cramps.

Figure (8): Sweet marjoram

❖ **Rose tea**[50]

Rose tea also proved safe, readily available and simple treatment for primary dysmenorrhea in a single randomizes clinical trial.

Figure (9): Rose tea

❖ **Ginger**

Oral intake of Ginger is found an effective remedy in pain relief of dysmenorrhea by several studies. Gingerol is present in ginger have anti-inflammatory effects and inhibits Cyclooxygenase and Lipooxygenase pathways.

Figure (10): Ginger

❖ **Chamomile:** This sweet little flower is both anti-inflammatory and antispasmodic. It is also helpful for women with digestive constipation contributing to pain.

Because this herb is also a nervine and mild sedative it may help to reduce stress, relax the nervous system and induce a restful state in the body. This can be very useful when experiencing menstrual cramping accompanied by anxiety and irritability.

Figure (11): Chamomile

❖ **Cinnamon:** Cinnamon has antispasmodic, anticlotting and anti-inflammatory properties that can relieve menstrual pain. Plus, Cinnamon is an excellent source of dietary fiber, Calcium, Iron and Manganese.

Figure (12): Cinnamon

❖ **Flaxseed:** Flaxseed is great for reducing the intensity of menstrual cramps. The essential fatty acids in flaxseed help stabilize the production of progesterone. Plus, flaxseed can improve uterine function and help treat fertility problems.

When suffering from menstrual cramps, consume one to two tablespoons of flaxseed daily. You can sprinkle ground flaxseed over a salad, cereal and yogurt or put it in a smoothie.

Figure (13): flaxseed

❖ **Basil**

Basil is another very effective herb for reducing menstrual pain and cramps. The Caffeic Acid present in Basil has analgesic, or pain-killing properties.

Figure (14): Basil

❖ **Heat application**

Concerning heat application on lower abdomen by ancient physicians, it has been showed that continuous, low-level, heat-wrap therapy applied to the suprapubic region is significantly reduced primary dysmenorrhea51a.

Figure (15): Heat application

❖ **Massage therapy**

Regarding massage on lower abdomen with aromatic oil positive response in pain relief of dysmenorrhea was seen by randomized clinical trial. (51b)

Figure (16): Massage therapy

Nutritional Considerations

Dysmenorrhea is an inflammatory state in the body, it is important to avoid foods that increase inflammation response. High glycemic foods are known to increase levels of inflammatory chemicals in the body, including PGF2.Many other therapies have been proposed, but most are not well studied. The studies suggest important to eat a lot of fresh fruits and vegetables that relive the menstrual pain.

❖ Avoid refined carbohydrates stick to whole grains, brown rice.

❖ Eliminate sugary foods and processed sugars choose very limited amounts of honey or agave.

❖ Consider eliminating dairy products are congesting to the body and many doctors have seen a reduction in menstrual cramp pain in women who eliminated dairy products. If you choose dairy, try to purchase organic or organic raw dairy only to avoid added hormones.

❖ Reduce red meat and egg yolk consumption to at most 2-3 times a week.

This is because both red meat and egg yolk are high in Arachidonic acid (AA). This has been found to increase cellular inflammation in some people. To find out if you are sensitive to Arachidonic acid, eliminate red meat and egg yolk for a month. Reintroduce it and see if your symptoms come back. Choose organic free range meats and eggs when possible to avoid added hormones.

Nutritional Supplements or Complementary and Alternative Medicines (Cam)

In considering complementary and alternative medicine (CAM) treatments for primary dysmenorrhea, a search of the conventional medical literature was undertaken. Though there may be CAMs other than those mentioned below which are used for dysmenorrhea, we are not aware of well-designed, published studies that demonstrate efficacy. When advising patients about CAM for primary dysmenorrhea, care should be taken to consider uncertainty about long-term efficacy, interactions, and possible harm. Evidence is limited by small study sizes.

❖ **Vitamin A**

Vitamin B1 supplementation may improve dysmenorrhea via a reversal of the symptoms common to B1 deficiency, namely muscle cramping, fatigue, and reduced pain tolerance.

When B1 supplementation was tested against placebo supplementation in a large randomized controlled trial for the treatment of dysmenorrhea, vitamin B1 was found to have a significantly greater effect on pain reduction than placebo.[52]

Vitamin E is a known inhibitor of protein kinase C, there by inhibiting the release of arachidonic acid from cell membrane phospholipids and decreasing PG synthesis. In a double blind, randomized, placebo-controlled trial, Ziaei et al investigated the effects of Vitamin E 200 units twice daily versus placebo in treating dysmenorrhea. While study findings revealed that pain was reduced by both medications, the reduction by vitamin E was significantly greater.[53]

Vitamin E increases the production of vasodilator prostacyclin and prostaglandin E2 (PGE2), as well as a dose-dependent upregulation of phospholipase A2 and arachidonic acid release, but inhibits COX posttranslational activity54. In macrophages, vitamin E abrogates peroxynitrite induction of COX55 and significantly suppresses arachidonic acid metabolism and prostaglandin production through inhibition of PLA2 and COX.56–58 In short, vitamin E and its analogues suppress phospholipase A2 and COX activities to inhibit prostaglandin production but promote vasodilator and uterine muscle relaxing prostanoids such as prostacyclin.

In a small study, vitamin B6 alone (200 mg/day) was helpful and even better than a combination of vitamin B6 (200 mg/day) with magnesium (500 mg/day) in reducing dysmenorrhea and the use of additional medications. No differences were seen between vitamin B6 alone (200 mg/day) and magnesium alone (500 mg/day).[59]

❖ **Magnesium**

Magnesium is also a cell membrane stabilizer, and when intracellular levels are reduced, as they are after progesterone withdrawal prior to menses, muscles become more contractile.60Magnesium helps to relax smooth muscle tissue. It has been shown to reduce menstrual cramping greatly. Magnesium deficiency is a leading cause of menstrual cramps.

While its mechanism of action is nonspecific, magnesium may work via a reduction in PGs and/or via a decrease in muscle contractility. Seifert found that women taking magnesium had substantially lower levels of prostaglandin F2 alpha (PGF2a) in their menstrual fluid compared to women taking placebo.[61]

❖ **Omega 6**

Omega-6 fats can assist fertility by improving reproductive cell structure, decrease risk of inflammation and improve the condition of organs in the body.[62]

Dysmenorrhea has been associated with diets high in omega-6 fatty acids and low in omega-3 fatty acids. Increased incorporation of omega-3 fatty acids (such as fish oil) into cell wall phospholipids ultimately leads to uterine production of less potent PGs and LEs. In a double blind crossover study by Harel and colleagues, patients taking fish oil were found to have less pain and a decreased need for additional medication when compared to patients taking placebo. Some minor adverse effects associated with the use of fish oil are nausea, acne exacerbation, and difficulty swallowing the capsules.[63]

CONCLUSION

Dysmenorrhea is an extremely common and sometimes debilitating condition for women of reproductive age. A multidisciplinary approach involving a combination of lifestyle, medications, and allied health services should be used to limit the impact of this condition on activities of daily living. In some circumstances, surgery is required to offer the desired relief. In summary, while NSAIDS and OCPs are considered the first and second line treatments for dysmenorrhea, other potential medical treatments are available. While studies of the aforementioned nontraditional treatments are limited in size and number, these therapies may be of help to patients seeking complementary or alternative therapies CAM has limited support and may be considered in the treatment of primary dysmenorrhea, though further study is required.

Surgery constitutes the final diagnostic and therapeutic option in the management of dysmenorrhea. Laparoscopy should be considered in women who have persistent dysmenorrhea despite medical therapy of NSAIDs and/or oral contraceptives.

Non-medicinal approaches such as exercise, heat, behavioral interventions, and dietary/herbal supplements are commonly utilized by women in an effort to relieve dysmenorrhea. The data on the effectiveness of such interventions remain inconclusive and controversial.

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