Dysmenorrhea in Adolescents

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Dysmenorrhea is the most common gynecologic complaint among adolescent females. Dysmenorrhea in adolescents is usually primary, and is associated with normal ovulatory cycles and with no pelvic pathology. In approximately 10% of adolescents with severe dysmenorrheic symptoms, pelvic abnormalities such as endometriosis or uterine anomalies may be found. Potent prostaglandins and leukotrienes play an important role in generating the symptoms of dysmenorrhea. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most common pharmacologic treatment for dysmenorrhea. A loading dose of NSAIDs (typically twice the regular dose) should be used as initial treatment for dysmenorrhea in adolescents, followed by a regular dose until symptoms abate. Adolescents with symptoms that do not respond to treatment with NSAIDs for three menstrual periods should be offered hormonal treatment such as combined estrogen/progestin oral contraceptive pills for three menstrual cycles. Adolescents with dysmenorrhea who do not respond to this treatment should be evaluated for secondary causes of dysmenorrhea. The adolescent care provider's role is to explain the pathophysiology of dysmenorrhea to every adolescent female, address any concern that the patient has about her menstrual period, and review effective treatment options for dysmenorrhea with the patient.

Key words: **dysmenorrhea; adolescents; secondary dysmenorrhea**

The Menstrual Cycle in the Adolescent Girl

Menarche, the onset of menstrual periods, marks an important point in life for the female adolescent, as it symbolizes the entrance into womanhood. Mean menarchal age in adolescents in the United States is 12.2 years in African American girls and 12.9 years in Caucasian girls.[1] In addition to genetic and racial/ethnic factors, environment and anthropometrics influence maturational timing in adolescents.[2]

In adolescents, the positive stimulatory feedback mechanism of estrogen on LH does not mature nor does the LH surge consistently occur until 2–5 years after menarche. As a consequence, 50–80% of the cycles are anovulatory and irregular during the first 2 years after menarche, and approximately 10%–20% of cycles remain anovulatory for up to 5 years after menarche. The length of the interval between the onset of menses and the establishment of ovulatory cycles is associated with the age at menarche, with early menarche indicating early onset of ovulatory cycles.[3] The eventual attainment of ovulatory cycles by the teenagers leads to normal, repetitive menstrual bleeding.

While dysmenorrhea (menstrual cramps and other menstruation-associated symptoms) is less common during the first 2–3 years after menarche, when most of the menstrual cycles are anovulatory, it becomes more prevalent during mid- and late adolescence, with the establishment of ovulatory menstrual cycles.[4]

Prevalence of Dysmenorrhea in Adolescents

Dysmenorrhea is the most common gynecologic complaint and the leading cause of recurrent short-term school or work absenteeism among female adolescents.[4] In a study among older adolescent urban Swedish girls, a majority (72%) reported experiencing dysmenorrhea, and approximately 15% of adolescents described the disorder as severe.[5] A school absenteeism rate of 14–52% has been reported among U.S. adolescents with dysmenorrhea, with girls experiencing severe cramps more likely to miss school than those with mild cramps.[4,6]

Despite the high prevalence of dysmenorrhea in adolescents, many girls either do not seek medical

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TABLE 1. Symptoms of dysmenorrhea

Cramps	Diarrhea
Nausea	Facial blemishes
Vomiting	Abdominal pain
Loss of appetite	Flushing
Headaches	Sleeplessness
Backaches	General aching
Legaches	Depression
Weakness	Irritability
Dizziness	Nervousness

advice or are undertreated.[7] In one study, a majority (98%) of adolescents used nonpharmacologic methods such as heat, rest, or distraction to treat dysmenorrhea, with perceived effectiveness of 40% or less.[8] In other studies from different populations, 30%-70% of girls reported at least occasionally self-medicating with over-the-counter (OTC) pain medications.[5,9,10] However, 57% of those who self-medicated with OTC preparations used subtherapeutic doses.[10] Only 54% of adolescents knew that certain medications could relieve menstrual cramps,[10] and 27% of girls were unable to recognize any of three nonsteroidal anti-inflammatory drugs (NSAIDs) listed as possible treatments for dysmenorrhea.[11]

In the U.S., some of the OTC medications marketed for relief of dysmenorrhea do not contain any of the NSAIDs that have been demonstrated to be effective in treating the disorder. Furthermore, while dysmenorrhea is a prevalent medical disorder (65%) among urban adolescent females, only few (2%) reported receiving information regarding menstruation from their health care provider.[12]

Dysmenorrhea: Symptoms and Risk Factors

While lower abdominal cramping is the most common symptom of dysmenorrhea, many adolescents suffer from other menstruation-associated symptoms such as headaches, nausea, and vomiting (TABLE 1). In a recent cross-sectional study among U.S. adolescents with dysmenorrhea, menstrual cramps were associated with nausea in 55%, and with vomiting in 24%.[7] Symptoms typically accompany the start of menstrual flow or occur within a few hours before or after onset and last for the first 24–48 hours. Severity of symptoms positively correlates with the onset of ovulatory cycles and with increased duration and amount of menstrual flow.[5,13] Low fish consumption correlated with severity of dysmenorrhea in two studies.[13,14] In addition, cigarette smoking may increase duration of dysmenorrhea, presumably because of nicotine-induced vasoconstriction.[15]

Pathophysiology of Primary Dysmenorrhea

The majority of cases of dysmenorrhea in adolescents are primary (or functional), are associated with a normal ovulatory cycle and with no pelvic pathology, and have a clear physiologic etiology.[4,16] After ovulation there is a build-up 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.[17] After the onset of progesterone withdrawal before menstruation, these omega-6 fatty acids, particularly arachidonic acid, are released, and a cascade of prostaglandins (PGs) and leukotrienes (LTs) is initiated in the uterus (FIG. 1). The inflammatory response, which is mediated by these PGs and LTs, produces both cramps and systemic symptoms such as nausea, vomiting, bloating, and headaches. In particular, the prostaglandin F2α, cyclooxygenase (COX) metabolite of arachidonic acid, causes potent vasoconstriction and myometrial contractions, leading to uterine ischemia and pain.[18]

Chan and Hill measured PGF2α activity in menstrual fluid from tampons and found that PG activity was twice as high in dysmenorrheic than in eumenorrheic women.[18] Similar findings were reported by Rees *et al.*[19] Lundstrom and Green examined endometrial specimens taken from both dysmenorrheic and eumenorrheic women during the menstrual period and found that women with dysmenorrhea receiving no medication had endometrial PGF2α levels four times higher than the eumenorrheic women did on the first day of the menstrual period.[20] The intensity of the menstrual cramps and dysmenorrhea-associated symptoms are directly proportional to the amount of PGF2α released.[21]

While the PG pathway has been extensively investigated in dysmenorrhea, there is a paucity of data regarding the LT pathway. Previous studies have shown that human uterine tissue has the capacity to synthesize and metabolize LTs,[22] and LT receptors have been detected in uterine tissue.[23] Rees *et al.* found that the highest LT values were present in uterine tissue obtained (during hysterectomy) from adult women with a complaint of dysmenorrhea.[22] Nigam *et al.* found a close correlation between menstrual flow LT-C_4/D_4 levels and the severity of dysmenorrheic symptoms in

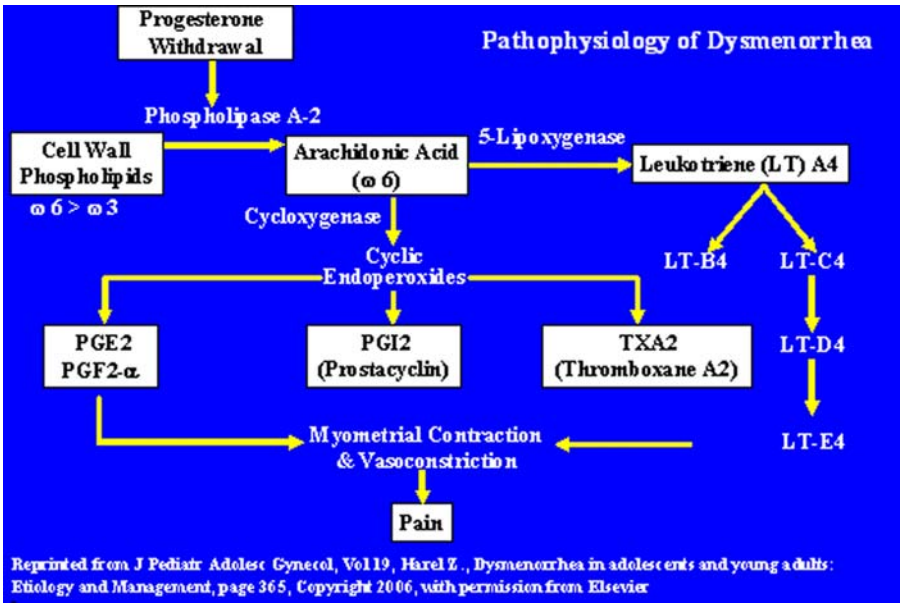

FIGURE 1. Pathophysiology of dysmenorrhea. (From Harel, Z.[97] Reprinted by permission.)

adult women with primary dysmenorrhea.[24] In a preliminary study, our group found an increase in urinary LT-E_4 in adolescent girls with dysmenorrhea,[25] further indicating a possible involvement of these potent vasoconstrictors and inflammatory mediators in generating symptoms of dysmenorrhea in adolescents.

Some other mechanisms that are involved in uterine contractility and relaxation have been suggested in the pathogenesis of dysmenorrhea. An increased level of circulatory vasopressin, which is known to induce uterine contractions, has been reported in women with dysmenorrhea during menstruation, but its involvement in the pathogenesis of primary dysmenorrhea remains controversial.[26] Similarly, more studies are needed to explore whether low levels of nitric oxide, which are known to induce myometrial contractions and vasoconstriction, play a role in generating the symptoms of dysmenorrhea.[27]

Pathophysiology of Secondary Dysmenorrhea

Secondary dysmenorrhea refers to painful menstruation associated with pelvic abnormalities, which may be seen in about 10% of adolescents with dysmenorrhea. Since the incidence of some of the causative conditions such as endometriosis and fibroids increases with age, secondary dysmenorrhea is more prevalent in adult women than in adolescents. Secondary dysmenorrhea is more likely to be associated with chronic pelvic pain, midcycle pain, dyspareunia, and metrorrhagia.

Endometriosis

Endometriosis is the most common cause of secondary dysmenorrhea in adolescents. 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. Other common sites of endometriosis include the pelvic peritoneum, anterior and posterior cul-de-sac, uterosacral ligaments, pelvic lymph nodes, cervix, uterus, vagina, vulva, rectosigmoid colon, and appendix. Rare sites of implantation include the umbilicus, surgical scars, bladder, kidneys, lungs, and extremities. The incidence of endometriosis in adolescents has been reported to be between 45% and 70% in a referral population presenting with chronic pelvic pain.[28] The youngest reported patient to have biopsy-proven endometriosis was 10 years of age.[29] The 6.9% incidence of endometriosis in first-degree relatives of women with the disease, compared with the 1%–2% incidence in the general population, implies a possible polygenic multifactorial model of inheritance.[30] Although the risk for endometriosis is about threefold higher among first-degree relatives, it is far less than the 50% incidence

one could expect with an autosomal dominant inheritance.

The most widely accepted theory about the development of endometriosis is Sampson's theory of retrograde menstruation. Deficient cell-mediated immunity with impaired clearing of endometriotic cells from aberrant locations has also been implicated. Other theories of origin include Meyer's theory of multipotential cells undergoing metaplasia, and Halban's theory of hematogenous and lymphatic dissemination of endometrial cells. Abnormal local hormonal activity and potent inflammatory mediators are also involved in the pathophysiology of 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.[31,32] 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 the ectopic 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.[33] Immunohistochemical studies have shown that the COX-2 expression is upregulated in endometriotic lesions,[34] and this increase in COX-2 is most likely secondary to the increase in estrogen.[35] The increased Cox activity results in production of PGs such as PGE_2, which, in turn, is a potent inducer of aromatase expression and activity in endometriotic stromal cells.[36] Another abnormality that contributes to the rise of estrogen in endometriosis is a deficient 17 β-hydroxysteroid dehydrogenase (17 β-HSD) type 2 expression which impairs the inactivation of estradiol to estrone.[37] This 17 β-HSD type 2 deficiency may also be viewed as a defective action of progesterone, which fails to induce this enzyme in endometriotic tissue. Thus, the positive feedback loop in endometriosis consists of high local levels of estrogen, which induce transcription of COX-2 and synthesis of PGE_2, resulting in further expression and activity of aromatase and further increase in estrogen (FIG. 2). The accumulation of estrogen and PG results in a potent inflammatory process and pelvic pain.

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.[38] However, the presence of symptoms does not always predict the extent of endometriosis.[39]

Reproductive Tract Anomalies and Other Causes of Secondary Dysmenorrhea

In the adolescent age group, the distinct possibility of a müllerian anomaly must also be considered. The patient may have a didelphic uterus with unilateral obstruction, resulting in pelvic pain that may or may not be cyclic. In particular, girls with an early onset of severe dysmenorrhea beginning with (or even before) menarche should be evaluated to rule out an obstructive or partially obstructive anomaly, such as longitudinal or transverse vaginal septum. In addition, an early age of presentation of endometriosis should raise suspicion of a genital outflow obstructive anomaly. In one study by Goldstein *et al.*, congenital anomalies of the reproductive tract were noted in 11% of teenagers with endometriosis.[40]

Patients with pregnancy-related complications such as miscarriage and ectopic pregnancy can present acutely with severe pain/cramping and bleeding, and this should be high on the list of differential diagnoses in a sexually active adolescent. Adhesions, pelvic inflammatory disease (PID), abscess, fibroids (myomas), adenomyosis, endometrial polyps, ovarian cysts, and, rarely, ovarian neoplasms are also included in the differential diagnosis of secondary dysmenorrhea.

Treatment of Dysmenorrhea

Nonpharmacologic Approach

Interventions such as herbal preparations,[41] transcutaneous nerve stimulation,[42] acupuncture,[43] and heat therapy[44] have been reported to lessen dysmenorrhea in some studies. Heat therapy can be administered with a heating pad, hot-water bottle, or commercially available adhesive pads which generate heat by a chemical reaction. Physical activity may also reduce dysmenorrhea[45] by improving pelvic blood flow as well as by stimulating the release of beta-endorphins, which act as nonspecific analgesics. A low-fat vegetarian diet was associated with a decrease in duration and intensity of dysmenorrhea in young adult women.[46] Dietary supplementation with omega-3 fatty acids had a beneficial effect on the symptoms of dysmenorrhea in adolescents in one study.[47] Increasing the intake of dietary omega-3 fatty acids 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. x

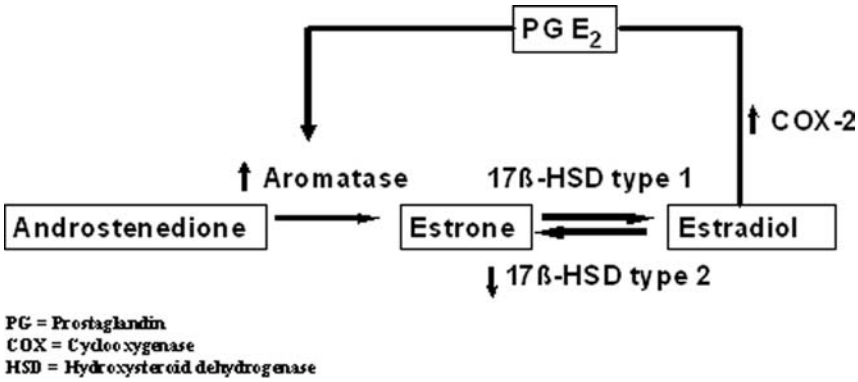

FIGURE 2. Pathophysiology of endometriosis. (From Harel.[97] Reprinted by permission.)

Nonsteroidal Anti-inflammatory Drugs

The most common pharmacologic treatments for dysmenorrhea are nonsteroidal anti-inflammatory drugs (NSAIDs). Conventional NSAIDs inhibit the activity of both cyclooxygenase-1 and -2 isoforms, leading to a reduction in prostaglandin production. The resulting lower level of prostaglandin leads to less vigorous contractions of the uterus, and, therefore, to less discomfort. Chan and Dawood found that PGF2α decreased and pain improved in a small number of dysmenorrheic women treated with NSAIDs.[48] Subsequent larger, randomized, placebo-controlled studies have shown several NSAID preparations, including naproxen sodium, zomepirac sodium, mefenamic acid, ketoprofen, ibuprofen, and diclofenac, to be effective treatments for primary dysmenorrhea.[49–54] While most NSAIDs inhibit only cyclooxygenase, meclofenamate sodium (a fenamate NSAID) has been shown *in vitro* to inhibit both cyclooxygenase and lipooxygenase pathways.[55] Although Owen found a trend favoring fenamates over ibuprofen, indomethacin, and naproxen,[56] Roy found no significant clinical difference between mefenamic acid and ibuprofen,[57] indicating that there is no clear-cut advantage of one NSAID over another in the treatment of dysmenorrhea. DuRant *et al.* randomized 45 girls with a mean age of 15 years to five naproxen sodium dosing regimens for the treatment of dysmenorrhea. By the third treatment month, a loading dose of 550 mg was associated with greater alleviation of the symptoms of dysmenorrhea than was the regular dose of 275 mg.[58] This suggests that a loading dose of NSAID (typically twice the regular dose) should be used as initial treatment for dysmenorrhea, followed by a regular dose as needed.

Specific cyclooxygenase isoform 2 (COX-2) inhibitors may also relieve dysmenorrhea symptoms.[59] These specific COX-2 inhibitors spare prostaglandins produced by COX-1 which are essential for the integrity of the gastric mucosa. Celecoxib (Celebrex®) is the only available COX-2 inhibitor approved by the U.S. Food and Drug Administration (FDA) for treatment of primary dysmenorrhea. Currently, it is approved for treatment of patients ≥18 years. The recommended dosage of celecoxib is 400 mg initially, followed by 200 mg every 12 hours as needed during the menstrual period.

Not all adolescents with dysmenorrhea respond to NSAIDs, and some of those who do respond report only partial relief.[56,60] One possible explanation is that most NSAIDs inhibit only cyclooxygenase and do not affect the production of other inflammatory mediators such as leukotrienes. However, treatment with the leukotriene receptor antagonist montelukast (Singulair®), in the FDA-approved dose (for asthma) and commencing immediately before the menstrual period, failed to alleviate symptoms of dysmenorrhea in adolescents.[61] Occasionally, adolescents who do not respond to NSAIDs may have a psychogenic component as part of their dysmenorrhea. In particular, a history of physical or sexual abuse has been associated with chronic pelvic pain.[62]

Hormonal Treatment

Combined Estrogen and Progestin Oral Contraceptive Pills

Combined oral contraceptive pills (OCPs) are a widely used treatment for primary dysmenorrhea in women. OCPs are perhaps an ideal treatment for adolescent dysmenorrhea; they are safe during

adolescence, have health benefits important to adolescents, such as alleviation of acne, and would provide protection against unintended pregnancy.

OCPs prevent or lessen dysmenorrhea directly by limiting endometrial growth and reducing the amount of endometrial tissue available for PG and LT production, and indirectly by inhibiting ovulation and subsequent progesterone secretion. The observed decrease in menstrual fluid PG and LT during OCP use[48,63] and the observed inconclusive serum levels of these inflammatory mediators[64,65] are consistent with a change in local uterine production of PGs and LTs. Ekstrom *et al.* found a decrease in intrauterine pressure and alleviation of pain on the first day of menstrual bleeding after treatment with low-dose OCPs.[66,67] Taken together, these studies suggest that OCPs may decrease pain by decreasing PG and LT production, as well as by decreasing intrauterine pressure.

Many studies have reported an association between OCPs use and decreased dysmenorrhea. While one study suggested that OCPs consisting of the potent progestin levonorgestrel might be more beneficial in treatment of dysmenorrhea,[68] other studies showed OCPs with other progestins to be beneficial as well.[69,70] Overall, the consistency of the effect of OCPs across populations and with different pill formulations[69–73] supports the use of OCPs in the treatment of dysmenorrhea.

Girls on OCPs who continue to experience menstrual symptoms or exacerbation of a medical condition (asthma, arthritis, seizures) during the active pill-free interval, may be considered for extension of the duration of active hormones to more than 21 days. Studies in adult women with menstruation-related problems showed that an extended cycle regimen (allowing menses every 3 or more months) was easier to follow, well tolerated, and efficacious in reducing menstrual symptoms.[74,75] The first extended regimen consisting of active pills (levonorgestrel 0.15 mg and ethinyl estradiol 0.03 mg daily) for 84 days of continued use followed by 7 days of inactive pills (Seasonale®) was approved by the FDA in September 2003. A modified version incorporating 7 pills of ethinyl estradiol 0.01 mg in place of the inactive pills (Seasonique®) was approved by the FDA in May 2006. A study evaluating the effect of Seasonique on dysmenorrhea in adolescents is ongoing. In May 2007, the FDA approved a low-dose annual regimen (Lybrel®) consisting of ethinyl estradiol 20 mcg and levonorgestrel 90 mcg taken daily for 365 days without a placebo phase or pill-free interval. The main concerns with the extended cycle regimen are: a potential decrease in endometrial stability, a possible deleterious effect on lipid profile, and the question of long-term safety .[76] Another concern is that sexually active adolescents may find it difficult to recognize an unexpected pregnancy during the use of an extended cycle regimen.

Injectable Long-Acting Hormonal Contraceptives

The injectable contraceptive depot medroxyprogesterone acetate (DMPA) is a progestin-only, long-acting, effective, and convenient contraceptive method. It is available in two formulations: the intramuscular formulation (Depo-Provera®, 150 mg DMPA/1 mL) approved by the FDA in 1992, and the subcutaneous formulation (Depo-subQ Provera 104®, 104 mg DMPA/0.65 mL) approved by the FDA in 2004, both administered every 12 weeks. Since ovulation is inhibited for as many as 7 to 9 months after a single DMPA intramuscular injection,[77] it may be used for alleviating the symptoms of dysmenorrhea. While the subcutaneous formulation of DMPA delivers a 30% lower total dose of DMPA than the intramuscular formulation, it was found to suppress ovulation for more than 13 weeks,[78] and thus may improve dysmenorrheic symptoms as well. About two-thirds (64%) of adolescents reported fewer symptoms of dysmenorrhea while using DMPA as a contraceptive method.[79] 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. On November 17, 2004, the FDA issued a "black box warning" for DMPA, stating that prolonged use of the method may result in significant loss of BMD, that the loss is greater the longer the drug is administered, and that BMD loss may not be completely reversible after discontinuation of DMPA.[80] In a 2006 position paper of the Society for Adolescent Medicine, Cromer *et al.* provided a list of clinical guidelines for continuation of DMPA use in the adolescent age group.[81]

Other Long-Acting Progestin-Only Hormonal Contraceptives

The levonorgestrel-releasing intrauterine system (Mirena®) releases levonorgestrel (20 μg/day) into the uterine cavity for 5 years. Women (aged 25–47 years) who used Mirena considered the absence or reduced intensity of menstruation and the amelioration of menstrual pain as the main advantages of this method.[82] In this study, the proportion of women with menstrual pain was reduced from 60% before use to 29% after 36 months of use of Mirena.

The etonogestrel subdermal implant (Implanon®), which was approved by the FDA in 2006, provides

effective contraception for up to 3 years. In a study by Funk *et al.*, 81% of women (aged 18–40 years) with a history of dysmenorrhea at baseline reported lessening of symptoms during the use of Implanon.[83]

Other Long-Acting Combined Estrogen and Progestin Hormonal Contraceptives

The combined estrogen and progestin transdermal patch (Ortho Evra®) also has the potential to alleviate dysmenorrhea. In one study of adolescent girls using Ortho Evra, 39% of participants reported decrease in dysmenorrhea symptoms, while 11% reported worsening of symptoms.[84] It remains to be determined in further studies whether Ortho Evra may be less beneficial than OCPs in the management of dysmenorrhea in adolescemts.

The combined estrogen and progestin vaginal ring (NuvaRing®) was approved by the FDA in 2001. It is designed for 3 weeks of use, followed by a 1-week ring-free interval. In one recent study in women (aged 20–39 years), the incidence of dysmenorrhea was reduced from 25.9% at baseline to 5.7% at the end of the sixth (NuvaRing) treatment cycle.[85]

Approach to Adolescents with Dysmenorrhea

Evaluation of the adolescent with dysmenorrhea starts with a history that is obtained privately and confidentially. The patient should be asked about age at menarche, menstrual pattern, onset and character of menstrual cramps and other menstruation-associated symptoms, response to analgesic medication, sexual activity, sexual abuse history, contraception, condom use, history of sexually transmitted diseases, vaginal discharge, school performance and school/work absenteeism, and family history of menstrual disorders (in particular, endometriosis in first-degree relatives). Psychological aspects of dysmenorrhea as well as psychological sequelae of chronic pelvic pain should be explored. The Cox Menstrual Symptoms Scale can be used to assess the frequency and severity of symptoms of dysmenorrhea.[86]

Pelvic examination is not necessary if the patient has never been sexually active, and if the history suggests primary dysmenorrhea. Because of the risk of pelvic inflammatory disease, a pelvic examination should be performed in a sexually active adolescent who develops new-onset or more severe dysmenorrhea. Pelvic and rectal examinations should be performed in adolescents with a history suggestive of secondary dysmenorrhea. Endometriosis is commonly associated with adnexal, uterine, or rectovaginal tenderness on pelvic examination. While palpable nodularity may be found on rectal examination in adult women with endometriosis, its presence in adolescents is quite uncommon.[87]

Adolescent care providers should explain the menstrual cycle, menstruation-associated symptoms, and the physiologic etiology of dysmenorrhea to every girl who suffers from menstrual cramps and/or other menstruation-associated symptoms. During counseling, an effort should be made to encourage girls who smoke to quit smoking, since smoking may be associated with prolonged dysmenorrheic symptoms.[15] In addition, girls should be encouraged to increase consumption of fish such as salmon, tuna, mackerel, and herring, which are rich in very-long-chain omega-3 polyunsaturated fatty acids. A review of effective treatment options for primary dysmenorrhea should be provided.

Response to treatment is an important component of the evaluation, because dysmenorrhea resulting from endometriosis is less likely to respond to NSAIDs than is primary dysmenorrhea.[88] If the pain does not abate with oral contraceptives, the patient should be evaluated by a gynecologist for consideration of laparoscopy in order to make a definitive diagnosis of endometriosis. Since endometriosis in adolescents is more likely to have an atypical appearance compared with its appearance in adults, it is important to refer to a gynecologist who frequently cares for adolescents with chronic pelvic pain. Pelvic magnetic resonance imaging is indicated if the medical history or/and physical examination raises suspicion of an obstructive pelvic anomaly.

Management of Primary Dysmenorrhea

Treatment with one of the NSAIDs in a therapeutic dose is the preferred initial treatment and should be tried for at least three menstrual periods. Treatment with NSAIDs is most effective when it starts 1–2 days before the onset of menses. Adolescents who cannot predict the initiation of their period should be instructed to start NSAID as soon as menstrual bleeding begins, or as soon as they have any menstruation-associated symptoms. It is important to provide the adolescent with specific instructions about the dose and maximum daily frequency of the recommended NSAID. If one preparation does not provide relief, a second NSAID preparation should be tried. The adolescent should be instructed to take the NSAID with food in order to prevent gastric irritation, and to increase fluid intake in order to prevent renal side effects.

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

Drug	Dosage
Ibuprofen	200–600 mg every 6 h as needed
Naproxen sodium	440–550 mg initially, followed by 220–275 mg every 8 h as needed
Mefenamic acid	500 mg initially, followed by 250 mg every 6 h as needed
Celecoxib[a,b]	400 mg initially, followed by 200 mg every 12 h as needed

[a]For girls ≥18 years
[b]Cyclooxygenase-2 specific inhibitor
NSAIDs = nonsteroidal anti-inflammatory drugs; h = hours
Source: From Harel.[97] Reprinted by permission.

Because primary dysmenorrhea typically resolves by day 2 to 3 of the menstrual period, the short course of treatment limits the development of the side effects of NSAIDs. A specific COX-2 inhibitor should be considered in adolescents with a prior history of peptic ulcer or gastrointestinal bleeding, in adolescents who require high doses of a conventional NSAID during the period, in adolescents with a history of conventional NSAID gastrointestinal adverse effects, and in adolescents with coagulation deficiencies. TABLE 2 delineates the most common conventional NSAIDs and the available specific COX-2 inhibitor used for treatment of dysmenorrhea in the United States.

If treatment with NSAIDs is not effective, a combination estrogen and progestin pill (OCP) should be offered for at least three menstrual cycles. Every OCP containing 20 to 35 mcg of estrogen has the potential for relieving dysmenorrhea. Dysmenorrhea that does not respond to NSAIDs administered for at least three menstrual periods and to combined OCPs administered for at least three ensuing menstrual cycles should raise suspicion of secondary dysmenorrhea.

Management of Secondary Dysmenorrhea

If dysmenorrhea is not alleviated within 6 months of treatment with NSAIDs and OCPs, consideration should be given to the performance of a laparoscopy to assess the presence of endometriosis. Because of wide variation in appearance and morphology of endometriosis, a histologic biopsy of the lesions should be performed during laparoscopy in order to confirm the diagnosis. Visible implants may also be obliterated by laser vaporization or resection during this procedure.[89,90]

Initial medical treatment for endometriosis consists of low-dose, monophasic oral contraceptives given in a noncyclic fashion.[91] The goals are to avoid endometrial proliferation, and to prevent endometrial implants from bleeding. It is the endometrial implants that cause the pain, scarring, and infertility associated with endometriosis. Medical management in patients refractory to noncyclic OCP treatment may proceed to gonadotropin-releasing hormone (GnRH) agonists, such as nafarelin or leuprolide, for 6 months. However, the low-estrogen state induced by these medications raises concern about bone metabolism, and the treatment may be associated with bothersome side effects such as hot flashes, emotional lability, and headaches.[90] Therefore, "add back" sex steroid therapy should be considered if long-term treatment with one of the GnRH agonists is planned.[92] Medications such as danazol and methyltestosterone, used in the past for treatment of endometriosis, are seldom utilized anymore because of high rate of adverse effects. Preliminary reports indicate that aromatase inhibitors, which can effectively block the local estrogen biosynthesis in the endometriotic lesions, significantly reduce lesion size and alleviate pelvic pain in patients with endometriosis.[93,94] To prevent ovarian folliculogenesis in adolescents and young adults, the aromatase inhibitor may be combined with a progestin, a combination oral contraceptive, or a GnRH analogue.[95] Another novel approach is the use of a selective progesterone receptor modulator, which has been shown to reduce dysmenorrhea and nonmenstrual pain in patients with endometriosis.[96]

The management of congenital malformations of the genital tract may be complex, and patients should be referred to a clinician who is experienced in management of these disorders. While it has been suggested that endometriosis in patients with genital tract anomalies usually resolves after a patent outflow tract is established, the evidence for this is not strong.

The management of secondary dysmenorrhea that is associated with ovarian disease is beyond the scope of this review. Functional cysts may resolve with time alone. Decisions about surgical management of other ovarian disorders should be made by a gynecologic surgeon who has experience in dealing with adolescents.

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Conflicts of Interest

The author declares no conflicts of interest.

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