JOURNAL CLUB

TEHRAN UNIVERSITY OF MEDICAL SCIENCES

Dysmenorrhea and Endometriosis: Diagnosis and Management in Adolescents

(Geri Hewitt. Clin Obstet Gynecol. 2020 Sep;63(3):536-543)

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Date: 04/05/1402

DYSMENORRHEA

- Dysmenorrhea, or menstrual pain, is the **most common** gynecologic complaint among adolescents and young women, and the leading cause of recurrent short-term school or work **absenteeism**.
- Dysmenorrhea impacts between 60%-93% of adolescents and up to 42% of adolescents report severe symptoms.
- Despite the high prevalence of dysmenorrhea and documented negative impact quality of life, many patients do not seek care, underreport their symptoms, and/or are undertreated.

SYMPTOMS

- Lower or generalized abdominal cramping pain,vomiting, loss of appetite, dyschezia, diarrhea are common GI symptoms.
- Also, generalized aching, weakness, leg aches, low back pain, headaches are reported.
- Additional symptoms include sleeplessness, dizziness, depression, irritability, and nervousness.
- Patients with dysmenorrhea are more likely to be diagnosed with depression/anxiety as well as PMS.

PRIMARY VS. SECONDARY

- About **90%** of impacted patients have **primary** dysmenorrhea, defined as dysmenorrhea in the absence of **pelvic pathology**. Primary dysmenorrhea is the result of pathophysiologic changes occurring throughout the menstrual cycle, including excess synthesis of **prostaglandins** and secretion of prostaglandins into the endometrial fluid.
- Secondary dysmenorrhea is due to varying underlying gynecologic etiologies, most commonly **endometriosis**, and **obstructive Mullerian anomalies**.

PATHOPHYSIOLOGY OF PRIMARY DYSMENORRHEA

- Following progesterone withdrawal premenstrually, phospholipids are released from the cell membrane, including ω6 FAs.

- A cascade follows where the enzyme **phospholipase A2** converts the FAs to arachidonic acid, **cyclooxygenase** converts the arachidonic acid to prostaglandins, and **lipoxygenase** converts the PGs to leukotrienes.

PATHOPHYSIOLOGY OF PRIMARY DYSMENORRHEA

- An **inflammatory** response, mediated by these PGs and leukotrienes, produces both the menstrual cramps and systemic symptoms.
- **PG-F2alpha** causes potent **vasoconstriction** and myometrial contractions, leading to uterine **ischemia** and **pain**. The intensity of the menstrual cramps and symptoms are directly proportional to the amount of PG-F2alpha released.
- Urinary leukotriene levels are increased in adolescent girls with dysmenorrhea.

Evaluation of Dysmenorrhea

- Hx including menstrual, sexual, gynecologic, medical, surgical, psychosocial, and family history.

- Assessment the likelihood of **primary vs. secondary** dysmenorrhea by learning about duration, timing, and severity of menstrual cramps and other associated symptoms; response to previous therapies; and family history of endometriosis.

Evaluation of Dysmenorrhea

- Primary dysmenorrhea is more likely than secondary dysmenorrhea to being just **before or concurrent** with the onset of menstrual bleeding, and to be worst on the 1st or 2nd day of flow, with subsequent improvement.
- Clues that raise concern for **secondary** dysmenorrhea include **failure** to respond to 1st-line treatments, symptoms presenting shortly **after menarche**, associated **heavy menstrual bleeding** and/or acyclic pain, sexual activity, family history of endometriosis, or a known renal anomaly.

EVALUATION OF DYSMENORRHEA

TABLE 1. Clinical Findings Raising Suspicion of Secondary Dysmenorrhea

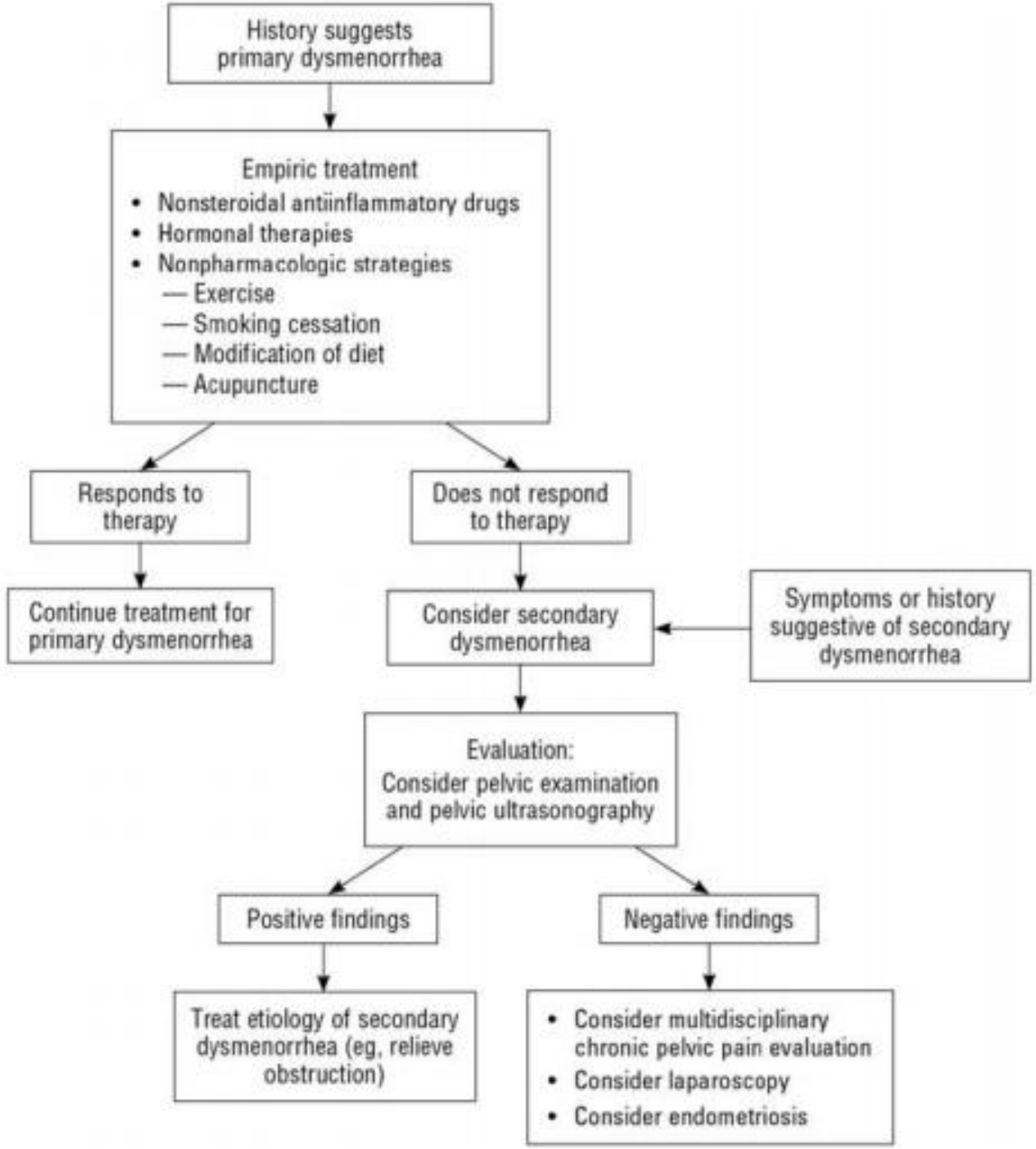
Symptoms occurring with the onset of or shortly after menarche
Associated heavy menstrual bleeding
Presence of acyclic pelvic pain
Family history of endometriosis
Presence of a renal anomaly
Symptoms unresponsive to nonsteroidal anti-inflammatory drugs and/or hormonal medications

Evaluation of Dysmenorrhea

- In patients with a history suggesting **primary** dysmenorrhea who have **never** been sexually active, a pelvic examination is **not** necessary and **empiric treatment** should be initiated. **Response to therapy** reinforces the diagnosis of primary dysmenorrhea.
- Suspicion of **secondary** dysmenorrhea may require **further evaluation**, but the initiation of therapy should **not be delayed**. Patients who have been **sexually active** require a **pelvic examination** to R/O PID. Anytime the patient's history suggests secondary dysmenorrhea, a pelvic examination should be attempted.
- **Endometriosis** is the most common etiology of **secondary** dysmenorrhea and most affected adolescents have **early-stage** disease.

FURTHER EVALUATION OF DYSMENORRHEA

- Pelvic **US**(TA or TV) is indicated when patients don't respond to standard therapies for primary dysmenorrhea or have signs and symptoms suggestive of secondary dysmenorrhea.
- A normal study doesn't R/O superficial endometriosis, but pelvic imaging can identify structural abnormalities associated with dysmenorrhea such as obstructive Mullerian anomalies, ovarian cysts or endometriomas, and uterine polyps or leiomyomata.
- Pelvic US is the 1st-line imaging tool for dysmenorrhea; pelvic MRI may be required to further delineate obstructive Mullerian anomalies. MRI is not cost-effective as a 1st-line screening tool; as ultrasound, MRI is **unable** to identify early-stage endometriosis.
- Diagnostic **laparoscopy** may be required to confirm some etiologies of secondary dysmenorrhea such as endometriosis, pelvic inflammatory disease, adhesions, and/or obstructive Mullerian anomalies. Laparoscopy is **reserved** for patients with suspected anatomic abnormalities suspected on pelvic examination and/or radiologic studies or patients who have failed standard medical therapies.


History suggests primary dysmenorrhea
Empiric treatment
• Nonsteroidal antiinflammatory drugs
• Hormonal therapies
• Nonpharmacologic strategies
— Exercise
— Smoking cessation
— Modification of diet
— Acupuncture
Responds to therapy
Does not respond to therapy
Continue treatment for primary dysmenorrhea
Consider secondary dysmenorrhea
Symptoms or history suggestive of secondary dysmenorrhea
Evaluation: Consider pelvic examination and pelvic ultrasonography
Positive findings
Negative findings
Treat etiology of secondary dysmenorrhea (eg, relieve obstruction)
• Consider multidisciplinary chronic pelvic pain evaluation
• Consider laparoscopy
• Consider endometriosis

TREATMENT OF PRIMARY DYSMENORRHEA

- Non-hormonal
- Hormonal
- Alternative and complementary agents

NON-HORMONAL THERAPIES

- **NSAIDs**
  - ✓ 1st line treatment for dysmenorrhea
  - ✓ Interrupt cyclooxygenase-mediated PGs production
  - ✓ Reasons for NSAIDs failure: **delayed initiation** of use and subtherapeutic **dose**
  - ✓ NSAIDs are most effective initiated **1-2 days before** the onset of menses and taken as weight-specific doses on a routine (**not** PRN) through the **first 2-3 days** of bleeding
- **Other drugs** include acetaminophen, acetaminophen with caffeine or pamabrom
  - ✓ **Acetaminophen** has fewer gastrointestinal side effects and can be used in addition to NSAIDs.
  - ✓ Opioids should **not** be used to treat dysmenorrhea because of risks of physical dependence, addiction, and hyperalgesia.

HORMONAL THERAPIES

- Hormonal therapies, either alone or in combination with other medications, are **another** 1st-line option
- All hormonal contraceptives are beneficial in alleviating dysmenorrhea; the most likely mechanism is decreasing **PGs and leukotriene** production by either limiting endometrial proliferation and/or ovulation.
- Evidence supports the use of combination **estrogen and progestin** methods such as the pill, patch, or ring as well as **progestin-only** methods such as DMPA, the contraceptive implant, and levonorgestrel IUDs. Using combination methods in an extended cycle regimen may lead to an earlier alleviation of symptoms, but cyclic use is as beneficial long term.

HORMONAL THERAPIES

- Noncontraceptive hormonal therapies can be helpful for patients who are **reluctant** to use a contraceptive method to treat dysmenorrhea. Norethindrone acetate, 5 mg daily, is as effective as cyclic combination OCPs to treat dysmenorrhea in young women.
- Empiric use of gonadotropin-releasing hormone agonists (GnRHa) or antagonists are **not** recommended to treat primary dysmenorrhea in adolescents due to concerns about bone mineralization.

ALTERNATIVE AND COMPLEMENTARY THERAPIES

- Currently, the strongest evidence supports the use of **local heat** and **exercise** to improve dysmenorrhea symptoms. Given the low cost and safety record of both exercise and heat, as well as the additional health benefits of exercise, both should be routinely recommended.

- With only limited (and sometimes conflicting) evidence of benefit, dietary supplements, transcutaneous electrical nerve stimulation, behavioral interventions, high dose vitamin D, yoga, herbal supplements, and acupuncture are not currently recommended as a first-line alternative or complimentary modalities to treat primary dysmenorrhea.

F/U AND TREATMENT FAILURE

- Patients benefit from regularly scheduled F/U appointments to monitor side effects, adherence, and response to therapy. A successful intervention is defined not by the complete absence of any pain or discomfort, but rather **full participation** in school, sports, and social functions and few, if any, trips to urgent care of emergency departments with dysmenorrhea symptoms. An **adequate response** to therapy reinforces the diagnosis of primary dysmenorrhea.
- If patients continue to have pain, adherence should be assessed. Patients should be encouraged to try alternative NSAIDs and hormonal agents if their initial choices are not helpful.
- Patients experiencing pain despite adherence with NSAIDs and hormonal agents for at least **3-6 months** require additional evaluation for potential etiologies of **secondary** dysmenorrhea.

ENDOMETRIOSIS

- Endometriosis is the **most common** cause of **secondary** dysmenorrhea in adolescents. While the exact prevalence of endometriosis in adolescents is unknown, in patients undergoing **laparoscopy** for dysmenorrhea unresponsive to hormonal therapy and NSAIDs, approximately **2/3** of patients will be diagnosed with endometriosis.
- **Risk factors** for adolescent endometriosis include an affected first-degree **family** member, an **obstructive Mullerian anomaly**, and increased exposure to menstruation including **earlier menarche**.
- The most common **symptoms** of adolescent endometriosis are **dysmenorrhea** and **chronic pelvic pain**. Adolescents with endometriosis may experience **dyspareunia** if they are sexually active, and they are more likely than adults to experience **acyclic pelvic pain**.
- Similar to primary dysmenorrhea, endometriosis is an inflammatory mediated estrogen-dependent disorder, stimulated by estrogen production from both the **ovaries** and endometriotic implants.

TREATMENT OF ENDOMETRIOSIS

- There is currently no clear evidence regarding the most effective treatment options for adolescent endometriosis, and therefore, treatment should be individualized with a focus on restoring function by **minimizing symptoms**, **suppressing the progression** of the disease, and **preserving fertility**. The mainstay of treatment is medical, including **hormonal** therapies combined with **NSAIDs**; **GnRHa** may benefit some older adolescents.
- **Surgical** interventions focus primarily on initial diagnosis combined with conservative treatment.

ROLE OF SURGERY IN ENDOMETRIOSIS

- Surgical interventions have a limited role in the management of adolescent endometriosis.
- Many patients with dysmenorrhea unresponsive to hormonal therapies and NSAIDs or chronic pelvic pain with is a high index of suspicion for endometriosis undergo **diagnostic laparoscopy**.
- The **advantages** of diagnostic laparoscopy include **confirmation** of any suspected pathology as well as an opportunity to treat with either **ablation or excision** of visible lesions. A negative diagnostic laparoscopy may reassure any patient with dysmenorrhea and/or chronic pain and particularly those with anxiety or somatization.
- Traditionally, **early diagnosis** and treatment of endometriosis has been advocated to help minimize disease progression and protect fertility.

ROLE OF SURGERY IN ENDOMETRIOSIS

- Endometriosis in adolescents most commonly presents in early-stage disease and with **clear or red** lesions as opposed to the **powder burn** lesions identified in older patients.
- Lesions suspicious for endometriosis should be **biopsied** for pathologic confirmation and additionally resected or coagulated. The adhesive disease should be lysed at the time of laparoscopy as potential sources of pain.
- Diagnostic laparoscopy is an ideal time to consider the placement of a levonorgestrel **IUD** to treat dysmenorrhea regardless of whether endometriosis is identified at the time of surgery, particularly in girls who are virginal or hesitant about in-office insertion.
- There is no definitive surgical cure for adolescent endometriosis. After diagnosis and treatment during the initial laparoscopy, treatment turns to **hormonal** suppressive therapy. Repeat laparoscopies are avoided unless in attempts to treat symptomatic endometriomas or deep, infiltrating disease.

MEDICAL THERAPIES IN ENDOMETRIOSIS

- Endometriosis is a **chronic** condition with the potential for progression. After surgical therapies, hormonal suppressive therapy is continued or initiated to manage symptoms, decrease the likelihood of progression, and potentially protect fertility.
- Hormonal suppressive therapy can be **individualized** based on the need for **contraception**, patient **preference**, and contraindications to combined hormonal methods.
- All contraceptive methods, as well as norethindrone acetate, have demonstrated benefit. Patients often benefit from trialing different hormonal therapies and extended cycle preparations.

MEDICAL THERAPIES IN ENDOMETRIOSIS

- Some adolescents with endometriosis have **persistent symptoms** despite conservative surgical therapy and hormonal suppression and may benefit from **GnRHa** treatment in combination with add-back therapy including conjugated equine **estrogen** (0.625 mg) with **norethindrone acetate** (5.0 mg) is superior to norethindrone acetate alone in both quality of life and bone mineral density.
- GnRHa treatment is typically reserved for older adolescents with surgically proven endometriosis given concerns about the accrual of bone mineral density during adolescence.
- Dual-energy x-ray absorptiometry is not indicated before initiation of GnRHa therapy or after treatment of <12-month duration. Weight-bearing exercise and supplementation with calcium and vitamin D should be encouraged during GnRHa therapy. Hormonal suppression should resume after a course of GnRHa therapy.

MEDICAL THERAPIES IN ENDOMETRIOSIS

- Gonadotropin-releasing hormone **antagonists** are a **newer** class of drugs being used to treat endometriosis. No trials have been done yet in women younger than 18 years of age and they are not Food and Drug Administration (FDA) approved for contraception. Endometrial suppression and rates of amenorrhea may be lower than with GnRHa.
- **NSAIDs**, in conjunction with **hormonal** suppression, play an important role for management of both the inflammation and pain associated with adolescent endometriosis.
- Opioids should not be used for pain relief in adolescents with endometriosis outside of a specialized pain clinic.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