FAX

Bestelldatum: **2015-01-16 20:38:57**

Bayerische StaatsBibliothek

NORMAL

Kopie

SUBITO-CB15011601508

Bibliotheque de la Faculte de Medecine
Centre Medical Universitaire
Frau Tamara Morcillo
1, rue Michel-Servet
1211 Geneve 4
SCHWEIZ

Ben.-Gruppe: USER-GROUP-4
Tel: +41 22 3795100
Mail: ge8-requester-medecine@unige.ch

Fax: +41 22 3795109

Subito-Kundennummer:
SLS02X00172
Subito-Bestellnummer:
SUBITO-CB15011601508

Z 2000.787 Hbzs 763-20 d = Neueste Hefte

Jahrgang: 2012

Band/Heft: 23;1

Seiten: 139-63

Verfasser: Allen LM

Titel: Premenstrual syndrome and dysmenorrhea in adolescents.

Adolescent medicine
ISSN: 1934-4287

Bemerkung: 95403

Beschreibung:

Die Abrechnung dieser Lieferung erfolgt über die subito-Zentralregulierung

Bei Rückfragen wenden Sie sich bitte innerhalb von 10 Tagen an die Bayerische Staatsbibliothek, Direktlieferdienste
Tel. ++49 89 28 638-26 43, doklief@bsb-muenchen.de

Adolesc Med 23 (2012) 139–163

Premenstrual Syndrome and Dysmenorrhea in Adolescents

Lisa M. Allen, MD, FRCSC*[a], Alexandra C. Nevin Lam, MD, FRCSC[b]

[a]*Section Head, Pediatric Gynecology, Hospital for Sick Children; Head, Gynecology, Mt. Sinai Hospital; Site Chief, Department of Obstetrics and Gynecology, Women's College Hospital; Associate Professor, Departments of Obstetrics and Gynecology and Pediatrics, University of Toronto, Toronto, Ontario, Canada*

[b]*North York General Hospital, Hospital for Sick Children; Lecturer, Department of Obstetrics and Gynecology, University of Toronto, Toronto, Ontario, Canada*

INTRODUCTION

Menstrual dysfunction and symptoms commonly affect adolescents. Adolescents may be concerned about whether these symptoms are normal or whether they represent abnormality, especially given their relative inexperience with the pubertal changes that represent their new reproductive capacity. Adolescent health care providers (HCPs) should be able to distinguish symptoms that accompany normal menstruation from those that represent significant pathology and be able to guide young women as to what treatments are available to decrease both symptoms and any impact on their quality of life. This article focuses on the pathophysiology, diagnosis, and management of premenstrual syndrome and dysmenorrhea, both primary and secondary.

PREMENSTRUAL SYNDROME IN ADOLESCENTS

Most females experience premenstrual symptoms as a component of normal ovulatory menstrual cycles. When these symptoms begin to impact on quality of life and result in functional impairment, they then warrant the diagnosis of premenstrual syndrome (PMS), or premenstrual dysphoric disorder (PMDD) at the most severe end of the spectrum. The mean age of presentation for treatment

*Corresponding author.
E-mail address: LAllen@mtsinai.on.ca (L. M. Allen).

 ISSN 1934-4287

of PMS is the late 20s; however, most women recount nearly 10 years of symptoms before this.[1] Retrospective data specific to prevalence in adolescents are provided by several large-scale studies and appear to be comparable to adults, with 20–30% and 5–8% meeting criteria for PMS and PMDD, respectively.[2-5]

Symptoms

The most common symptom endorsed by adolescents is that of negative affect, including mood swings (59%), stress (87.6%), and nervousness (87.6%).[5] Physical symptoms are also quite prominent, with abdominal bloating and pain reported by two-thirds of adolescents in the same study. The impact of these symptoms on quality of life is significant, as more than half of teens attending a primary care gynecology clinic rated their symptoms as moderate to severe, and 59% of this group rated their impairment at home and with family to be moderate to severe.[4]

Diagnosis

The diagnostic criteria for PMDD[6] and PMS[7] are outlined in Box 1 and Box 2, respectively. The hallmark of each diagnosis is its temporal relationship to the menstrual cycle. For the diagnosis, there must be symptom onset in the periovulatory period (after day 13) with continuation until the early follicular phase of the next cycle. The symptoms must then completely abate during the week following menses. In addition, marked functional impairment is required, as is the exclusion of the symptoms as an exacerbation of another disorder. Prospective evaluation of symptoms for at least 2 consecutive cycles is a requirement. It has been documented that 50% of women who complain of PMS do not confirm their retrospective reports when their symptoms are evaluated prospectively.[8] One device to aid with documentation and to establish appropriate cycle timing is the Daily Record of Severity of Problems (DRSP).[9] The importance of an appropriate screening tool in adolescents is key to early identification of those who warrant prospective evaluation, education, and possible treatment. The Premenstrual Symptoms Screening Tool (PSST-A) has been revised for use in adolescents (Table 1), and results from a recent pilot study suggest it is valid for use in this population.[3]

Etiology

The precise pathophysiology of PMS is still unknown. Current knowledge suggests that it is due to a complex set of interactions between periovulatory fluctuating sex steroids and central neurotransmitters, such as serotonin and γ-aminobutyric acid (GABA), in susceptible individuals. A genetic predisposition has been suggested by twin studies.[10] The obvious relationship of PMS to the later phase of the menstrual cycle suggests that periovulatory changes in sex hormones may play a pivotal role. However, there is no difference in the periph-

Box 1. DSM-IV-TR Criteria for Premenstrual Dysphoric Disorder

A. In most menstrual cycles during the past year, 5 (or more) of the following symptoms were present for most of the time during the last week of the luteal phase, began to remit within a few days after the onset of the follicular phase, and were absent in the week postmenses, with at least 1 of the symptoms being either (1), (2), (3), or (4):
   (1) markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts
   (2) marked anxiety, tension, feelings of being "keyed up," or "on edge"
   (3) marked affective lability (eg, feeling suddenly sad or tearful or increased sensitivity to rejection)
   (4) persistent and marked anger or irritability or increased interpersonal conflicts
   (5) decreased interest in usual activities (eg, work, school, friends, hobbies)
   (6) subjective sense of difficulty in concentrating
   (7) lethargy, easy fatigability, or marked lack of energy
   (8) marked change in appetite, overeating, or specific food cravings
   (9) hypersomnia or insomnia
   (10) subjective sense of being overwhelmed or out of control
   (11) other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of "bloating," weight gain

NOTE: In menstruating females, the luteal phase corresponds to the period between ovulation and the onset of menses, and the follicular phase begins with menses. In nonmenstruating females (eg, those who have had a hysterectomy), the timing of luteal and follicular phases may require measurement of circulating reproductive hormones.

B. The disturbance markedly interferes with work or school or with usual social activities and relationships with others (eg, avoidance of social activities, decreased productivity and efficiency at work or school).
C. The disturbance is not merely an exacerbation of the symptoms of another disorder, such as Major Depressive Disorder, Panic Disorder, Dysthymic Disorder, or a Personality Disorder (although it may be superimposed on any of these disorders).
D. Criteria A, B, and C must be confirmed by prospective daily ratings during at least 2 consecutive symptomatic cycles. (The diagnosis may be made provisionally prior to this confirmation.)

eral levels of sex steroids between PMS-affected individuals and controls across the menstrual cycle,[11] suggesting that the symptomatology results from an exaggerated response to normal fluctuations in these hormones in predisposed individuals.[12] Sex steroids are further implicated by the fact that treatment with a gonadotropin-releasing hormone (GnRH) agonist for ovulation suppression has been shown in studies to relieve PMS symptoms, as has oophorectomy.[13,14] Evidence for the "susceptible individual" theory is that women with PMS, but not asymptomatic women, experience recurrence of their PMS symptoms when given a physiologic dose of either estrogen or progesterone after induction of medical menopause with a GnRH agonist.[15]

Experimental models have demonstrated that sex steroids modulate serotonin transmission,[16,17] and it is well-established that aberrant serotonin neurotrans-

Box 2. American College of Obstetricians and Gynecologists Diagnostic Criteria for Premenstrual Syndrome

1. The presence by self-report of at least 1 of the following somatic *and* affective symptoms during the 5 days before menses in each of the 3 prior menstrual cycles:

Affective	*Somatic*
Depression	Breast tenderness
Angry outbursts	Abdominal bloating
Irritability	Headache
Anxiety	Swelling of extremities
Confusion	
Social withdrawal	

2. The symptoms are relieved within 4 days of the onset of menses, without recurrence until at least cycle day 13
3. The symptoms are present in the absence of any pharmacologic therapy, hormone ingestion, or drug or alcohol use
4. The symptoms occur reproducibly during 2 cycles of prospective recording
5. Identifiable dysfunction in social or economic performance by 1 of the following criteria:
   - Marital or relationship discord confirmed by partner
   - Difficulties in parenting
   - Poor work or school performance, poor attendance, or tardiness
   - Increased social isolation
   - Legal difficulties
   - Suicidal ideation
   - Seeking medical attention for a somatic symptom

Adapted from Mortola JF, Girton L, Yen SSC. Depressive episodes in premenstrual syndrome. *Am J Obstet Gynecol.* 1989;161:1682–1687, with permission from Elsevier.

mission is associated with depression, irritability, anger, and increased cravings for carbohydrates.[18] Women with PMS/PMDD have been shown to have abnormally low serotonin levels during the luteal phase of the menstrual cycle.[19] Further indirect evidence of the association between sex steroids and serotonin are the facts that selective serotonin reuptake inhibitors (SSRIs) rapidly and effectively treat PMS/PMDD,[20-24] treatment with a serotonin-receptor antagonist exacerbates symptoms,[25] and reduced libido is a very common side effect of long-term treatment with SSRIs.[22] Another neurotransmitter implicated in this complex interaction is the GABA-A receptor, which is well recognized to play a regulatory role in affect and is modulated by sex steroids, most notably the progesterone metabolite allopregnanolone.[26] Allopregnanolone binds to the GABA receptor with anxiolytic effects,[27] and studies have shown reduced GABA receptor sensitivity in the luteal phase in women with PMS/PMDD.[28]

Treatment

The treatment of PMS is solely symptom driven, with the goal being improvement in quality of life. It involves supportive care, lifestyle and dietary modifications, and/or pharmacologic interventions. The cornerstone of management of

Table 1.
The Premenstrual Symptoms Screening Tool for Adolescents (PSST-A)
(Please indicate "X" for each symptom under the appropriate rating.)
Do you experience some or any of the following premenstrual symptoms which *START BEFORE* your period and *STOP* within a few days of bleeding?

Symptom	Not at all	Mild	Moderate	Severe
1. Anger/irritability				
2. Anxiety/tension				
3. Tearful/increased sensitivity to rejection				
4. Depressed mood/hopelessness				
5. Decreased interest in work activities				
6. Decreased interest in home activities				
7. Decreased interest in social activities				
8. Difficulty concentrating				
9. Fatigue/lack of energy				
10. Overeating/food cravings				
11. Insomnia				
12. Hypersomnia (needing more sleep)				
13. Feeling overwhelmed or out of control				
14. Physical symptoms (including breast tenderness, headaches, joint/muscle pain, bloating, and weight gain)				

Have your symptoms, as listed above, interfered with:

	Not at all	Mild	Moderate	Severe
A. Your social/work efficiency or productivity				
B. Your relationships with friends or classmates/coworkers				
C. Your relationships with your family				
D. Your social life activities				
E. Your home responsibilities				

Scoring
The following criteria must be present for a diagnosis of PMDD:

1. At least one of #1, #2, #3, or #4 is severe
2. In addition at least four of #1–14 are moderate to severe
3. At least one of A, B, C, D, or E is severe

The following criteria must be present for a diagnosis of moderate to severe PMS:

1. At least one of #1, #2, #3, or #4 is moderate to severe
2. In addition at least four of #1–14 are moderate to severe
3. At least one of A, B, C, D, or E is moderate to severe

Reproduced from Steiner M, Peer M, Palova E, et al. The Premenstrual Symptoms Screening Tool revised for adolescents (PSST-A): prevalence of severe PMS and premenstrual dysphoric disorder in adolescents. *Arch Womens Ment Health.* 2011;14:77–81.

PMS in the adolescent population is education about (1) the menstrual cycle and PMS, (2) self-care measures to reduce symptom severity, and (3) acknowledgment of symptoms and the impact that they may have on overall functioning. One study of an educational program involving secondary school females resulted

in a significant reduction in PMS scores in adolescents who received the education versus controls.[29] This response was sustained for 3 months posteducation.

Specific self-care activities that have been advocated include stress management techniques, namely exercise and dietary modification. The role of exercise in treating premenstrual symptoms has been investigated in small interventional studies in adult women only. Of the 4 studies identified by a recent review,[30] all reported a reduction in PMS symptoms following exercise interventions, with one specifically showing symptom improvement following aerobic exercise over strength training.[31]

Many dietary modifications for the treatment of PMS/PMDD have been investigated, including calcium and vitamin D, magnesium, vitamin E, primrose oil, vitamin B6, chaste berry, and carbohydrate-rich diets.[2,12,32] Of these, level 1 evidence only exists in support of calcium supplementation (1200 mg per day in divided doses) for significant improvements in negative affective symptoms, water retention symptoms, food craving, and pain symptoms.[33] Subsequent studies have documented a significant difference in calcium metabolism parameters throughout the menstrual cycle in women with PMDD versus asymptomatic controls.[34] Adequate vitamin D, which is required for calcium absorption, is likely an integral part of this effect, as shown in studies documenting a significant negative relationship between milk consumption and PMS symptoms in adolescents,[5] a cross-sectional study confirming that a higher intake of vitamin D is significantly associated with a lower prevalence of PMS,[35] and a randomized controlled trial (RCT) that demonstrated a significant reduction in PMS symptoms versus placebo.[36]

As one of the presumed underlying mechanisms predisposing an individual to PMS is periovulatory fluctuation in sex steroids, ovulation suppression with a combined oral contraceptive pill (COCP) seems a natural treatment choice. However, past studies have shown inconsistent results for COCPs regardless of the type of progestin or the variable progestin dose used throughout the pack (monophasic vs. triphasic).[37,38] In one study, 71.4% of women stated that the COCP had no effect at all on their PMS symptoms.[39] Recently, the introduction of the novel progestin drospirenone and the established efficacy of a shortened hormone-free interval (HFI) with lower estrogen dosing has resulted in a resurgence of COCP use for the treatment of PMS with significant results. Drospirenone is unique in that it is derived from a compound similar to spironolactone, not testosterone, as are traditional progestins used in COCPs. As a consequence of this, drospirenone has the dual benefit of possessing antimineralocorticoid and antiandrogenic properties. The shortening of the HFI results in constant suppression of gonadotropins such that follicular growth and estradiol production remain arrested,[40] whereas conventional 21-day active/7-day placebo (21/7) dosing regimens are associated with incomplete suppression and often PMS symptom exacerbation with hormone withdrawal.[41] Further maintenance of a

more stable hormonal milieu is likely related to the longer half-life of drospirenone.[42]

A lower ethinyl estradiol (EE) dose is also likely important in the prevention of symptoms.[43] Two large multicenter, double-blind RCTs have shown that the drospirenone/20mcg EE-24/4 pill combination is significantly effective in treating the mood, somatic, and behavioral symptoms of PMDD versus controls.[44,45] Furthermore, Pearlstein et al (2005) found a 2-fold improvement in overall quality of life. Evidence in support of extended and continuous cycles is provided by a prospective study, which showed that a 168-day extended cycle of drospirenone/30 mcg EE led to a significant decrease in premenstrual symptoms compared to a 21/7 regimen of the same pill, with the largest effect being seen in the sixth month of continuous use.[46] Recent controversy surrounding the use of drospirenone-containing COCPs and increased venous thromboembolic (VTE) risk has been addressed in clinical practice guidelines, wherein it is concluded that rates are comparable between these and other COCPs on the market.[47] Unfortunately, none of the studies have involved adolescents. The additional benefits of COCPs, including contraception, make this a very attractive option to treat PMS/PMDD in adolescents, when education, lifestyle, and dietary modifications are insufficient.

The use of SSRIs are generally considered to be first-line treatment for severe PMS and PMDD in adult women. Placebo-controlled trials have confirmed a 60–90% response rate with significant improvement versus placebo,[20,24] and a Cochrane systematic review confirmed efficacy in treating physical, functional, and behavioral symptoms.[22] Only fluoxetine, sertraline, and paroxetine have been approved for use in the treatment of PMDD by the US Food and Drug Administration (FDA) (dosing schedule in Table 2). Despite this, a recent meta-analysis including 2964 women concluded that no SSRI was demonstrably better than any other but that the effect size is smaller than previously reported, with an odds ratio of 0.4.[23] The most common adverse effects of SSRIs include nausea,

Table 2.
Dosing of the FDA-Approved SSRIs for Severe PMS/PMDD

SSRI	Dose (once daily or for luteal phase dosing)
Fluoxetine	10–20 mg[20]
Sertraline	Start 25–50 mg up to max 150 mg/day Most need 100 mg/day[21]
Paroxetine-CR	12.5–25 mg[24]
Paroxetine	20–30 mg[12]

FDA: Food and Drug Administration;
SSRIs: selective serotonin reuptake inhibitors;
PMS: premenstrual syndrome;
PMDD: premenstrual dysphoric disorder

insomnia, headache, and decreased libido.[22] Studies specific to adolescents are lacking.

Unlike SSRI use in the treatment of mood disorders, clinical response to SSRIs in PMDD occurs within days of exposure. As such, intermittent luteal phase dosing beginning around day 14 of a 28-day cycle (or at symptom onset) and continuing until a few days after the onset of menses (symptom cessation) has been proven to be effective.[48,49] This dosing strategy can be considered for PMS/PMDD-affected women without comorbid mood disorders who experience side effects with conventional daily dosing, and it carries the added benefit of not producing discontinuation symptoms.[32] A recent meta-analysis, however, concluded that although both continuous and intermittent luteal dosing with SSRIs are effective, continuous dosing regimens appear superior.[23]

In the published adolescent literature to date, there is one case report of 3 PMDD-affected adolescents treated successfully with fluoxetine for 2 years.[50] Of the SSRIs approved for the treatment of severe PMS/PMDD, fluoxetine is the only one with FDA approval for use in children and adolescents, and this is for the indication of major-depressive disorder and obsessive-compulsive disorder. In 2004, the FDA issued a "black box warning" for SSRIs based on the results of studies that documented a significant 4% increased rate of suicidal thinking or behavior in youths prescribed SSRIs for treatment of depression versus 2% for placebo. Subsequently, a comprehensive review of trials confirmed that SSRIs are efficacious for the treatment of pediatric mood disorders and that the benefits outweigh the risks regardless of the mood disorder being treated.[51] However, SSRIs are generally not considered first-line treatment as a pharmacologic intervention in adolescents with PMS/PMDD. If required, fluoxetine would be preferable and would require appropriate prospective diagnosis and diligent monitoring, likely under the care of a multidisciplinary team.[2] Fluoxetine is also known to have the least association with a discontinuation syndrome in adolescents, due to its longer half-life than other SSRIs, thereby highlighting it as the SSRI of choice in refractory, severe cases of PMS/PMDD.[52] Other treatment options shown to be effective in adults, such as use of a GnRH-agonist, would not be employed in adolescents due to their associated health implications, including detrimental bone, cardiovascular, and vaginal health effects, unless in absolutely refractory cases. One study suggests that add-back hormonal support concurrent to GnRH-agonist treatment is protective of bone health at the hip, but not at the spine, in adolescents with endometriosis.[53] Theoretically, add-back may cause symptom relapse in the setting of severe PMS/PMDD, thereby limiting its use.

DYSMENORRHEA

Dysmenorrhea is common among women, particularly in middle and late adolescence. Reviewing the literature, a prevalence of 48–93% is reported across multiple countries in this age group.[54-60] The upper prevalence is published both

in a Canadian population of 289 high school students and in an Australian cohort of 1055 senior high school girls completing a questionnaire on menstrual disorders.[54,55] United States' data document similar frequencies, from 65% in an urban, primarily black health care population to 85% of 606 Hispanic adolescents in a school-based cohort.[56,61] A recent meta-analysis on factors predisposing women to chronic pelvic pain found no significant difference in dysmenorrhea rates related to ethnicity.[62]

Severe dysmenorrhea affects a smaller proportion of adolescents, 5–42%.[54-56,59] For many, their quality of life is affected. Twenty six percent report missing school due to pain, and this may be even higher (46%) when dysmenorrhea is moderate or severe.[55,63] Fourteen percent usually missed 2 or more days per month due to their pain.[63] Not only is school attendance impacted, but severity of pain also has been shown to significantly affect participation in sports and socialization with peers.[56] Despite the large numbers affected, many do not seek medical attention. Two separate studies, 20 years apart, indicate that only 14% of adolescents with dysmenorrhea consult with a physician.[56,58] Unfortunately, adolescents may not perceive benefit from health care encounters related to this concern; 77% of Hispanic youth who visited a school nurse reported no relief from the encounter.[56] The aforementioned data emphasize to health care providers that menstrual pain is common, and it significantly affects adolescents' quality of life, and yet most adolescents still do not seek out medical care. Inserting questions into routine adolescent health care encounters with regards to menstrual symptoms is essential. Only 2% of adolescents at an urban tertiary adolescent health care center reported having received information on menstruation from their HCP.[61]

Pathophysiology

Dysmenorrhea may be primary or secondary. Primary dysmenorrhea, which comprises 90% of adolescent menstrual pain, is a result of physiologic changes that occur during a menstrual cycle. Secondary dysmenorrhea reflects an underlying pathologic process or disease (eg, endometriosis, Müllerian anomalies, pelvic inflammatory disease, adenomyosis/adenomyotic cysts).

In primary dysmenorrhea, following progesterone withdrawal premenstrually, phospholipids are released from cell membranes, in particular omega-6 fatty acids. The fatty acids are converted to arachidonic acid (AA) by the enzyme phospholipase A2. Prostaglandin (PG) synthesis follows with conversion of AA via cyclooxygenase (COX). The PGs are then transformed to leukotrienes (LTs) via lipoxygenase. Prostaglandin F2 alpha (PGF2 alpha) is a potent vasoconstrictor and stimulates myometrial contractions, leading to uterine ischemia and pain.[64] The PGs and LTs are responsible not only for the cramps in dysmenorrhea but also for the systemic symptoms accompanying menses (nausea, vomiting, bloating, and headaches). Levels of PG activity have been documented to be higher in the menstrual fluid and endometrium of women with dysmenorrhea

compared to those who do not have pain. Similarly, LT C4 and D4 levels are correlated with the occurrence of dysmenorrhea, as well as with its severity. Nitrous oxide, a vasodilator may play a role. Transdermal patches of nitrous oxide have been shown to reduce pain in those with dysmenorrhea. The role of vasopressin in the pathogenesis of primary dysmenorrhea remains unclear.[65]

Additional factors that are associated with dysmenorrhea besides young age are a body mass index (BMI) less than 20, smoking, early menarche (younger than 12 years of age), menstrual cycles that are long, heavy, or irregular, and the presence of premenstrual symptoms.[59,62]

Diagnosis

Once one understands the pathophysiology of primary dysmenorrhea, the natural history becomes clear. Primary dysmenorrhea occurs with ovulatory cycles, and hence occurs more frequently in middle and late adolescence when the proportion of ovulatory cycles increases.[58] The normal history is that after a mean of 12 months of relatively symptom-free menses, adolescents may begin to experience pain that occurs transiently with or in close proximity to the onset of menstrual flow. Ninety percent of adolescents report symptoms for less than 48 hours.[55,66] As previously mentioned, PGs mediate systemic symptoms in adolescents with moderate or severe dysmenorrhea. Nausea (55%) and vomiting (24%) are common symptoms.[67] Other reported symptoms are fatigue (67%), headaches (59%), back pain (56%), and dizziness (28%).[56]

The diagnosis of primary dysmenorrhea is made largely on history. If a classic history of primary dysmenorrhea is obtained, a trial of therapy is warranted. History should assess the presenting menstrual symptoms (ie, severity and duration of pain) and the impact of those symptoms on activities such as school performance and attendance and life activities. Severity of pain can be estimated in part from the use of analgesia. Harada et al[68] graded mild, moderate, and severe dysmenorrhea as mild: analgesics required for 1 day; moderate: analgesia required for 2 days; and severe: analgesia required for 3 or more days. Tools such as menstrual calendars or a menstrual distress questionnaire may aid with accurate documentation of symptoms in the adolescent age group.[55] Given that the history is inherent in determining which adolescents would benefit from further investigations, a comprehensive review of the sexual history, the past medical history, and the family history is essential.

Clues obtained on history may lead to a suspicion of secondary dysmenorrhea (Table 3). In an Australian study, the authors aimed to establish not only contemporary data on the teenage experience of menstruation but also features that may identify those requiring management for underlying pathologic disorders. In this study, students were administered a menstrual disorder of teenagers (MDOT) questionnaire. Questions were developed to identify atypical men-

strual symptoms (see Table 3). Although 93% of respondents indicated pain with menses, only 15% answered affirmatively with 2 or more atypical symptoms and only 6% with 3 or more. Further research may be able to translate these features into a noninvasive screening tool to assist HCPs in identifying young women at risk for secondary dysmenorrhea.[55]

In nonsexually active adolescents, a pelvic examination is not essential in making a diagnosis of primary dysmenorrhea. In a sexually active adolescent, a pelvic examination should be performed, maintaining awareness that pelvic inflammatory disease may present with the new onset of dysmenorrhea. Endometriosis in adolescents is most often early stage disease, stage 1 or 2 by American Society for Reproductive Medicine (ASRM) classification; therefore, while a bimanual examination may elicit pelvic tenderness, it is rare to palpate evidence of deep infiltrating disease such as uterosacral or cul-de-sac nodularity, uterine fixed retroversion, or endometriomas.[69,70] Müllerian outflow tract anomalies, in particular the asymmetric anomalies such as a uterine didelphys with an obstructing

Table 3.
Clues on History to Consider Secondary Dysmenorrhea in Adolescents

History	Clue	Association
Response to first-line medical therapy	Persistent pain despite NSAID or CHC therapy	Consider secondary dysmenorrhea, up to 69% diagnosis of endometriosis on laparoscopy
Timing of first onset of dysmenorrhea	Dysmenorrhea occurred in close temporal relationship to onset of menarche	PD typically occurs with establishment of ovulatory cycles. Pain that occurs with onset of first menstrual cycles may reflect Müllerian anomalies with outflow tract obstruction
Atypical symptoms	Dyschezia, pain with flatus, dysuria, pain with bladder distension, dyspareunia	These symptoms were reported far less frequently by adolescents and may indicate underlying secondary dysmenorrhea
Family history	Positive family history of a relative with endometriosis	Adolescents have higher rate of first degree relatives affected with endometriosis than adults (30% vs. 8%)
Sexual activity	Sexually active adolescent, may have symptoms of PID (pelvic pain, vaginal discharge), with or without history of STI	PID may present with new-onset dysmenorrhea
Medical history	Known renal tract anomaly	Müllerian anomalies and renal anomalies often coexist; Müllerian anomalies with outflow tract obstruction can present with pelvic pain and secondary dysmenorrhea

NSAID: nonsteroidal anti-inflammatory drug;
CHC: combined hormonal contraception;
PD: primary dysmenorrhea;
PID: pelvic inflammatory disease;
STI: sexually transmitted infection

hemivaginal septum or a noncommunicating uterine horn with a functional endometrium, are a less common but important consideration in the adolescent with secondary dysmenorrhea. Assessing the patency of the outflow tract is important, both by physical examination and by imaging. Initial pelvic imaging should begin with sonography (pelvic, transvaginal, 3D), and subsequently, Müllerian anomalies are often confirmed with magnetic resonance imaging (MRI). Diagnostic laparoscopy may be required when an etiology is not determined, initial treatment modalities have failed, or in combination with surgical management of pathology, such as in endometriosis.

Treatment

Primary Dysmenorrhea Given the high prevalence of dysmenorrhea in adolescents compared to the proportion seeking medical care, it is not surprising that many treat themselves with either nonpharmacologic therapies or over-the-counter (OTC) medications. In fact, 98% of adolescents in one study reported having attempted to relieve their pain with at least one nonpharmacologic method and 91% with OTC medications.[54] HCPs should be aware of what initial modalities adolescents may use to cope during menses, why they select them, and the potential benefits they perceive from these methods.

Adolescents indicate various reasons for their use of alternative strategies. Most commonly cited are that these methods ease discomfort, are convenient or easier than going to a HCP, are preferable to medications, or are used because medication does not provide relief or is not available. Strategies are either physically oriented (rest, heat, exercise, massage, more or less alcohol consumption, change in diet) or psychologically oriented (distraction, imagining, praying/hoping for relief, discussing with others). Most are perceived to be only 30–40% effective, with a large variability in effectiveness scores with each method, suggesting an idiosyncratic response. The least likely to provide relief are those that are psychologically oriented.[54] With OTC medications, young women may unfortunately chose medications that are not effective (ie, acetaminophen, narcotics) or do not maximize use, either by taking less than the recommended dose or less often than the maximum recommended daily frequency.[63,71] In one study, up to 71% of adolescents used less than 50% of the maximum daily dose of analgesia in the first 2 days of their menses.[63] Given that accessible, nonpharmacologic strategies have low to moderate perceived effectiveness, HCPs should be prepared to counsel adolescents on additional strategies for symptom management. In addition, if an OTC therapy is reported to have failed to relieve pain, a thorough history of dose and frequency of use is advised before determining that a change of therapeutic modality is required.

Nonpharmacologic Management Interventions such as exercise/yoga, acupuncture, dietary alterations, and cessation of smoking have been proposed as therapy for dysmenorrhea.[72] Fifteen percent of adolescents use exercise to relieve

symptoms.[56] Exercise may exert its beneficial effect by shunting blood flow away from the viscera to the muscles, thereby reducing pelvic congestion; by acting as a mechanism for vasodilation; by suppressing PG release; via release of beta endorphins to act as a nonspecific analgesic; or indirectly by reducing stress.[73,74] The existing literature on exercise and primary dysmenorrhea is conflicting; some smaller observational studies suggest that regular exercise reduces primary dysmenorrhea, whereas others report a lack of association.[73,75,76] A recent meta-analysis of risk factors for dysmenorrhea demonstrated a small protective effect, with an odds ratio of 0.89 (confidence intervals, 0.80 to 0.99).[62] Only a single RCT has been performed to address this question. It included 36 college-aged women with clinically diagnosed primary dysmenorrhea. The young women were randomized to a 12-week walk/jogging program or to no exercise, for 3 cycles. There was a decrease in the Moos Menstrual Distress Questionnaire scores during the menstrual phase for the training group compared to the control group, with a significant linear trend over the 3 cycles.[74] Based on the availability of only this single RCT, the Cochrane Database concluded that there is a lack of evidence to recommend exercise for the treatment of primary dysmenorrhea.[77] Authors unable to demonstrate sufficient evidence that exercise improves primary dysmenorrhea do recognize, however, that there are other broad health benefits of exercise that should be discussed with women.[73,75]

Young smokers have an increase in self-reported menstrual symptoms (pain, premenstrual negative affect, fluid retention) in a dose response relationship, increasing with younger age at onset of smoking, especially for those who start younger than age 13, and the number of cigarettes smoked per day.[62,78,79] The exact mechanism whereby smoking increases severity of dysmenorrhea is unclear. HCPs, however, can use this information in counseling adolescents on smoking risks. The immediate potential benefit of reducing menstrual pain may be a motivator for change that HCPs can promote to adolescents to encourage them to cease smoking.

Dietary modifications to increase consumption of fish/fish oils containing long chain omega-3 polysaturated fatty acids (salmon, tuna, mackerel, herring) may serve as a strategy to reduce pain. The prostaglandins formed from these fatty acids are less potent than those containing omega-6 fatty acids.[65,72] Additional dietary modifications with evidence of benefit over placebo in reducing dysmenorrhea include supplements of vitamins E and B1 and magnesium.[72]

Acupuncture and acupressure as complementary and alternative medicine techniques may assist in the relief of dysmenorrhea. In acupuncture, needles placed at specific skin locations are manipulated, exciting nerve fibers, resulting in the production of endorphins, serotonin, and acetylcholine, which act to enhance analgesia in the central nervous system through dampening or inhibiting of pain impulses.[72,80] Cho reviewed the literature, assessing 27 trials that compared acupuncture/acupressure to a control group (no treatment or placebo treatment

using sham acupuncture), nonsteroidal anti-inflammatory drugs (NSAIDs), or herbal medicines for the treatment of primary dysmenorrhea. The studies favored acupuncture/acupressure over indomethacin, ibuprofen, or herbal medicines. Three studies compared acupuncture to sham acupuncture, where needles are placed either via a superficial insertion technique or at nonacupoints. Only one study demonstrated a statistically greater reduction of pain in the acupuncture treatment group. The authors concluded that there is promise for acupuncture but that the conflicting evidence of acupuncture versus sham acupuncture needs further investigation. Sham acupuncture may not be totally inert physiologically, as placement of a needle even minimally through the skin or at nontrigger points may have benefit in itself, or the effect of acupuncture may be attributed to a placebo effect.[80,81]

Pharmacologic Management Pharmacologic therapies aim to reduce the production of PGs and inflammatory cytokines, as well as to reduce menstrual flow, both antegrade and retrograde. When the adolescent seeks assistance from HCPs, the approach to relief of dysmenorrhea is stepwise. First-line therapies to be considered include NSAIDs, combined hormonal contraceptives, and long-acting reversible contraceptives (LARCs), depending on the additional need for contraception.

NSAIDs inhibit the enzymes of the cyclooxygenase pathway (COX-1 and COX-2), preventing conversion of AA into PGs. This class of medications is often considered first-line therapy, unless a woman has a contraindication to their use. NSAIDs fall into 2 classes, those that are nonspecific and inhibit both COX-1 and COX-2 enzymes (eg, ibuprofen, naproxen, diclofenac, meclofenamate) and those that are COX-2 specific inhibitors (celecoxib, rofecoxib, valdecoxib). COX-1 is expressed throughout the body (including the endometrium), is involved in the maintenance of normal hemostasis, and provides gastrointestinal mucosal protection. COX-2 is induced by proinflammatory cytokines and endotoxins at inflammatory sites. Hence the side effects of NSAIDs are related to inhibition of COX-1, whereas the therapeutic and anti-inflammatory effects are related to inhibition of COX-2.[82] COX-2 specific inhibitors are available; however, because they have been linked with an increased risk of cardiac complications, they are no longer indicated for the treatment of primary dysmenorrhea.[64] A Cochrane systematic review has confirmed that NSAIDs are consistently superior to placebo in providing pain relief, with an odds ratio of 4.50 (confidence intervals, 3.85–5.27). Most of the 73 RCTs that have been performed have involved naproxen; however, 21 different NSAIDs have been studied. Equivalent improvement of symptoms has been demonstrated between different products, hence there is insufficient evidence to suggest that any one is superior to the others. Diclofenac and naproxen have demonstrated translation of treatment into improvement of quality of life, as evidenced by less school or work absenteeism.[77]

Many studies of NSAIDs exclude adolescents. One that specifically assessed the adolescent age group included 45 young women, ages 12–18, evaluating the

response of symptoms to varying dosing regimens of naproxen. The study determined that a loading dose of 550 mg was more beneficial in 3 treatment cycles compared to a lesser loading dose.[66] When choosing an NSAID for treatment of primary dysmenorrhea in an adolescent, because no single NSAID is superior, choosing one that requires less frequent dosing may be more convenient for the adolescent, particularly during school attendance. Providing a loading dose preemptively may improve success of therapy. Failure of relief of pain with NSAIDs may reflect their failure to inhibit production of other substances involved in the pathophysiology of primary dysmenorrhea, such as LTs. Although the side effects of NSAIDs may include gastrointestinal disturbances, renal failure, and skin reactions, short-term use with menses minimizes these effects. Select suggested NSAID regimens with their effective doses are presented in Table 4.

Combined hormonal contraceptives (CHCs), such as oral contraceptive pills, the transdermal contraceptive patch, and the contraceptive ring, limit the growth of the endometrium, subsequently reducing the amount of PGs and LTs formed and released. Inhibition of ovulation and subsequent progesterone production may be an additional indirect mechanism of effect.[65] The contraceptive benefits of these methods may lead the HCP to prescribe them as first line therapy. Both primary and some causes of secondary dysmenorrhea, in particular endometriosis, may respond to their administration. In 2005 Davis et al reported the first RCT on the effectiveness of oral contraceptives for primary dysmenorrhea in adolescents, despite the widespread clinical use before that time. Adolescents were included if they suffered from moderate or severe dysmenorrhea. Low dose (ethinyl estradiol 20 μg and levonorgestrel 100 mg) therapy was demonstrated to reduce the Moos Menstrual Distress questionnaire pain score, lessen the worst pain experienced, and decrease amount of analgesia required in users compared to placebo therapy, when prescribed cyclically.[67]

Although one would expect similar benefits when administering combined contraceptives either with the transdermal patch (releasing 20 μg of ethinyl estradiol

Table 4.
NSAID Regimens for Adolescent Dysmenorrhea

NSAID	Dosage
Ibuprofen	200–400 mg by mouth every 4–8 hours
Naproxen sodium	550 mg by mouth loading dose, followed by 275 mg every 6–8 hours or 550 mg every 12 hours
Naproxen	250–500 mg by mouth twice a day
Diclofenac	100 mg by mouth loading dose followed by 50 mg every 6–8 hours, maximum 200 mg/day
Mefenamic acid	500 mg by mouth loading dose, then 250 mg every 6 hours or 500 mg every 8 hours

*Usual duration of treatment is with menses for less than or equal to 5 days.
NSAID: nonsteroidal anti-inflammatory drug

and 150 μg of norelgestromin daily) or the vaginal ring (ethinyl estradiol and etonogestrel), the data on relief of dysmenorrhea appear stronger for the vaginal ring than the transdermal patch. In 389 adult women newly starting on a vaginal ring, 26.5% reported improvement in moderate or severe dysmenorrhea, whereas only 1% indicated an increase in pain.[83] In a 1 year randomized, open-labeled, European trial comparing the vaginal ring and a COCP (30 μg ethinyl estradiol and drospirenone), both demonstrated equivalent efficacy in reducing reported moderate or severe dysmenorrhea, from 17.4 to 5.9% for the ring and from 19 to 6.4% for the COC.[84] When the patch was prescribed to 28 US adolescents primarily as a contraceptive, 39% reported a subjective improvement in dysmenorrhea; however, 11% indicated their pain worsened.[85] In a Thai cohort of 58 adolescents and young adult women using contraception, only 13.8% of participants reported a reduction in dysmenorrhea.[57] Comparing side effects of the patch and an OCP in adult women, 13.3% of patch users reported dysmenorrhea as an adverse event, whereas only 9.6% of those prescribed an OCP did so, a statistically significant difference.[86]

Further benefit may be achieved for relief of menstrual symptoms when OCPs are prescribed in extended regimens, reducing the hormone-free interval. In a small study of 32 women randomized to cyclic use of a 20 ug ethinyl estradiol/0.1 mg levonorgestrel OCP or an extended regimen of 168 days without a hormone-free interval, menstrual pain was present on only a mean of 1.9 days in the extended regimen group compared to 13.3 days in the cyclic group over 6 months.[87] Extended regimens can be prescribed for nonoral routes of administration. The vaginal ring prescribed for extended use, 84 days continuously with a 7 day ring-free interval, demonstrated a statistically significant reduction in frequency of dysmenorrhea from a baseline of 56% to 20% in those who continued the method at 1 year.[88]

Further clarification with regards to the optimum mode of administration of CHCs for treatment of dysmenorrhea requires specific studies in adolescents whereby pain is the primary outcome measure and is assessed by standardized methods, rather than by subjective report. The options of nondaily administration may enhance ease of method use in adolescents, although it is unclear if the transdermal patch in adolescents provides equivalent relief of dysmenorrhea as do COCs.

LARCs consist of methods of contraception that require administration less than once per month or cycle. The LARCs that are beneficial in the treatment of either primary or secondary dysmenorrhea include the levonorgestrel-releasing intrauterine system (LNG IUS), depo-medroxyprogesterone acetate (DMPA), or the single-rod progestin contraceptive implant.[89] Not only may these methods provide symptom relief, but for the sexually active adolescent they provide reliable contraception as well. Each has a different mechanism of action, administration, and side effect profile. DMPA may reduce dysmenorrhea; however, it has

the concerns of hypoestrogenic loss of bone density with prolonged use and, for some adolescents, a potential side effect of weight gain.[90]

The LNG IUS acts locally within the uterus to cause deciduation of the endometrial stroma, apoptosis in endometrial glands and stroma, and endometrial atrophy.[91] Its primarily local effect limits systemic side effects. In a cohort of 48 adolescents in the United Kingdom (UK) between menarche and age 18, 92% reported improvement in dysmenorrhea at assessments up to 18 months after LNG IUS insertion.[92] Comparing COC to LNG IUS use, one RCT assessing continuation rates of the contraceptive methods suggested superior alleviation of dysmenorrhea with the LNG IUS, when analyzed as a secondary outcome.[93] Usually, LNG IUS use in adolescents for primary dysmenorrhea or endometriosis has not been considered a first-line therapy but has been employed after failure of response to other methods or due to contraindications to standard therapy.[92,94] Previously, barriers to IUS use in adolescents included concern about the possibility of increasing the risk of developing pelvic inflammatory disease (PID). Clarification of the risk demonstrates that PID may be increased briefly around the time of insertion, by transient contamination of the uterine cavity with microorganisms, but then the risk is low over the remaining period of use.[95] There may be a protective effect of LNG IUS compared to a copper IUD, with lower rates of PID reported at 36 months for the LNG IUS.[96] For contraception use, both the World Health Organization (WHO, 2004) and the US Medical Eligibility Criteria (2010), in young women younger than 20 years of age, consider the LNG IUS to be category 2 (ie, the benefits of use generally outweigh the theoretical or proven risks). In nonsexually active adolescents, insertion can be accomplished under general anesthesia, with conscious sedation or with a paracervical block if required.[94] Insertion on or within a few days of menses or with preinsertion treatment with vaginal misoprostol may decrease failure of placement due to an inability to negotiate the cervical os.

The single-rod progestin (etonogestrel) nonbiodegradable implant is an effective method of contraception for 3 years when inserted subdermally. Its mechanism of action is via inhibition of ovulation through maintenance of sufficiently high plasma levels of progestin. When used for contraception, the implant reduces dysmenorrhea, with 81% of 187 women with dysmenorrhea at time of insertion reporting improvement after treatment and only 5% reporting an increase in pain.[97]

Treatments for Specific Causes of Secondary Dysmenorrhea In the adolescent with persistent pelvic pain despite the use of an NSAID and CHC, endometriosis is documented at laparoscopy in up to 69%,[70] making it the most common etiology of secondary dysmenorrhea. Historically there has been a longer delay from onset of symptoms to diagnosis in adolescents compared to adult women, which may result from a different symptom profile.[98] Many young women present with an acyclic component rather than only cyclic pain, and they may

not be sexually active or challenging their fertility, hence dyspareunia and infertility are not present to suggest the diagnosis. The youngest reported child to have had a histologically proven diagnosis of endometriosis was 9 years of age.[99] A positive family history of relatives with endometriosis is more common in adolescents than in adult women (30% vs 7.6%).[69]

A suggested approach to the adolescent with dysmenorrhea is demonstrated in Figure 1. In a young woman who has failed initial medical therapy for pain, pelvic imaging and consideration of laparoscopy for diagnosis and treatment of endometriosis is warranted. As endometriosis lesions in adolescents are more

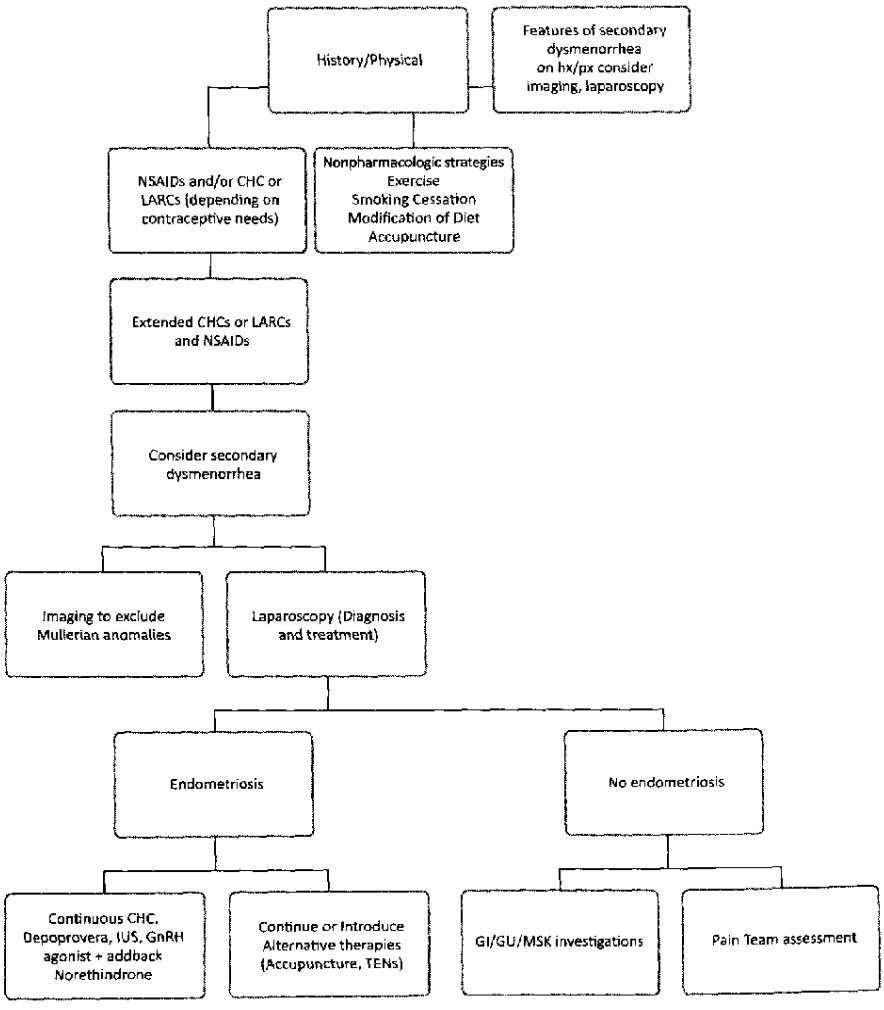

Figure 1. Approach to Dysmenorrhea in Adolescents

often of an atypical form (vesicular or red lesions in approximately 75% of cases), surgery for diagnosis is ideally performed by a surgeon who performs minimally invasive surgery and is familiar with endometriosis in adolescents: The procedure should include an excisional biopsy for histological confirmation.[69]

Early recognition of the symptoms of endometriosis is paramount. A recent study documented that the presence of deep infiltrating endometriosis lesions at laparoscopy in adult women is positively correlated with previous absenteeism from school during menstruation in adolescence, as well as early and prolonged use of OCPs for dysmenorrhea. The authors concluded that early identification of these features could reduce delay in diagnosis.[100]

In many instances, when caring for the adolescent, data regarding the success of therapy are extrapolated from adult populations. Studies of treatment in adolescents are beginning to enhance our knowledge regarding response to therapy in this age group. A recent comparison of adolescents and adults with laparoscopic-proven endometriosis in New Zealand demonstrated a similar positive effect of surgical excision on quality of life questionnaires and visual analogue scales for both populations, one of the first to assess the improvement in pain in adolescents following surgery.[69]

Goals of treatment for the adolescent with endometriosis include establishing a long-term reduction in pain and slowing progression of disease. Once a diagnosis is established, the adolescent should receive medical therapy until a decision is made to pursue conception. It is unclear if the use of medical therapy changes the subsequent development of severe and deeply infiltrating endometriosis.[100,101] The medical therapies previously described for primary dysmenorrhea can be chosen for pain management of the patient with endometriosis with good results (extended use of CHC, Depo-Provera, the LNG IUS).[102,103] GnRH agonists are an additional tool in the management of the pain caused by endometriosis.[104] Theoretical concerns have been expressed regarding their use in younger adolescents, particularly younger than the age of 16, due to concerns about bone health.[101] If prescribed, add-back combined hormone or progesterone-only replacement therapy is advised to minimize symptoms and morbidity while maintaining symptom control.[103]

In order for a Müllerian anomaly to present as secondary dysmenorrhea, there must be partial patency of the outflow tract to allow for visible menarche, whereas cryptomenorrhea leads to the pain. Asymmetric outflow tract obstruction presents as secondary dysmenorrhea, with or without a pelvic mass. The 2 most common variations in Müllerian duct development that result in an asymmetric outflow tract obstruction are a uterine didelphys with a septum obstructing one uterus (OHVIRA syndrome—obstructed hemivagina ipsilateral renal anomaly) or a unicornuate uterus with an associated uterine horn, which both contains an endometrium and is noncommunicating (Figures 2 and 3).

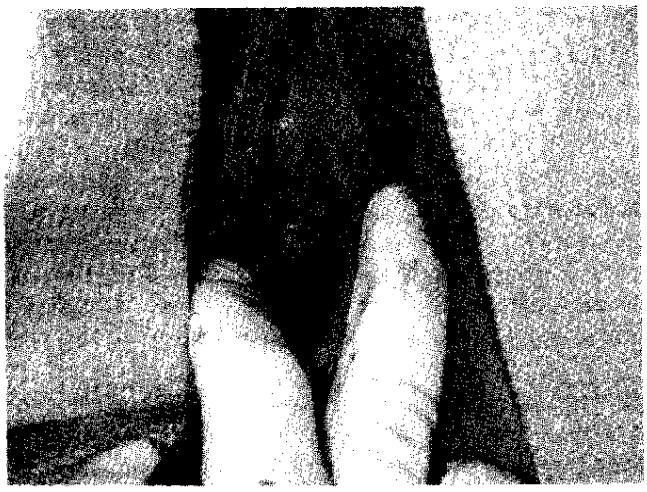

Figure 2. OHVIRA Syndrome The bulge from the left lateral side wall is evident at the time of surgery, and this reflects the hematocolpos behind the obstructing hemivaginal septum in OHVIRA syndrome.

Figure 3. Uterine Horn The small uterine horn on the right contained an endometrium and caused secondary dysmenorrhea.

As uterine didelphys results from a failure of lateral fusion of the Müllerian ducts, 75% of didelphic uteri have an associated longitudinal vaginal septum; a subset of those are obstructing one uterus.[105] OHVIRA syndrome is associated with a renal anomaly in 89% of cases, most commonly renal agenesis ipsilateral to the vaginal obstruction.[106] Uterine horns arise due to an arrest of development of 1 Müllerian

duct. A unicornuate uterus is associated with a rudimentary horn in 74% of cases; 26% of horns are both functional and noncommunicating. The treatment of both of these conditions is surgery to relieve the obstruction of the outflow tract by resection of either the obstructing vaginal septum or the uterine horn.[70,107]

SUMMARY

PMS/PMDD is a pervasive problem with a significant impact on the quality of life of affected individuals. This condition most often begins in adolescence with the establishment of normal ovulatory menstrual cycles; however, the underlying pathophysiology has yet to be delineated. Prospective evaluation is key to the confirmation of the diagnosis before the initiation of pharmacotherapy, especially psychotropic therapies, due to the possibly harmful side effect profile for adolescents compared to adults. Similarly, dysmenorrhea is common in adolescents. Although the majority of cases are primary, the HCP must be vigilant to allow for early diagnosis and treatment of secondary causes, thereby preventing long-term sequelae of delayed diagnosis. Stepwise therapy for dysmenorrhea treatment is usually employed; the choice of therapy should account for contraceptive needs of the adolescent in addition to symptom relief. For both PMSS/PMDD and dysmenorrhea, most studies of therapy have been performed in adults and, as such, adolescent-specific trials are required to confirm applicability to this age group.

References

1. Robinson RL, Swindle RW. Premenstrual symptom severity: impact on social functioning and treatment-seeking behaviors. *J Womens Health Gend Based Med.* 2000;9:757–768
2. Rapkin AJ, Mikacich JA. Premenstrual syndrome and premenstrual dysphoric disorder in adolescents. *Curr Opin Obstet Gynecol.* 2008;20:455–463
3. Steiner M, Peer M, Palova E, et al. The Premenstrual Symptoms Screening Tool revised for adolescents (PSST-A): prevalence of severe PMS and premenstrual dysphoric disorder in adolescents. *Arch Womens Ment Health.* 2011;14:77–81
4. Vichnin M, Freeman EW, Lin H, Hillman J, Bui S. Premenstrual syndrome (PMS) in adolescents: severity and impairment. *J Pediatr Adolesc Gynecol.* 2006;19:397–402
5. Derman O, Kanbur NO, Tokur TE, Kutluk T. Premenstrual syndrome and associated symptoms in adolescent girls. *Eur J Obstet Gynecol Reprod Biol.* 2004;116:201–206
6. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* Washington, DC: American Psychiatric Association; 1994
7. Premenstrual Syndrome. *ACOG Practice Bulletin.* 2000;15:1–19
8. Halbreich U. The diagnosis of premenstrual syndromes and premenstrual dysphoric disorder—clinical procedures and research perspectives. *Gynecol Endocrinol.* 2004;19:320–334
9. Borenstein JE, Dean BB, Yonkers KA, Endicott J. Using the daily record of severity of problems as a screening instrument for premenstrual syndrome. *Obstet Gynecol.* 2007;109:1068–1075
10. Treloar SA, Heath AC, Martin NG. Genetic and environmental influences on premenstrual symptoms in an Australian twin sample. *Psychol Med.* 2002;32:25–38
11. Rubinow DR, Hoban MC, Grover GN, et al. Changes in plasma hormones across the menstrual cycle in patients with menstrually related mood disorder and in control subjects. *Am J Obstet Gynecol.* 1988;158:5–11
12. Yonkers KA, O'Brien PM, Eriksson E. Premenstrual syndrome. *Lancet.* 2008;371:1200–1210

13. Hammarback S, Backstrom T. Induced anovulation as treatment of premenstrual tension syndrome. A double-blind cross-over study with GnRH-agonist versus placebo. *Acta Obstet Gynecol Scand.* 1988;67:159–166
14. Casper RF, Hearn MT. The effect of hysterectomy and bilateral oophorectomy in women with severe premenstrual syndrome. *Am J Obstet Gynecol.* 1990;162:105–109
15. Schmidt PJ, Nieman LK, Danaceau MA, Adams LF, Rubinow DR. Differential behavioral effects of gonadal steroids in women with and in those without premenstrual syndrome. *N Engl J Med.* 1998;338:209–216
16. Rubinow DR, Schmidt PJ, Roca CA. Estrogen-serotonin interactions: implications for affective regulation. *Biol Psychiatry.* 1998;44:839–850
17. Bethea CL, Lu NZ, Gundlah C, Streicher JM. Diverse actions of ovarian steroids in the serotonin neural system. *Front Neuroendocrinol.* 2002;23:41–100
18. Meltzer H. Serotonergic dysfunction in depression. *Br J Psychiatry Suppl.* 1989(8):25–31
19. Rapkin AJ, Edelmuth E, Chang LC, et al. Whole-blood serotonin in premenstrual syndrome. *Obstet Gynecol.* 1987;70:533–537
20. Steiner M, Steinberg S, Stewart D, et al. Fluoxetine in the treatment of premenstrual dysphoria. Canadian Fluoxetine/Premenstrual Dysphoria Collaborative Study Group. *N Engl J Med.* 1995;332:1529–1534
21. Yonkers KA, Halbreich U, Freeman E, et al. Symptomatic improvement of premenstrual dysphoric disorder with sertraline treatment. A randomized controlled trial. Sertraline Premenstrual Dysphoric Collaborative Study Group. *JAMA.* 1997;278:983–988
22. Brown J, O'Brien PM, Marjoribanks J, Wyatt K. Selective serotonin reuptake inhibitors for premenstrual syndrome. *Cochrane Database Syst Rev.* 2009:CD001396
23. Shah NR, Jones JB, Aperi J, et al. Selective serotonin reuptake inhibitors for premenstrual syndrome and premenstrual dysphoric disorder: a meta-analysis. *Obstet Gynecol.* 2008;111:1175–1182
24. Cohen LS, Soares CN, Yonkers KA, et al. Paroxetine controlled release for premenstrual dysphoric disorder: a double-blind, placebo-controlled trial. *Psychosom Med.* 2004;66:707–713
25. Roca CA, Schmidt PJ, Smith MJ, et al. Effects of metergoline on symptoms in women with premenstrual dysphoric disorder. *Am J Psychiatry.* 2002;159:1876–1881
26. Sundstrom Poromaa I, Smith S, Gulinello M. GABA receptors, progesterone and premenstrual dysphoric disorder. *Arch Womens Ment Health.* 2003;6:23–41
27. Girdler SS, Straneva PA, Light KC, Pedersen CA, Morrow AL. Allopregnanolone levels and reactivity to mental stress in premenstrual dysphoric disorder. *Biol Psychiatry.* 2001;49:788–797
28. Sundstrom I, Andersson A, Nyberg S, et al. Patients with premenstrual syndrome have a different sensitivity to a neuroactive steroid during the menstrual cycle compared to control subjects. *Neuroendocrinology.* 1998;67:126–138
29. Chau JP, Chang AM. Effects of an educational programme on adolescents with premenstrual syndrome. *Health Educ Res.* 1999;14:817–830
30. Daley A. Exercise and premenstrual symptomatology: a comprehensive review. *J Womens Health (Larchmt).* 2009;18:895–899
31. Steege JF, Blumenthal JA. The effects of aerobic exercise on premenstrual symptoms in middle-aged women: a preliminary study. *J Psychosom Res.* 1993;37:127–133
32. Braverman PK. Premenstrual syndrome and premenstrual dysphoric disorder. *J Pediatr Adolesc Gynecol.* 2007;20:3–12
33. Thys-Jacobs S, Starkey P, Bernstein D, Tian J. Calcium carbonate and the premenstrual syndrome: effects on premenstrual and menstrual symptoms. Premenstrual Syndrome Study Group. *Am J Obstet Gynecol.* 1998;179:444–452
34. Thys-Jacobs S, McMahon D, Bilezikian JP. Cyclical changes in calcium metabolism across the menstrual cycle in women with premenstrual dysphoric disorder. *J Clin Endocrinol Metab.* 2007;92:2952–2959
35. Bertone-Johnson ER, Chocano-Bedoya PO, Zagarins SE, Micka AE, Ronnenberg AG. Dietary vitamin D intake, 25-hydroxyvitamin D3 levels and premenstrual syndrome in a college-aged population. *J Steroid Biochem Mol Biol.* 2010;121:434–437

36. Khajehei M, Abdali K, Parsanezhad ME, Tabatabaee HR. Effect of treatment with dydrogesterone or calcium plus vitamin D on the severity of premenstrual syndrome. *Int J Gynaecol Obstet.* 2009;105:158–161
37. Andersch B. The effect of various oral contraceptive combinations on premenstrual symptoms. *Int J Gynaecol Obstet.* 1982;20:463–469
38. Graham CA, Sherwin BB. A prospective treatment study of premenstrual symptoms using a triphasic oral contraceptive. *J Psychosom Res.* 1992;36:257–266
39. Joffe H, Cohen LS, Harlow BL. Impact of oral contraceptive pill use on premenstrual mood: predictors of improvement and deterioration. *Am J Obstet Gynecol.* 2003;189:1523–1530
40. Willis SA, Kuehl TJ, Spiekerman AM, Sulak PJ. Greater inhibition of the pituitary—ovarian axis in oral contraceptive regimens with a shortened hormone-free interval. *Contraception.* 2006;74:100–103
41. Sulak PJ, Scow RD, Preece C, Riggs MW, Kuehl TJ. Hormone withdrawal symptoms in oral contraceptive users. *Obstet Gynecol.* 2000;95:261–266
42. Rapkin AJ, Winer SA. The pharmacologic management of premenstrual dysphoric disorder. *Expert Opin Pharmacother.* 2008;9:429–445
43. Greco T, Graham CA, Bancroft J, Tanner A, Doll HA. The effects of oral contraceptives on androgen levels and their relevance to premenstrual mood and sexual interest: a comparison of two triphasic formulations containing norgestimate and either 35 or 25 micrograms of ethinyl estradiol. *Contraception.* 2007;76:8–17
44. Yonkers KA, Brown C, Pearlstein TB, et al. Efficacy of a new low-dose oral contraceptive with drospirenone in premenstrual dysphoric disorder. *Obstet Gynecol.* 2005;106:492–501
45. Pearlstein TB, Bachmann GA, Zacur HA, Yonkers KA. Treatment of premenstrual dysphoric disorder with a new drospirenone-containing oral contraceptive formulation. *Contraception.* 2005;72:414–421
46. Coffee AL, Kuehl TJ, Willis S, Sulak PJ. Oral contraceptives and premenstrual symptoms: comparison of a 21/7 and extended regimen. *Am J Obstet Gynecol.* 2006;195:1311–1319
47. Reid R, Leyland N, Wolfman W, et al. SOGC clinical practice guidelines: oral contraceptives and the risk of venous thromboembolism: an update: no. 252, December 2010. *Int J Gynaecol Obstet.* 2010;112:252–256
48. Eriksson E, Ekman A, Sinclair S, et al. Escitalopram administered in the luteal phase exerts a marked and dose-dependent effect in premenstrual dysphoric disorder. *J Clin Psychopharmacol.* 2008;28:195–202
49. Steiner M, Ravindran AV, LeMelledo JM, et al. Luteal phase administration of paroxetine for the treatment of premenstrual dysphoric disorder: a randomized, double-blind, placebo-controlled trial in Canadian women. *J Clin Psychiatry.* 2008;69:991–998
50. Silber TJ, Valadez-Meltzer A. Premenstrual dysphoric disorder in adolescents: case reports of treatment with fluoxetine and review of the literature. *J Adolesc Health.* 2005;37:518–525
51. Bridge JA, Iyengar S, Salary CB, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. *JAMA.* 2007;297:1683–1696
52. Hosenbocus S, Chahal R. SSRIs and SNRIs. A review of the discontinuation syndrome in children and adolescents. *J Can Acad Child Adolesc Psychiatry.* 2011;20:60–67
53. Divasta AD, Laufer MR, Gordon CM. Bone density in adolescents treated with a GnRH agonist and add-back therapy for endometriosis. *J Pediatr Adolesc Gynecol.* 2007;20:293–297
54. Campbell MA, McGrath PJ. Non-pharmacologic strategies used by adolescents for the management of menstrual discomfort. *Clin J Pain.* 1999;15:313–320
55. Parker MA, Sneddon AE, Arbon P. The menstrual disorder of teenagers (MDOT) study: determining typical menstrual patterns and menstrual disturbance in a large population-based study of Australian teenagers. *BJOG.* 2010;117:185–192
56. Banikarim C, Chacko MR, Kelder SH. Prevalence and impact of dysmenorrhea on Hispanic female adolescents. *Arch Pediatr Adolesc Med.* 2000;154:1226–1229
57. Piyasirisilp R, Taneepanichskul S. A clinical study of transdermal contraceptive patch in Thai adolescence women. *J Med Assoc Thai.* 2008;91:137–141

58. Klein JR, Litt IF. Epidemiology of adolescent dysmenorrhea. *Pediatrics.* 1981;68:661–664
59. Ortiz MI, Rangel-Flores E, Carrillo-Alarcon LC, Veras-Godoy HA. Prevalence and impact of primary dysmenorrhea among Mexican high school students. *Int J Gynaecol Obstet.* 2009;107:240–243
60. Farquhar CM, Roberts H, Okonkwo QL, Stewart AW. A pilot survey of the impact of menstrual cycles on adolescent health. *Aust N Z J Obstet Gynaecol.* 2009;49:531–536
61. Houston AM, Abraham A, Huang Z, D'Angelo LJ. Knowledge, attitudes, and consequences of menstrual health in urban adolescent females. *J Pediatr Adolesc Gynecol.* 2006;19:271–275
62. Latthe P, Mignini L, Gray R, Hills R, Khan K. Factors predisposing women to chronic pelvic pain: systematic review. *BMJ.* 2006;332:749–755
63. O'Connell K, Davis AR, Westhoff C. Self-treatment patterns among adolescent girls with dysmenorrhea. *J Pediatr Adolesc Gynecol.* 2006;19:285–289
64. Zahradnik HP, Hanjalic-Beck A, Groth K. Nonsteroidal anti-inflammatory drugs and hormonal contraceptives for pain relief from dysmenorrhea: a review. *Contraception.* 2010;81:185–196
65. Harel Z. Dysmenorrhea in adolescents and young adults: from pathophysiology to pharmacological treatments and management strategies. *Expert Opin Pharmacother.* 2008;9:2661–2672
66. DuRant RH, Jay MS, Shoffitt T, Linder CW, Taylor W. Factors influencing adolescents' responses to regimens of naproxen for dysmenorrhea. *Am J Dis Child.* 1985;139:489–493
67. Davis AR, Westhoff C, O'Connell K, Gallagher N. Oral contraceptives for dysmenorrhea in adolescent girls: a randomized trial. *Obstet Gynecol.* 2005;106:97–104
68. Harada T, Momoeda M, Terakawa N, Taketani Y, Hoshiai H. Evaluation of a low-dose oral contraceptive pill for primary dysmenorrhea: a placebo-controlled, double-blind, randomized trial. *Fertil Steril.* 2011;95:1928–1931
69. Roman JD. Adolescent endometriosis in the Waikato region of New Zealand—a comparative cohort study with a mean follow-up time of 2.6 years. *Aust N Z J Obstet Gynaecol.* 2010;50:179–183
70. Laufer MR, Goitein L, Bush M, Cramer DW, Emans SJ. Prevalence of endometriosis in adolescent girls with chronic pelvic pain not responding to conventional therapy. *J Pediatr Adolesc Gynecol.* 1997;10:199–202
71. Campbell MA, McGrath PJ. Use of medication by adolescents for the management of menstrual discomfort. *Arch Pediatr Adolesc Med* 1997;151:905–913
72. Sanfilippo J, Erb T. Evaluation and management of dysmenorrhea in adolescents. *Clin Obstet Gynecol.* 2008;51:257–267
73. Daley AJ. Exercise and primary dysmenorrhoea: a comprehensive and critical review of the literature. *Sports Med.* 2008;38:659–670
74. Israel RG, Sutton M, O'Brien KF. Effects of aerobic training on primary dysmenorrhea symptomatology in college females. *J Am Coll Health.* 1985;33:241–244
75. Blakey H, Chisholm C, Dear F, et al. Is exercise associated with primary dysmenorrhoea in young women? *BJOG* 2010;117:222–224
76. Wilson C, Emans SJ, Mansfield J, Podolsky C, Grace E. The relationships of calculated percent body fat, sports participation, age, and place of residence on menstrual patterns in healthy adolescent girls at an independent New England high school. *J Adolesc Health Care.* 1984;5:248–253
77. Brown J, Brown S. Exercise for dysmenorrhoea. *Cochrane Database Syst Rev* 2010:CD004142
78. Dorn LD, Negriff S, Huang B, et al. Menstrual symptoms in adolescent girls: association with smoking, depressive symptoms, and anxiety. *J Adolesc Health.* 2009;44:237–243
79. Mishra GD, Dobson AJ, Schofield MJ. Cigarette smoking, menstrual symptoms and miscarriage among young women. *Aust N Z J Public Health.* 2000;24:413–420
80. Cho SH, Hwang EW. Acupuncture for primary dysmenorrhoea: a systematic review. *BJOG.* 2010;117:509–521
81. Liu CZ, Xie JP, Wang LP, et al. Immediate analgesia effect of single point acupuncture in primary dysmenorrhea: a randomized controlled trial. *Pain Med.* 2011;12:300–307
82 Warner TD, Giuliano F, Vojnovic I, et al. Nonsteroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: a full in vitro analysis. *Proc Natl Acad Sci U S A.* 1999;96:7563–7568
83. Merki-Feld GS, Hund M. Clinical experience with the combined contraceptive vaginal ring in Switzerland, including a subgroup analysis of previous hormonal contraceptive use. *Eur J Contracept Reprod Health Care.* 2010;15:413–422

84. Milsom I, Lete I, Bjertnaes A, et al. Effects on cycle control and bodyweight of the combined contraceptive ring, NuvaRing, versus an oral contraceptive containing 30 microg ethinyl estradiol and 3 mg drospirenone. *Hum Reprod.* 2006;21:2304–2311
85. Harel Z, Riggs S, Vaz R, et al. Adolescents' experience with the combined estrogen and progestin transdermal contraceptive method Ortho Evra. *J Pediatr Adolesc Gynecol.* 2005;18:85–90
86. Sibai BM, Odlind V, Meador ML, et al. A comparative and pooled analysis of the safety and tolerability of the contraceptive patch (Ortho Evra/Evra). *Fertil Steril.* 2002;77:S19–26
87. Kwiecien M, Edelman A, Nichols MD, Jensen JT. Bleeding patterns and patient acceptability of standard or continuous dosing regimens of a low-dose oral contraceptive: a randomized trial. *Contraception.* 2003;67:9–13
88. Barreiros FA, Guazzelli CA, Barbosa R, de Assis F, de Araujo FF. Extended regimens of the contraceptive vaginal ring: evaluation of clinical aspects. *Contraception.* 2010;81:223–225
89. ACOG Practice Bulletin No. 110. Noncontraceptive uses of hormonal contraceptives. *Obstet Gynecol.* 2010;115:206–218
90. Harel Z, Biro FM, Kollar LM. Depo-Provera in adolescents: effects of early second injection or prior oral contraception. *J Adolesc Health.* 1995;16:379–384
91. Fraser IS. Non-contraceptive health benefits of intrauterine hormonal systems. *Contraception.* 2010;82:396–403
92. Aslam N, Blunt S, Latthe P. Effectiveness and tolerability of levonorgestrel intrauterine system in adolescents. *J Obstet Gynaecol* 2010;30:489–491
93. Suhonen S, Haukkamaa M, Jakobsson T, Rauramo I. Clinical performance of a levonorgestrel-releasing intrauterine system and oral contraceptives in young nulliparous women: a comparative study. *Contraception.* 2004;69:407–412
94. Paterson H, Ashton J, Harrison-Woolrych M. A nationwide cohort study of the use of the levonorgestrel intrauterine device in New Zealand adolescents. *Contraception.* 2009;79:433–438
95. Farley TM, Rosenberg MJ, Rowe PJ, Chen JH, Meirik O. Intrauterine devices and pelvic inflammatory disease: an international perspective. *Lancet.* 1992;339:785–788
96. Toivonen J, Luukkainen T, Allonen H. Protective effect of intrauterine release of levonorgestrel on pelvic infection: three years' comparative experience of levonorgestrel- and copper-releasing intrauterine devices. *Obstet Gynecol.* 1991;77:261–264
97. Funk S, Miller MM, Mishell DR Jr, et al. Safety and efficacy of Implanon, a single-rod implantable contraceptive containing etonogestrel. *Contraception.* 2005;71:319–326
98. Ballweg ML. Tips on treating teens with endometriosis. *J Pediatr Adolesc Gynecol.* 2003;16:S27–28
99. Ebert AD, Fuhr N, David M, Schneppel L, Papadopoulos T. Histological confirmation of endometriosis in a 9-year-old girl suffering from unexplained cyclic pelvic pain since her eighth year of life. *Gynecol Obstet Invest.* 2009;67:158–161
100. Chapron C, Lafay-Pillet MC, Monceau E, et al. Questioning patients about their adolescent history can identify markers associated with deep infiltrating endometriosis. *Fertil Steril.* 2011;95:877–881
101. ACOG Committee Opinion No. 310, April 2005. Endometriosis in adolescents. *Obstet Gynecol.* 2005;105:921–927
102. Stavroulis AI, Saridogan E, Creighton SM, Cutner AS. Laparoscopic treatment of endometriosis in teenagers. *Eur J Obstet Gynecol Reprod Biol.* 2006;125:248–250
103. Leyland N, Casper R, Laberge P, Singh SS. Endometriosis: diagnosis and management. *J Obstet Gynaecol Can.* 2010;32:S1–32
104. Gilliam ML. Gonadotrophin-releasing hormone analogues for pain associated with endometriosis. *Obstet Gynecol.* 2011;117:727–728
105. Troiano RN, McCarthy SM. Müllerian duct anomalies: imaging and clinical issues. *Radiology.* 2004;233:19–34
106. Smith NA, Laufer MR. Obstructed hemivagina and ipsilateral renal anomaly (OHVIRA) syndrome: management and follow-up. *Fertil Steril.* 2007;87:918–922.
107. Spitzer RF, Kives S, Allen LM. Case series of laparoscopically resected noncommunicating functional uterine horns. *J Pediatr Adolesc Gynecol.* 2009;22:e23–28