Chapter 106: Menstrual-Related Disorders

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KEY CONCEPTS

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1. A urine pregnancy test should be one of the first steps in evaluating amenorrhea; however, most primary amenorrhea cases can be attributed to either physical anomalies of the gonads, outflow tract, or anomalies of the hypothalamic–pituitary–ovarian (HPO) axis.
2. For hypoestrogenic conditions associated with primary and secondary amenorrhea, estrogen (with a progestin) is recommended if correction of the underlying cause does not restore menses.
3. Heavy menstrual bleeding (HMB) is generally caused by either uterine structural abnormalities or nonstructural causes.
4. Pregnancy, including intrauterine pregnancy, ectopic pregnancy, and miscarriage, is at the top of the differential diagnosis for any person presenting with heavy menses.
5. The levonorgestrel intrauterine system (IUS) is associated with a 61% lower discontinuation rate and 82% fewer treatment failures when compared to other conventional pharmacotherapies for HMB.
6. Intrauterine devices (IUDs) or IUS are considered therapeutic options in a variety of menstruation-related disorders. The American College of Obstetricians and Gynecologists (ACOG) guidelines indicate that both nulliparous and multiparous females at low risk of sexually transmitted diseases are good candidates for IUS use.
7. Abnormal uterine bleeding associated with ovulatory dysfunction (AUB-O) is caused by oligo- or anovulation, leading to irregular, HMB due to chronic unopposed estrogen on the endometrium.
8. Polycystic ovary syndrome (PCOS) can present as AUB-O, and symptoms include amenorrhea, oligomenorrhea, intermenstrual bleeding, and HMB. Its exact definition continues to evolve, but it is a disorder of androgen excess accompanied by ovulatory dysfunction and/or polycystic ovarian morphology. Insulin resistance is often present, and PCOS is a risk factor for the metabolic syndrome, type 2 diabetes, dyslipidemia, hypertension, and possibly cardiovascular disease.
9. Combined hormonal contraceptives (CHCs) alone should be recommended for the management of irregular menstrual cycles and clinical hyperandrogenism in adults and adolescents with PCOS.
10. The selective serotonin reuptake inhibitors (SSRIs) are first-line pharmacologic treatment options for premenstrual dysphoric disorder (PMDD).

BEYOND THE BOOK

BEYOND THE BOOK

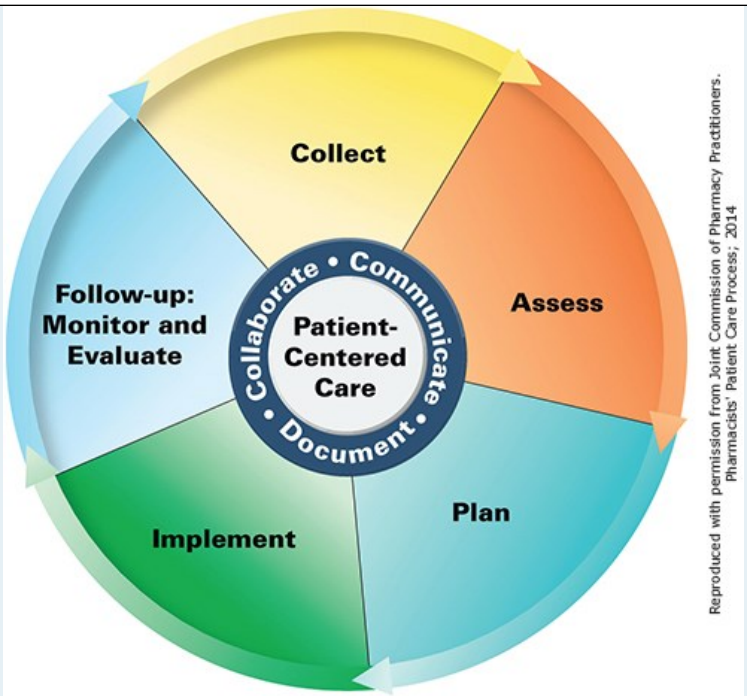
Watch the video entitled "The Menstrual Cycle" which provides an overview of a normal menstrual cycle and its hormonal regulation and is useful to enhance understanding of the pathophysiology of various menstrual disorders.

Guided questions for videos:

1. Describe the major role of the following hormones in regulation of the normal menstrual cycle:
    a. GnRH
    b. LH
    c. FSH
    d. Estrogen
    e. Progesterone
2. What hormone levels are highest and lowest in the follicular phase of the normal menstrual cycle and what outcome occurs as a result?
3. What hormone levels are highest and lowest in the luteal phase of the normal menstrual cycle and what outcome occurs as a result?
4. Describe folliculogenesis. What does this term mean, in what phase of the menstrual cycle does this occur, and what hormones are most active during this process?
5. Describe the corpus luteum. What is it, in what phase of the menstrual cycle does it develop, and what hormones are most active while it is present?
6. Draw the hypothalamus–pituitary–ovarian (HPO) axis and associated hormones. Plot the negative or positive feedback loops that occur in the follicular phase, during ovulation, and in the luteal phase.

PATIENT CARE PROCESS

Patient Care Process for Menstruation-related Disorders



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Collect

- Patient characteristics (age)
- Patient medical history
  - First day of the last menstrual cycle
  - Age of menarche
  - Cycle length and predictability
  - Number of days of each menstrual cycle, and the number of absorbent products used per day
  - History of current symptoms including relationship with menstrual cycles
  - Menstrual diary and recorded symptoms
- Social history (eg, tobacco/ethanol use), dietary and physical activity habits (especially for those with PCOS)
- Current medications including over-the-counter nonsteroidal anti-inflammatory drug (NSAID) use, herbal products, and dietary supplements
- Objective data
  - BP, HR, RR, height, weight
  - Labs depend on suspected underlying conditions. Common labs include follicle-stimulating hormone (FSH) and thyroid-stimulating hormone (TSH) (see Table 106-1). Total and free testosterone, other androgen precursors, glucose tolerance test, and fasting lipids may be obtained if PCOS is suspected. If anemia associated with HMB is suspected, obtain CBC with differential.

Assess

- Presence of severe anemia or acute bleeding that necessitates immediate treatment

- Presence of suicidal ideation associated with premenstrual dysphoric disorder (PMDD) that necessitates immediate psychiatric evaluation and treatment
- Whether the patient desires contraception or is attempting pregnancy
- Comorbid conditions that may affect treatment choice (eg, a nonestrogen-containing regimen should be considered in a patient with a history of deep venous thrombosis, and NSAID should not be an initial choice for a patient with a history of GI bleed)
- Acceptability of available treatment choice to the patient

Plan*

- Pharmacotherapy regimen including specific agent(s), dose, route, frequency, and duration (see Table 106-3)
- Monitoring parameters including efficacy and safety (see Table 106-4)
- Patient education (eg, purpose of treatment, dietary and lifestyle modification, invasive procedures, medication-specific information)
- Referrals to other providers when appropriate (eg, thrombosis specialist to evaluate bleeding disorders, behavioral health, dietician)

Implement*

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence to lifestyle interventions for individuals with PCOS

Follow-up: Monitor and Evaluate*"

- Resolution of symptoms
- Presence of adverse effects
- Patient adherence to treatment plan using multiple sources of information
- Reevaluate therapy as life goals change (eg, changing from desiring contraception to desiring fertility)

****Collaborate with patients, caregivers, and other healthcare professionals.***

INTRODUCTION

Problems related to the menstrual cycle are exceedingly common in females of reproductive age. This chapter discusses the most frequently encountered menstruation-related difficulties: amenorrhea, heavy menstrual bleeding (HMB), premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD), dysmenorrhea, and abnormal uterine bleeding associated with ovulatory dysfunction (AUB-O), including polycystic ovary syndrome (PCOS). The need for effective treatments of these disorders stems from their negative impact on an individual's quality of life, reproductive health, and long-term detrimental health effects, such as increased risk of osteoporosis with amenorrhea and risk of diabetes with PCOS.

Similar to other chapters in this section, general discussions around menstruation-related disorders and their treatment are primarily framed around cisgender women. However, any individual with a female reproductive system may experience issues with menstruation. Therefore, the use of the term *female* is specifically meant to refer to biology, and this chapter has been written to include transgender individuals.

Before menstrual disorders are discussed, what constitutes a normal menstrual cycle needs to be considered. The American College of Obstetrics and Gynecologists recommends that clinicians ask about an individual's first day of the last menstrual period, as well as the pattern of menses, during every clinical encounter. Identification of menstrual patterns should begin in adolescence, which may improve the early detection of potential health concerns. Before menstrual disorders are discussed, what constitutes a normal menstrual cycle for the individual needs to be considered.

In adolescents, immaturity of the hypothalamic–pituitary–ovarian (HPO) axis in the early years after menarche may lead to longer cycles due to anovulation. However, 90% of these cycles will be within the range of 21 to 45 days. The following menstrual characteristics and patterns are considered normal:

- Median age of menarche of 12.4 years, and menarche by age 15
- Menstrual cycle interval between 21 and 45 days
- Menstrual flow length 7 days or less
- Menstrual product use of 3 to 6 pads or tampons per day

In adult females not using hormonal contraception, a normal menstrual period lasts between 4.5 and 8 days, and cycle lengths range from 24 to 28 days. Normal variation in cycle length is considered to be 7 to 9 days, depending on a patient's age: 18 to 25 years ≤9 days, 26 to 41 ≤7 days, 42 to 45 ≤9 days. Blood loss between 5 and 80 mL during each period is considered normal.

AMENORRHEA

Epidemiology

Amenorrhea is defined as no menstrual bleeding in a 90-day period and can be either primary or secondary in nature. Primary amenorrhea is the absence of menses by age 15 years in females who have never menstruated. Secondary amenorrhea is the absence of menses for three months in a previously menstruating female or for 6 months in a previously irregularly menstruating individual.

Primary amenorrhea occurs in less than 0.1% of the general population. Secondary amenorrhea, in comparison, has an incidence of 3% to 4% in the general population and occurs more frequently in individuals younger than 25 years with a history of menstrual irregularities and in those involved in competitive athletics.

Etiology

In two-thirds of females, menses occur at 28 ± 3 days; however, cycle lengths of 18 to 40 days are considered within the normal range. Amenorrhea is not itself a diagnosis, but often a sign of a disorder or pregnancy. There are three broad categories of amenorrhea etiology:

- Anatomical causes, including pregnancy and uterine structural abnormalities
- Endocrine disturbances leading to chronic anovulation
- Ovarian insufficiency/failure

1 While a urine pregnancy test is one of the first steps in evaluating amenorrhea, most primary amenorrhea cases can be attributed to either anomalies involving (i) the hypothalamic–pituitary axis resulting in endocrine disturbances, (ii) ovarian function, or (iii) outflow tract. Similarly, greater than 50% of secondary amenorrhea cases are due to the impact of disturbances of the hypothalamic–pituitary–adrenal (HPA) axis or the HPO axis. Therefore, in organizing an approach to diagnosis and treatment, it is helpful to consider the organ systems involved in the menstrual cycle, which include the uterus, ovaries, anterior pituitary, and hypothalamus.

Pathophysiology

Ovulation is required for the follicle (an estrogen-secreting body) to become a corpus luteum (a progesterone-secreting body). Without ovulation, the proper sequence of estrogen production, progesterone production, and estrogen/progesterone withdrawal will not occur. This can result in amenorrhea. Anovulation can occur secondary to endocrine disturbances or ovarian insufficiency.

Each organ in the HPO axis, along with the uterus, is of importance in determining amenorrhea's etiology and pathophysiology. Beginning with the uterus/outflow tract and progressing caudally will result in a comprehensive differential diagnosis. However, coexisting physical signs and symptoms,

and a thorough history, typically help the clinician prioritize evaluation steps. Table 106-1 lists the pathophysiology of amenorrhea relative to the organ system(s) involved and the specific condition(s) that results in amenorrhea.

TABLE 106-1

Pathophysiology of Selected Menstrual Bleeding Disorders

Organ System	Condition	Pathophysiology/Laboratory Findings
Amenorrhea		
Uterus	Asherman's syndrome	Postcurettage/postsurgical uterine adhesions
	Congenital uterine abnormalities	Abnormal uterine development
Ovaries	Turner's syndrome	Lack of ovarian follicles
	Gonadal dysgenesis	Other genetic abnormalities
	Premature ovarian failure	Early loss of follicles
	Chemotherapy/radiation	Gonadal toxins
Anterior pituitary	Pituitary prolactin-secreting adenoma	↑ Prolactin suppresses the HPO axis
	Hypothyroidism	TRH causes ↑ prolactin, other abnormalities
	Medication (antipsychotics, verapamil)	↑ Prolactin suppresses the HPO axis
Hypothalamus	FHA	↓ Pulsatile GnRH secretion in the absence of other abnormalities
	Eating disorder	↓ Pulsatile GnRH secretion, ↓ FSH and LH secondary to weight loss
	Exercise	↓ Pulsatile GnRH secretion, ↓ FSH and LH secondary to low body fat
	Anovulation/PCOS	Asynchronous gonadotropin and estrogen production, abnormal endometrial growth
AUB-O		
Physiologic causes	Adolescence	Immaturity of the HPO axis: no LH surge
	Perimenopause	Declining ovarian function
Pathologic causes	Hyperandrogenic anovulation (PCOS)	Hyperandrogenism: high testosterone, high LH, hyperinsulinemia, and insulin resistance
	Hypothalamic dysfunction (physical or emotional stress, exercise, weight loss)	Suppression of pulsatile GnRH secretion and estrogen deficiency: low LH, low FSH

	Hyperprolactinemia (pituitary gland tumor, psychiatric medications)	High prolactin
	Hypothyroidism	High TSH
	Premature ovarian failure	High FSH
HMB		
Hematologic	von Willebrand disease	Factor VII defect causing impaired platelet adhesion and increased bleeding time
	Idiopathic thrombocytopenic purpura	Decrease in circulating platelets, can be acute or chronic
Hepatic	Cirrhosis	Decreased estrogen metabolism, underlying coagulopathy
Endocrine	Hypothyroidism	Alterations in the HPO axis
Uterine	Fibroids	Alteration of endometrium, changes in uterine contractility
	Adenomyosis	Alteration of endometrium, changes in uterine contractility
	Endometrial polyps	Alteration of endometrium
	Gynecologic cancers	Various dysplastic alterations of endometrium, uterus, cervix

FHA, functional hypothalamic amenorrhea; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; TRH, thyrotropin-releasing hormone.

Uterus/Outflow Tract

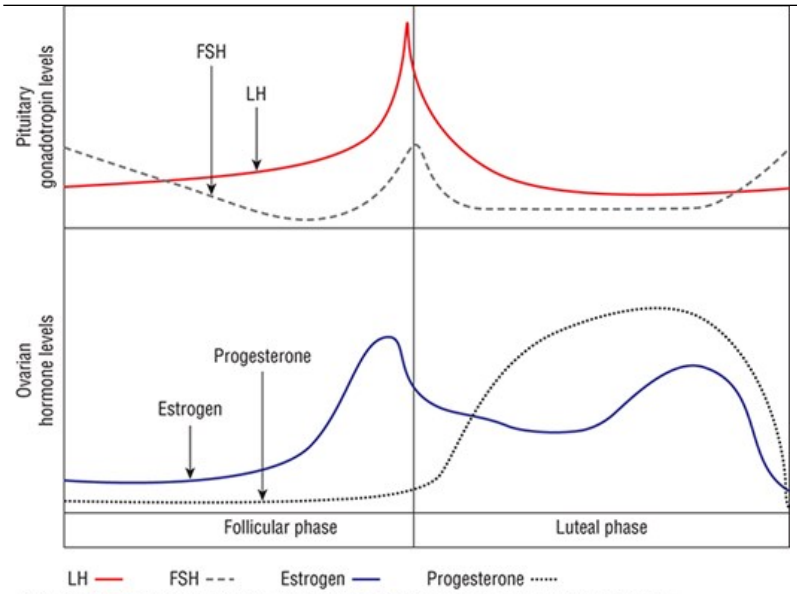
For menstruation to occur, a uterus, functional endometrium, and patent vagina must be present. Several anatomic abnormalities herein may cause amenorrhea. Congenital anomalies such as imperforate hymen or uterine agenesis may be discovered by physical examination. An acquired condition of the genital tract, such as Asherman's syndrome or cervical stenosis, is more likely in secondary amenorrhea.

Ovaries

Normal ovarian function is critical for menstruation to occur. The ovaries must respond appropriately to FSH and LH by secreting estrogen and progesterone in the proper sequence to influence endometrial growth and shedding (Fig. 106-1).

FIGURE 106-1

Hormonal fluctuations with the normal menstrual cycle.



Primary ovarian insufficiency occurs when potentially viable primordial follicles in the ovaries have been depleted. Estrogen production from the remaining ovarian follicles is insufficient to stimulate endometrial growth in the absence of follicles. The etiologies for primary ovarian insufficiency include bilateral oophorectomy, genetic anomalies, autoimmunity, and iatrogenic causes as a result of radiation or chemotherapy. However, in 90% of cases, the cause cannot be identified.

Pituitary Gland

The anterior pituitary gland secretes FSH and LH in sequential fashion in response to hypothalamic stimulation and a complex ovarian feedback mechanism. Normal secretion of FSH and LH is altered by several endocrinologic and iatrogenic conditions, including thyroid disease, hyperprolactinemia, and dopaminergic medication administration.

Hypothalamus

The hypothalamus secretes cyclic GnRH, which causes the pituitary to produce FSH and LH. Disrupting this cyclic process interrupts the hormonal cascade that results in normal menstruation. Anorexia nervosa, bulimia, intense exercise, and stress may cause hypothalamic amenorrhea, known as FHA. Further, research has confirmed that leptin insufficiency causes hypogonadotropic hypogonadism which leads to hypothalamic amenorrhea.

Amenorrhea Clinical Presentation

CLINICAL PRESENTATION: Amenorrhea

General

- Although patients may be concerned about the cessation of menses and implications for fertility, patients are generally not in acute physical distress.

Symptoms

- Patients will note cessation of menses.
- Patients may complain of infertility, vaginal dryness, or decreased libido.

Signs

- Cessation of menses for more than 6 months in individuals with established menstruation, absence of menses by age 16 in the presence of normal secondary sexual development, or absence of menses by age 14 in the absence of normal secondary sexual development.
- Recent significant weight loss or weight gain.
- The presence of acne, hirsutism, hair loss, or acanthosis nigricans may suggest androgen excess.

Laboratory Tests

- Pregnancy test
- Serum FSH and LH
- TSH
- Prolactin
- If hyperandrogenic state (eg, PCOS) is suspected, consider free and total testosterone, dehydroepiandrosterone, fasting glucose, and fasting lipid panel

Other Diagnostic Tests

- Progesterone challenge to confirm functional anatomy and adequate estrogenization.
- Pelvic ultrasound to evaluate for polycystic ovaries, presence/absence of uterus, and/or structural abnormalities of the reproductive tract organs.

Treatment

Desired Outcomes

In general, the treatment options for amenorrhea depend on its causes. Therapeutic modalities for amenorrhea should ensure the occurrence of normal puberty and restore the menstrual cycle. Treatment goals include bone density preservation, bone loss prevention, and ovulation restoration to improve fertility if desired. Hypoestrogenism may affect the quality of life via hot flash induction (premature ovarian failure), dyspareunia, and, in prepubertal females, lack of secondary sexual characteristics and absence of menarche. Treatment is targeted at reversing these effects.

General Approach to Treatment

The overall success of any intervention to treat amenorrhea depends on proper identification of the disorder's underlying cause(s). Once the cause is

identified, the appropriate intervention(s) can be made. For patients experiencing amenorrhea secondary to hypoestrogenic states, a diet rich in calcium and vitamin D is essential to minimize any negative impact on bone health.

Nonpharmacologic Therapy

Nonpharmacologic therapy for amenorrhea varies depending upon the underlying cause and should be considered using shared decision-making. Amenorrhea secondary to undernutrition or anorexia may respond to weight gain and psychotherapy. In young individuals for whom excessive exercise is an underlying cause, reduction of exercise quantity and intensity is important. Evaluation for a possible eating disorder may be appropriate (see Chapter e87, "Eating Disorders" for more information). Cognitive behavioral therapy restores ovarian function in individuals with FHA. In 2017, the Endocrine Society Clinical Practice Guideline recommended a reasonable trial of psychological, nutrition, and/or modified exercise intervention prior to use of pharmacotherapy in patients with FHA. In medication-induced hyperprolactinemia (Table 106-2), the clinician may consider alternative agents that do not inhibit dopamine receptors or increase prolactin levels.

TABLE 106-2

Medications That May Induce Hyperprolactinemia

Medication Class	Agents
First-generation antipsychotics	Phenothiazines (eg, prochlorperazine, chlorpromazine), butyrophenones (eg, haloperidol), thioxanthenes (eg, chlorprothixene)
Second-generation antipsychotics	Molindone, paliperidone, risperidone
Antidepressants	Clomipramine
Monoamine oxidase inhibitors	Corgyline, pargyline
Antihypertensives	Methyldopa, verapamil
Gastrointestinal promotility agents	Metoclopramide, domperidone
Opioids	Morphine
Gonadotropins and GnRH agonists	Human chorionic gonadotropin, human menopausal gonadotropin, leuprolide

Pharmacologic Therapy

2 For hypoestrogenic conditions associated with primary or secondary amenorrhea, estrogen supplementation in the form of combined hormonal contraceptives (CHCs), conjugated equine estrogen (CEE), or estradiol patch, in conjunction with progestin, was historically used to decrease osteoporosis risk. However, data supporting estrogen supplementation for the purpose of osteoporosis prevention in FHA are based on a limited number of studies with small sample size and short follow-ups. Therefore, the primary approach for FHA should be the correction of energy balance to restore HPO axis function. The 2017 Endocrine Society Clinical Practice Guideline for FHA recommends the short-term use of transdermal estradiol with cyclic oral progestins, after an adequate trial of nonpharmacological therapy (eg, psychological and nutritional intervention). Synthetic ethinyl estradiol and CHC are no longer recommended as first-line agents for patients with FHA. However, CHCs are also useful for pregnancy prevention, treatment of acne, and other conditions in this population. For individuals with primary ovarian insufficiency, a prospective study with estradiol 100 mcg/day transdermal patch suggested improvement in bone mineral density to normal population values. Table 106-3 lists therapeutic agents for

amenorrhea treatment, including recommended doses. Figure 106-2 illustrates a treatment algorithm for the management of amenorrhea.

FIGURE 106-2

Treatment algorithm for amenorrhea.

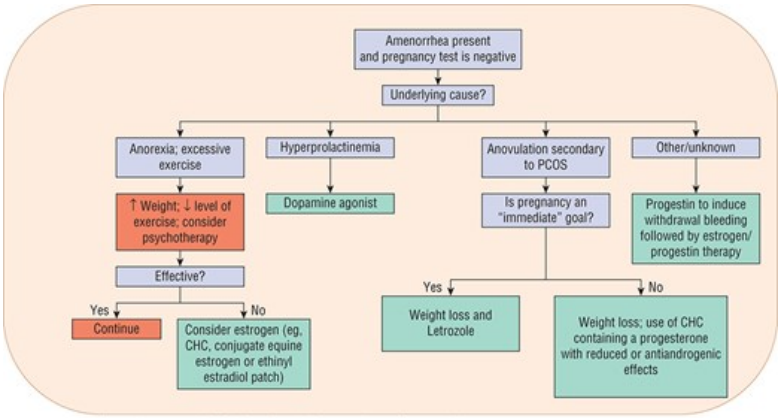


TABLE 106-3

Therapeutic Agents for Selected Menstrual Disorders

Agent (Brand Name)	Usual Recommended Dose
Amenorrhea (Primary or Secondary)	
CEE (Premarin)	0.625-1.25 mg by mouth daily on days 1-25 of the cycle
Ethinyl estradiol patch (Alora, Climara, Dotti, Lyllana, Minivelle, Vivelle-Dot)	50 mcg/24 hr
CHC (Various)	30-40 mcg estrogen component formulations
Amenorrhea (Secondary)	
Oral MPA (Provera)	5-10 mg by mouth daily for 5 to 10 days
Progesterone vaginal gel (Cirone)	1.125 g of 4% gel intravaginally every other day for 6 doses; if no response, increase to 8% gel for 6 doses
Norethindrone	2.5-10 mg by mouth daily for 5-10 days
Micronized progesterone (Prometrium)	400 mg by mouth daily at bedtime for 10 days
Amenorrhea Related to Hyperprolactinemia	
Bromocriptine (Cycloset, Parlodel)	2.5-15 mg daily in 2 to 3 divided doses
Cabergoline	0.25-2 mg by mouth once weekly or in 2 divided doses
Anovulatory Bleeding	

CHC (Cyred 28, Emoquette 28, Yasmin 28, Yaz, Beyaz, and others)	≤35 mcg ethinyl estradiol
Dysmenorrhea	
CHC (examples include: Norgestrel containing: Cryselle 28, Low-Ogestrel; Levonorgestrel containing: Levora 28, Camrese, Aviane 28, Lessina 28; other progestins: Sprintec 28, Yasmin 28, Yaz; Extended-cycle: Introvale, Setlakin, Seasonique, LoSeasonique)	<35 mcg formulations; use of extended-cycle formulations may be beneficial for this indication
Injectable MPA (Depo-Provera, Depo-SubQ Provera 104)	150 mg intramuscularly or 104 mg subcutaneously every 12 weeks
LNG-IUS (Mirena)	20 mcg released daily
NSAIDs (Ibuprofen: Motrin, Advil; Naproxyn: Naprosyn; Mefenamic acid; Celecoxib: Celebrex)	Ibuprofen: 800 mg by mouth, followed by 400-800 mg every 8 hours as needed
	Naproxen: 440-550 mg by mouth, followed by 220-550 mg every 12 hours as needed
	Mefanic Acid: 500 mg by mouth, followed by 250 mg every 6 hours as needed
	Celecoxib: 400 mg by mouth, followed by 200 mg every 12 hours as needed
Heavy Menstrual Bleeding	
CHC (Various: Estradiol valerate/dienogest [Natazia])	1 tablet daily in the order presented in the blister pack
LNG-IUS (Mirena)	20 mcg released daily
Oral MPA (Provera)	5-10 mg by mouth on days 5-26 of the cycle or during the luteal phase
Tranexamic acid	1,300 mg by mouth every 8 hr once heavy bleeding begins; dose for 4-7 days as needed per cycle
Heavy Menstrual Bleeding Associated with Uterine Fibroids	
Elagolix/estradiol/norethindrone acetate (Oriahnn)	Elagolix 300 mg/estradiol 1 mg/norethindrone acetate 0.5 mg in the morning and elagolix 300 mg in the evening for up to 24 months
Relugolix/estradiol/norethindrone acetate (Myfemfree)	Relufolix 40 mg/estradiol 1 mg/norethindrone acetate 0.5 mg once daily for up to 24 months
PCOS-Related Amenorrhea and/or AUB-O	
Injectable MPA, CHC (Depo-Provera, Depo-SubQ Provera 104; Desogestrel containing: Cyred 28, Cred EQ 28; Norgestimate containing: Tri-Lo Sprintec; Drospirenone containing: Yasmin 28, Yaz, Beyaz)	150 mg intramuscularly or 104 mg subcutaneously every 12 weeks ≤30 mcg ethinyl estradiol with either desogestrel, norgestimate, or drospirenone
Oral MPA (Provera)	10 mg by mouth for 10 days

Metformin (Glumetza)	1,500-2,000 mg by mouth daily
PMDD	
Clomipramine (Anafranil)	25-75 mg by mouth daily taken either continuously or during the luteal phase
Drospirenone (Yasmin 28, Yaz, Beyaz)	3 mg (+ ≤30 mcg ethinyl estradiol) by mouth on days 1-21 of the menstrual cycle
Leuprolide (Lupron Depot)	3.75 mg intramuscularly
SSRIs (Citalopram, escitalopram, fluoxetine [Sarafem or Prozac], paroxetine, sertraline)	Citalopram 10-30 mg; escitalopram 10-20 mg; fluoxetine 10-20 mg; fluvoxamine 50 mg; paroxetine 10-30 mg; sertraline 25-150 mg; all agents are given by mouth daily and dosed either continuously or during the luteal phase
SNRIs (Venlafaxine [IR and XR], duloxetine)	Venlafaxine 50-200 mg, dosed continuously or during the luteal phase; duloxetine 60 mg dosed continuously

LNG-IUS, levonorgestrel intrauterine system; MPA, medroxyprogesterone acetate; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin–norepinephrine reuptake inhibitors.

When hyperprolactinemia is the cause of amenorrhea, dopamine agonists such as bromocriptine and cabergoline aid in reducing prolactin concentrations and resuming menses. Bromocriptine normalizes prolactin levels in 58% of affected patients, while cabergoline has the same effect in 85%.

Progestins induce withdrawal bleeding in those with secondary amenorrhea. Absence of withdrawal bleeding after a progestin challenge may suggest outflow tract obstruction or insufficient endometrial estrogen exposure.

Progestin efficacy for secondary amenorrhea varies by formulation used. Progesterone in oil administered intramuscularly results in withdrawal bleeding in 70% of treated patients, whereas oral MPA induces withdrawal bleeding in 95% of treated patients. Table 106-3 identifies the types and doses of progestins used for secondary amenorrhea treatment, and Fig. 106-2 illustrates when to consider progestin use for amenorrhea treatment.

Amenorrhea related to PCOS-induced anovulation is discussed subsequently in the "Abnormal Uterine Bleeding" section.

Adolescents

Amenorrhea in the adolescent population is of concern because this is the time when peak bone mass is achieved. The cause of amenorrhea, whether primary or secondary, must be promptly identified, as amenorrhea and its related hypoestrogenism negatively affect bone development. In addition, consideration should be made to the emotional needs of the adolescent, given the implication of diagnosis and potential impact on long-term fertility.

For patients with absent or incomplete breast development, estrogen therapy should be initiated and titrated before adding progesterone to allow for breast development and prevent tubular breast development. Once puberty is complete, the goal is maintenance of normal ovarian functioning levels of estradiol. Per the 2017 Endocrine Society Clinical Practice Guideline, estrogen supplementation via transdermal estradiol is recommended. Progesterone should be added to estrogen therapy for 10 to 12 days each month to prevent endometrial hyperplasia and endometrial cancer. Oral contraceptives often contain higher doses of estrogen than what is needed and are no longer recommended as first-line therapy for this indication. They may, however, be useful in the management of other conditions in adolescence such as acne, dysmenorrhea, or pregnancy prevention. In addition to treating or eliminating amenorrhea's underlying cause and estrogen replacement as necessary, ensuring that the patient is receiving adequate amounts of calcium and vitamin D is also an important counseling point.

EVALUATION OF THERAPEUTIC OUTCOMES

Table 106-4 identifies the mechanisms of action, expected outcomes, and monitoring parameters for pharmacologic agents used for amenorrhea management.

TABLE 106-4

Pharmacologic Properties and Monitoring for Select Medications/Classes Used in the Management of Menstrual Disorders

Mechanism of Action	Adverse Medication Reactions	Monitoring for Specific Menstrual Disorders	Comments
Dopamine Agonists (Bromocriptine and Cabergoline)			
Suppresses prolactin production from pituitary tumors such that resumption of normal FSH and LH production occurs	Hypotension, nausea, constipation, anorexia, Raynaud's phenomenon, fatigue, headache	*Amenorrhea related to hyperprolactinemia*: Baseline and weekly prolactin levels should be measured with dosage increases until resumption of menses is observed. Continue therapy for 6-12 months following return of menses and continued normalization of serum prolactin levels	Inhibits and is metabolized by CYP3A4 St John's Wort induces CP3A4; coadministration may lead to treatment failure
Tricyclic Antidepressants (Clomipramine)			
Exact mechanism unknown (PMDD)	Dry mouth, constipation, fatigue, vertigo, sweating	Reduction in or absence of initial symptoms and improved quality of life within 1-3 menstrual cycles of therapy	
Oral CHC			
Exogenous estrogen and progesterone that suppresses FSH and LH production and thus inhibits ovulationCan be used to reduce menstrual flow (HMB, dysmenorrhea) and control menstrual cycle (anovulatory bleeding secondary to hypoestrogenism)	Thromboembolism, breast enlargement, breast tenderness, bloating, nausea, GI upset, headache, peripheral edema	*Amenorrhea*: Resumption of menses within 1-2 months of therapyAnovulatory bleeding: Improvement in pattern of abnormal bleeding within 1-2 months of therapy*Dysmenorrhea*: Reduction in or absence of pelvic pain within 1-2 months of therapy*HMB*: Reduction in blood loss with menses over 1-2 months of therapy. Improvement in hemoglobin/hematocrit after 3 months of therapy compared to baseline	St John's Wort contributes to altered menstrual bleeding. Rifampin induces estrogen metabolism, possibly contributing to treatment failure. Sulfa-containing medications may contribute to increased photosensitivity
Drospirenone-containing CHCs			
Progesterone with antimineralocorticoid and antiandrogenic properties; decreases emotional lability associated with PMDD	As noted for oral CHC; increased risk of hyperkalemia	*PCOS-related amenorrhea or anovulatory bleeding*: In addition to the improvement in the pattern of abnormal bleeding within 1-2 months of treatment, patients should also experience an improvement in androgen-excess symptoms such as acne/oily skin and hirsutism	Same as oral CHC. Coadministration of potassium-sparing diuretics or diets high in potassium may contribute to increased serum potassium concentrations, particularly in patients with renal dysfunction

CEE			
Estrogen replacement for hypoestrogenic states leading to anovulatory bleeding	As noted for oral CHC	*Anovulatory bleeding*: Improvement in pattern of abnormal bleeding within 1-2 months of therapy	Same as oral CHC
Ethinyl Estradiol Transdermal Patch			
Same as combination oral CHC and CEE	As noted for oral CHC; however, lesser effects on serum cholesterol concentrations because patch avoids first-pass metabolism	*Amenorrhea*: Resumption of menses within 1-2 months of therapy	Same as oral CHC
GnRH Agonist (Leuprolide)			
GnRH agent that contributes to suppression of FSH and LH and ultimately a reduction in estrogen and progesterone, inhibiting the normal menstrual cycle/hormonal fluctuations	Hot flashes, night sweats, headache, nausea	*PMDD*: Improvement in PMDD signs and symptoms within 1-2 months of therapy	
GnRH Antagonists/Hormone Derivative Combination (Elagolix, Relugolix/Estradiol/Norethindrone)			
GnRH that results in suppression of FSH and LH and ultimately a reduction in estrogen and progesterone, inhibiting the normal menstrual cycle/hormone fluctuations	Hot flashes, night sweats, headache, hypercholesterolemia for relugolix Hot flashes for elagolix	*HMB*: reduction in blood loss within 1-3 months of therapy initiation	Total duration of treatment 24 months
LNG-IUS			
Suppresses FSH and LH and ultimately estrogen and progesterone, inhibiting the usual growth of the endometrium	Irregular menses, amenorrhea	*Dysmenorrhea*: Reduction in or absence of pelvic pain after 1-2 months of therapy*HMB*: Reduction in blood loss with menses over 1-2 months of therapy. Improvement in hemoglobin/hematocrit after 3 months of therapy compared to baseline	
MPA (Oral and Injectable)			
Suppresses FSH and LH and ultimately estrogen and progesterone, inhibiting the usual growth of the endometrium	Edema, anorexia, depression, insomnia, weight gain or loss, increase in serum total and LDL cholesterol may	*Dysmenorrhea*: Reduction in or absence of pelvic pain after 1-2 months of therapy*HMB*: Reduction in blood loss with menses over 1-2 months of therapy Improvement in hemoglobin/hematocrit after 3 months of therapy compared to baseline*PCOS-related amenorrhea and/or anovulatory bleeding*: Resumption of menses over 1-2	

	reduce HDL cholesterol	courses of therapy	
Metformin			
Inhibits hepatic glucose production and increases sensitivity of tissues to insulin, thus reducing insulin resistance	Anorexia, nausea, vomiting, diarrhea, flatulence, lactic acidosis (rare)	*PCOS-related amenorrhea and/or anovulatory bleeding*: If desired, monitor for ovulation after 3-6 months of therapy	IV contrast dye may increase the risk of lactic acidosis; stop metformin 1 day prior and restart when renal function is normal and stabilized following the IV dye
NSAIDs			
Inhibits prostaglandin release that occurs with menses, thus reducing inflammatory response contributing to dysmenorrhea	GI upset, stomach ulcer, nausea, vomiting, heartburn, indigestion, rash, dizziness	*Dysmenorrhea*: Reduction in or absence of pelvic pain within hours of initiating *HMB*: Reduction in blood loss with menses over 1-2 months of therapy	
SSRIs and Venlafaxine			
Exact mechanism unknown (PMDD)	Sexual dysfunction (reduced libido, anorgasmia), insomnia, sedation, hypersomnia, nausea, diarrhea	*PMDD*: Improvement in signs and symptoms observed within 1-3 months of therapy	
Tranexamic Acid			
Antifibrinolytic effects by reversibly blocking lysine binding sites on plasminogen, preventing fibrin degradation and a reduction in menstrual blood loss	Nausea, vomiting, diarrhea, dyspepsia	*HMB*: Reduction in blood loss with menses should be noticeable with the first month of therapy. Improvement in hemoglobin/hematocrit after 3 months of therapy compared to baseline	

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

HEAVY MENSTRUAL BLEEDING

Epidemiology

HMB is the term now used in place of menorrhagia. The classical definition, however, remains the same: menstrual blood loss greater than 80 mL per cycle or menstrual bleeding lasting greater than 7 days per cycle. This definition has been questioned because of difficulty quantifying menstrual loss in clinical practice. Additionally, many individuals with “heavy menses” but whose blood loss is less than 80 mL merit treatment consideration because of flow containment issues, unpredictably heavy flow days, or other associated symptoms. Diagnosis has also been considered based upon the impact of HMB on quality of life and social, professional, familial, or sexual roles.

HMB is one of the most encountered gynecological problems, accounting for 18% to 30% of gynecologic visits. HMB affects an individual's physical, psychological, and social function. The amount of blood loss may make it impractical or embarrassing to leave home for fear of soiling outer garments, leading to decreased work productivity and limited social activities.

Etiology

[3,4] The International Federation of Gynecology and Obstetrics Menstrual Disorders Working Group created the PALM-COEIN classification system to define the causes of abnormal uterine bleeding (AUB) such as HMB. The PALM group of classification includes structural causes of AUB: **P**olyp, **A**denomyosis (endometrial tissue within the myometrium), **L**eiomyoma (also known as Fibroids), and **M**alignancy. The COEIN components include nonstructural causes: **C**oagulopathy, **O**vulatory disorders, **E**ndometrial disorders, **I**atrogenic causes, and **N**ot classified. The PALM-COEIN classification also characterizes intermenstrual bleeding as bleeding that occurs between predictable and clearly cyclic menses, while AUB is defined as bleeding that is abnormal in either regularity, timing, or volume. Under these definitions, HMB specifically refers to an abnormally excessive volume of menstrual bleeding that affects the individual's quality of life. Causes of HMB may include AUB due to polyps (AUB-P), adenomyosis (AUB-A), leiomyoma (AUB-L), as well as nonstructural causes such as coagulopathy (AUB-C) and endometrial dysfunction (AUB-E). Pregnancy, including intrauterine pregnancy, ectopic pregnancy, and miscarriage, must be at the top of the differential diagnosis list for any patient presenting with heavy menses. Bleeding disorders including von Willebrand disease, symptomatic hemophilia, platelet dysfunction, and Factor VIII and IX deficiencies must also be considered as these were found to exist in 20% of patients with HMB. Hypothyroidism also may be associated with heavy menses. Additionally, uterine structural abnormalities, such as polyps, adenomyosis, and leiomyoma, are not uncommon in those with HMB, with fibroids, specifically, being identified in as many as 40% of patients with HMB.

Pathophysiology

HMB may be the result of one of several very diverse causes including hematologic, hepatic, endocrine, and/or uterine disorders. Table 106-1 lists the pathophysiology of HMB relative to the organ system(s) involved and the specific conditions that may result in HMB.

HMB Clinical Presentation

CLINICAL PRESENTATION: HMB

General

- Patients may or may not be in acute distress.

Symptoms

- Patients may complain of heavy/prolonged menstrual flow. They also may have signs of fatigue and lightheadedness in cases of severe blood loss. These symptoms may or may not occur with dysmenorrhea.

Signs

- Orthostasis, tachycardia, and pallor may be noted in cases of significant anemia or acute blood loss.

Laboratory Tests

- Complete blood count and ferritin levels; hemoglobin and hematocrit results may be low.
- If the history dictates, testing (eg, prothrombin time, activated partial thromboplastin time, international normalized ratio, von Willebrand factor antigen, Factor VIII, factor IX activity) may be performed to identify coagulation disorder(s) as a cause.

Other Diagnostic Tests

- Pelvic ultrasound
- Pelvic magnetic resonance imaging
- Papanicolaou (Pap) smear
- Endometrial biopsy
- Hysteroscopy
- Sonohysterogram

Treatment

Desired Outcomes

The primary goal of treatment for HMB is to reduce menstrual flow. Along with this, treatments should be initiated to prevent or correct iron deficiency anemia, improve the patient's quality of life, and defer the need for surgical intervention.

General Approach to Treatment

As several treatment options exist for HMB, the choice regarding which specific agent to use depends on the patient's treatment history, concomitant concerns, and the adverse medication effect profile for the various agents.

Nonpharmacologic Therapy

Nonpharmacologic interventions for HMB include surgical procedures which may be considered based on the severity of bleeding, stability of the patient, contraindications, preferences, or nonresponse to pharmacologic treatment. These interventions vary from conservative endometrial ablation to hysterectomy and may be based on the desire for future fertility.

Pharmacologic Therapy

While surgical treatment may be an option for HMB, pharmacotherapy is recommended as the initial treatment choice. Estrogen is the recommended treatment for managing acute severe bleeding episodes in patients without suspected or known bleeding disorders. Following its initial use to control acute bleeding episodes, therapy continuation may be necessary to prevent future occurrences. Both estrogen-containing CHCs and progestin-only regimens can be used for maintenance therapy. Although it is assumed that all CHCs will reduce menstrual blood loss, the only agent that has been FDA-approved is a combination of estradiol valerate and dienogest. Table 106-3 identifies the variety of pharmacologic treatment options and their recommended dosing for HMB management.

Among the agents used to treat HMB, the NSAIDs have the advantage of administration only during menses and are associated with a 10% to 51% reduction in blood loss. For individuals desiring to avoid pregnancy, CHC should be considered, as a 30% to 60% reduction in menstrual blood loss has been observed. The 1-year continuation rates of CHCs in individuals with HMB range from 72% to 84%. The best-studied CHC option for HMB and the only agent approved by the FDA for the indication of HMB is the four-phasic formulation containing estradiol valerate and dienogest.

For those with contraindications to CHCs, progestin-only methods induce amenorrhea and reduce menstrual blood loss. Cyclic progesterone therapy for 14 days, administered as oral norethindrone acetate or MPA, reduces menstrual blood loss in only 2% to 30% of patients. However, when administered as long course (for 21 days, starting on day 5 after onset of menses), they reduce menstrual blood loss in 63% to 78% of patients.

Another progestin-only treatment option for HMB is the levonorgestrel-releasing intrauterine system (LNG-IUS). This is considered the most effective treatment to reduce menstrual flow. In particular, a 70% to 96% reduction in blood loss has been observed with its use, and its use has also resulted in postponing or canceling scheduled endometrial ablation surgery or hysterectomy. Among those using this treatment option, only 9% eventually opted for surgery. Further, its therapeutic efficacy of the LNG-IUS is similar to endometrial ablation up to 2 years following treatment.

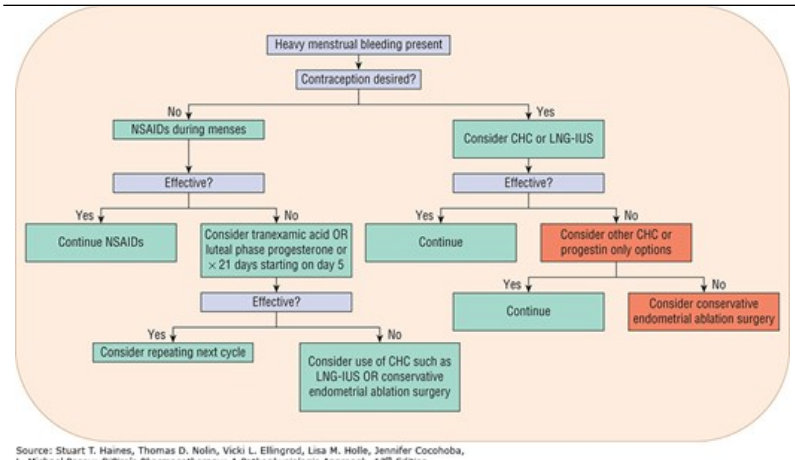
Tranexamic acid is a nonhormone pharmacotherapeutic option also approved in the United States for primary HMB treatment. Its use is associated with 34% to 56% reduction in menstrual blood loss. Compared to many of the other options, its use may be preferable among those desiring pregnancy or in whom hormonal therapy may not be appropriate.

5 For individuals in whom pregnancy is not an immediate goal, it is reasonable to start with either a CHC or the LNG-IUS. While either choice is acceptable for both nulligravid and multiparous patients who desire a long-term reversible form of contraception, cost-effectiveness and recent systematic review data suggest that the LNG-IUS is the best first-line choice for those desiring contraception. Clinical trial data illustrate a higher failure rate with the oral CHCs (32%) compared to the LNG-IUS (11%) as the primary treatment method. When compared to other conventional medical therapies used for HMB, the LNG-IUS is associated with a 61% lower discontinuation rate and 82% fewer treatment failures.

For those who have HMB associated with ovulatory cycles and do not desire hormonal therapy and/or contraception, tranexamic acid (second-line choice behind LNG-IUS) or NSAIDs during menses is a reasonable choice in the absence of any contraindications or GI disorders such as peptic ulcer disease or gastroesophageal reflux disease. They are convenient, in that they are only taken during menses and NSAIDs are comparatively inexpensive. Given their adverse effects, reduced efficacy compared to the first-line agents, and/or cost, use of oral progesterone, and depot MPA should be reserved. Figure 106-3 presents an algorithm for HMB treatment.

FIGURE 106-3

Treatment algorithm for HMB. (LNG-IUS, levonorgestrel-releasing intrauterine system.)



For patients with HMB associated with uterine fibroids, newer oral agents, elagolix/estradiol/norethindrone acetate (Oriahnn) and relugolix/estradiol/norethindrone acetate were approved in 2020 and 2022, respectively. Elagolix and relugolix are short-acting GnRH receptor antagonists. Dosing can be seen in Table 106-3. Based on data from clinical trials, it is reasonable to consider elagolix/estradiol/norethindrone acetate or elagolix/estradiol/norethindrone acetate as an oral option for the management of HMB associated with uterine fibroids. There are some clinically relevant safety considerations that may limit the use of this agent in some patient populations. One of the primary concerns is the risk of potentially irreversible BMD loss due to estrogen blockade. As a result, use of these agents should be limited to 24 months. It is also contraindicated in individuals with existing cardiovascular disease or at high risk of a cardiovascular event. Individuals taking this medication must also utilize nonhormonal contraception for the duration of treatment, as pregnancy is contraindicated with therapy.

Special Populations and Adolescents

6 Although it was believed IUS use should be avoided in nulliparous patients, guidelines from the American College of Obstetricians and Gynecologists (ACOG) indicate that both multiparous and nulliparous females (including adolescents) at low risk of sexually transmitted infections are good candidates for IUS use. Therefore, any of the treatments discussed (including the LNG-IUS) are options for those presenting with HMB. An estimated 50% of adolescents with HMB have a bleeding disorder, most commonly von Willebrand disease or platelet dysfunction. After assessment for bleeding disorders and correction of acute bleeding, management of HMB in adolescence often follows that of adult patients.

Dosage adjustment for tranexamic acid is recommended for reduced renal function. Patients with serum creatinine between 1.4 and 2.8 mg/dL (124 and 252 µmol/L) should receive only 1,300 mg by mouth twice daily; those with serum creatinine between 2.9 and 5.7 mg/dL (253 and 504 µmol/L) should receive 1,300 mg by mouth once daily; those with serum creatinine above 5.7 mg/dL (504 µmol/L) should receive 650 mg by mouth once daily. Additionally, due to its potential to increase the risk for venous thromboembolism, it should be used with extreme caution in individuals with a history of thrombosis and should not be combined with estrogen-containing contraceptives.

Evaluation Of Therapeutic Outcomes

Table 106-4 identifies the significant pharmacologic properties of agents used for the management of HMB, the expected outcomes for each agent, and specific monitoring parameters for the treatment modalities used in HMB management.

PREMENSTRUAL SYNDROME AND PREMENSTRUAL DYSPHORIC DISORDER

Epidemiology

PMS is represented by a cyclic pattern of symptoms (Table 106-5) occurring in the late luteal phase of the menstrual cycle that resolves at the onset of menses. Up to 80% of menstruating patients experience PMS symptoms. However, most do not report impairment of their daily activities. There have been over 100 symptoms reported by patients with PMS and they will often present differently, thus requiring an individualized treatment plan. Charting symptoms is helpful for the patient and clinician to identify the symptoms, severity, and patterns in which they occur as well as response to treatment. Diagnosis requires that at least one moderate-to-severe somatic or psychiatric symptom is present in the last week of the luteal phase for at

least 3 months.

TABLE 106-5

Symptoms Often Reported with PMS

At least one of the following somatic or affective symptoms should be present during the 5 days before menses in the last three menstrual cycles					
Somatic Symptoms			**Affective Symptoms**		
Abdominal bloating Breast swelling or tendernessHeadache Muscle or joint painSwelling of extremities	Weight gain Fatigue Dizziness Nausea/vomiting	Acne Pelvic pressure/heaviness Constipation or diarrhea Menstrual migraines Appetite changes	Angry outbursts Anxiety Depression Difficulty in concentration Confusion	Change in libido Irritability Social withdrawal Forgetfulness Sadness	Tension Tearfulness Restlessness Loneliness Food cravings

Some patients experience severe mood symptoms known as PMDD. This is a mood-related condition recognized by the *Diagnostic and Statistical Manual, 5th edition* (*DSM-5*; see diagnostic criteria) and can have significant impact on a patient's quality of life, productivity, and interpersonal relationships. The prevalence of PMDD ranges from 1.3% to 9%.

Individuals experiencing PMS and PMDD symptoms miss significantly more work and school compared to those without PMS or PMDD. They also report significant impairment in their ability to participate in social activities, hobbies, and in their relationships with others, as well as have a lower health-related quality of life and higher medical expenses.

An exact PMS prevalence is difficult to ascertain, because symptoms and severity tend to fluctuate.

Etiology

While it is unclear why PMS occurs, there are theories. First, it is thought that patients with PMS have an underlying neurological vulnerability to the normal cyclic hormonal fluctuations that occur during the menstrual cycle. When ovulation is suppressed medically or surgically, symptoms usually improve. It is thought that abnormal serotonergic function plays a role with mood-related symptoms and cravings as well as PMDD.

Pathophysiology

According to some evidence, PMS and PMDD symptoms are related to low levels of the centrally active progesterone metabolite allopregnanolone in the luteal phase and/or lower cortical γ-aminobutyric acid levels in the follicular phase. A number of studies suggest a link between PMS and PMDD and low serotonin levels. In 2019, the World Health Organization added PMDD to the International Statistical Classification of Disease and Related Health Problems, Eleventh Revision.

PMDD Clinical Presentation

CLINICAL PRESENTATION: PMDD

A summary of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* criteria for PMDD is as follows:

- Symptoms are temporally associated with the last week of the luteal phase and remit with the onset of menses.
- At least five of the following symptoms are present: affective lability, anger, or irritability often characterized by interpersonal conflicts, markedly depressed mood, anxiety, decreased interest in activities, fatigue, difficulty concentrating, changes in appetite, sleep disturbance, feelings of being overwhelmed, and physical symptoms, such as breast tenderness or bloating.
- One of the symptoms must be affective lability, irritability, markedly depressed mood, or anxiety.
- Symptoms interfere significantly with work and/or social relationships.
- Symptoms are not an exacerbation of another underlying psychiatric disorder.
- The criteria are confirmed prospectively by daily ratings over two menstrual cycles and must have occurred during most menstrual cycles in the past year.

Treatment

Desired Outcome

Treatment of PMS and PMDD attempts to relieve psychiatric and somatic symptoms through ovulation suppression, or through affecting neurotransmitter (eg, serotonin, norepinephrine, or dopamine) concentrations in the brain. Therefore, PMS and PMDD interventions should alleviate the presenting symptoms and subsequently improve quality of life. Table 106-3 lists the various agents used in managing PMS and PMDD and their recommended dosing.

General Approach to Treatment

A treatment modality that is minimally invasive or without systemic effects is desired for initial therapy. Key to the successful choice of pharmacologic therapy for PMS and PMDD is having the patient chart their specific symptoms for at least two menstrual cycles to assist in ruling out premenstrual exacerbation of underlying psychiatric disorders.

Nonpharmacological Therapy

Some lifestyle changes for the management of mild-to-moderate premenstrual symptoms include minimizing intake of caffeine, refined sugar, and sodium, and increasing exercise. Although exercise appears to improve PMS symptoms, definitive, evidence-based recommendations cannot be made due to methodological limitations of these studies. Vitamin and mineral supplements, such as vitamin B_6 (50-100 mg daily) and calcium carbonate (1,200 mg daily), may help in reducing the physical symptoms associated with PMS; however, clinical trial data is limited and/or mixed, precluding a definitive conclusion regarding their use. Cognitive behavioral therapy has also been studied, showing moderate efficacy. However, the frequency and duration therapy have not been defined. Nonetheless, acceptance-based cognitive behavior therapy and mindfulness-based exercises may be helpful in reducing symptoms. A Cochrane review of herbal supplements for PMS, including angelica root, bitter orange, dragon's teeth, ginkgo, peppermint, saffron, turmeric, tangerine leaf, and vitex agnus-castus, among others, does not support their use. Although acupuncture and acupressure appear to improve physical and psychological symptoms of PMS, evidence was from limited sample sizes and of low quality.

Pharmacologic Therapy

[10] ACOG recommends SSRIs for the management of affective premenstrual symptoms including PMDD. Studies have revealed positive results relative to most symptoms associated with PMDD. Other agents that have been studied and are alternatives include the selective SNRI venlafaxine, as well as

CHCs and GnRH agonists.

Among SSRIs, data support the use of citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline for the treatment of severe mood-related symptoms of PMS and PMDD. Research evaluating the dosing of these agents continuously or only during the luteal phase (ie, days 14-28 of the menstrual cycle) has illustrated similar efficacy between the two regimens, such that one cannot be recommended over another, although more studies directly comparing continuous versus luteal phase administration are needed. Treatment decisions will often be based on patient preference as some prefer continuous dosing, so they do not have to track their cycle as closely, whereas some prefer just taking the medication during the luteal phase to minimize medication exposure. Interestingly, when used in PMDD, antidepressants tend to be very effective and have a faster onset than what is typically seen in the treatment of major depression. Most medication adverse effects also appear to be similar between continuous and luteal dosing, except decreased libido which occurs at a higher rate with continuous dosing. In addition, abrupt cessation of SSRI at the end of the menstrual cycle is not associated with discontinuation symptoms. All SSRI doses appear to be effective for psychiatric symptoms and should be titrated to individual patient's symptom improvement and tolerability. The safety of SSRI use during early pregnancy has been an active area of investigation. In a large-scale analysis, reassuring evidence was provided for some SSRIs, but birth defects (including anencephaly, atrial septal defects, right ventricular outflow tract obstruction, and gastroschisis) can be 2 to 3.5 times more frequent with paroxetine or fluoxetine use in early pregnancy.

The SNRI, venlafaxine, has been studied for PMDD and, similar to the SSRIs, found to result in a 50% or greater improvement in symptoms in 60% of treated patients compared with only 35% in the control group. The norepinephrine and dopamine reuptake inhibitor, bupropion, has not been proven effective for PMS or PMDD.

It is important that concomitant pharmacotherapy be evaluated closely for pharmacokinetic interactions when an SSRI or venlafaxine is prescribed, given the interface of these medications with cytochrome P450 isoenzyme systems. Additional information regarding antidepressant dosing, adverse medication effects, pharmacokinetics, and medication interactions can be found in Chapter 92, "Depressive Disorders."

The use of a monophasic oral CHC containing 20 mcg of ethinyl estradiol and 3 mg of drospirenone, a progesterone with antiandrogenic effects, improves premenstrual symptoms in persons with PMDD, and is FDA-approved for this indication. The continuous cycle CHC regimen delivering 90 mcg of levonorgestrel and 20 mcg of ethinyl estradiol daily has also been studied in controlled trials, resulting in a 30% to 59% improvement in PMDD symptoms. For PMS symptoms, in a large-scale study, both triphasic and monophasic CHCs led to reduction in physical symptoms but not mood symptoms. Superiority of one CHC relative to another has not been established.

If treatment with the above options is unsuccessful, hormonal treatment with a GnRH agonist, such as leuprolide, can be considered. Leuprolide improves premenstrual emotional symptoms as well as some physical symptoms, such as bloating and breast tenderness. However, its cost, the need for intramuscular administration, and its hypoestrogenism effects (eg, vaginal dryness, hot flashes, and bone demineralization) severely limit its use. Table 106-4 lists the significant pharmacologic properties of agents used to treat PMDD that require monitoring.

Evaluation of Therapeutic Outcomes

Table 106-4 lists the expected outcomes and specific monitoring parameters for the treatment modalities used in PMDD management.

DYSMENORRHEA

Epidemiology

Dysmenorrhea is one of the most encountered gynecologic complaints and is defined as crampy pelvic pain occurring with or just prior to menses. Primary dysmenorrhea implies pain in the setting of normal pelvic anatomy and physiology, while secondary dysmenorrhea is associated with underlying pelvic pathology. Dysmenorrhea prevalence rates vary but range from 16% to 90%, and its presence may be associated with significant interference in work and school attendance. In addition, significant reductions in quality of life and lower overall life satisfaction and contentment ratings have been observed in patients with dysmenorrhea compared to controls. Risk factors include menarche before the age of 12 years, current age less than 30 years, heavy menses, nulliparity, low body mass index, and a history of sexual abuse.

Etiology

For most patients, dysmenorrhea is accompanied by normal ovulatory cycles and normal pelvic anatomy. This is referred to as primary, or functional,

dysmenorrhea. Primary dysmenorrhea typically occurs within 6 to 12 months of menarche, when adolescents attain ovulatory cycles. However, in approximately 10% of adolescents and young adults presenting with painful menses, an underlying anatomic or physiologic cause exists. Comparatively, secondary dysmenorrhea associated with pelvic pathology should be suspected in patients over 30 years of age without a history of dysmenorrhea.

Pathophysiology

The most significant mechanism for primary dysmenorrhea is the release of prostaglandins and leukotrienes into the menstrual fluid, initiating an inflammatory response and vasopressin-mediated vasoconstriction. The most common cause of secondary dysmenorrhea is endometriosis. Other causes include current or history of pelvic inflammatory disease, uterine fibroids, Müllerian anomalies, obstructive reproductive tract abnormalities, and adenomyosis leiomyomata. Pregnancy and miscarriage must be considered in new-onset dysmenorrhea.

Dysmenorrhea Clinical Presentation

CLINICAL PRESENTATION: Dysmenorrhea

General

- Patients may or may not be in acute distress, depending on the level of menstrual pain experienced

Symptoms

- Patients complain of crampy pelvic pain beginning shortly before or at the onset of menses. Symptoms typically last from 8 to 72 hours.
- Associated symptoms may include low back pain, headache, diarrhea, fatigue, and/or nausea and vomiting.

Laboratory Tests

- Pelvic examination should be performed to screen for sexually transmitted diseases and/or pelvic inflammatory disease as a cause of the pain in sexually active females.
- Gonorrhea, Chlamydia cultures or polymerase chain reaction, wet mount.

Other Diagnostic Tests

- Transvaginal/pelvic ultrasound can be used to identify potential anatomic abnormalities such as masses/lesions or to detect ovarian cysts and endometriomas.

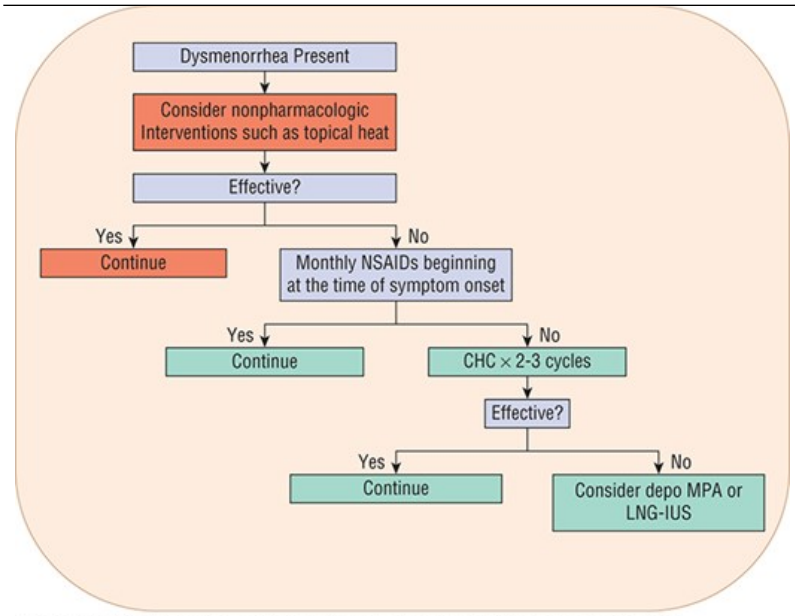
Treatment

Desired Outcomes

Initial treatment choice is influenced by whether the patient desires pregnancy. Medical management of dysmenorrhea should relieve the pelvic pain, result in reducing lost school and workdays, and contribute to an improved quality of life. Table 106-3 identifies the agents used to manage dysmenorrhea and their recommended doses. Figure 106-4 shows a treatment algorithm for dysmenorrhea management. Note that if symptoms persist for 3 to 6 months further work-up for secondary dysmenorrhea is warranted.

FIGURE 106-4

Treatment algorithm for dysmenorrhea. (LNG-IUS, levonorgestrel-releasing intrauterine system.)



General Approach to Treatment

A variety of effective treatment options for dysmenorrhea are available, including nonhormonal and hormonal pharmacologic options and noninvasive nonpharmacologic options. Treatment choice is influenced by the desire for contraception, the patient's level of sexual activity, potential for adverse effects, and cost. For patients suffering from secondary dysmenorrhea due to endometriosis, treatment is directed toward management of symptoms, prevention of disease progression, and protection of future fertility, if desired. Treatment of endometriosis is covered in Chapter 107.

Nonpharmacologic Therapy

Several nonpharmacologic interventions are used for managing dysmenorrhea. Among these, topical heat therapy, exercise, acupuncture, and a low-fat vegetarian diet have been shown to reduce dysmenorrhea intensity. Dietary changes may shorten dysmenorrhea duration. Topical heat application via an abdominal patch is as effective as 400 mg of ibuprofen dosed three times daily. Because topical heat, exercise, and dietary changes do not impart systemic effects, they are associated with little to no risk compared to the pharmacologic options. Although a variety of dietary supplements, including fenugreek, fish oil, vitamin B^1, ginger, valerian, and zinc sulfate, have been evaluated for dysmenorrhea, a Cochrane analysis concluded that evidence supporting their use is of low or very low quality due to limited sample sizes and methodological concerns. Similarly, although there is some evidence supporting the use of acupuncture and acupressure, a Cochrane analysis also concluded that the quality of evidence was low or very low.

Pharmacologic Therapy

Given the role of prostaglandins in dysmenorrhea pathophysiology, NSAIDs are the initial treatment of choice. These agents do not differ in efficacy with the most used agents being naproxen and ibuprofen.

All NSAIDs have a propensity for causing GI distress and ulceration; their administration with food or milk minimizes these effects. In patients who have a history of NSAID-induced gastric effects, the use of celecoxib, a cyclo-oxygenase-2 (COX-2) inhibitor, is an alternative. Increasing fluid intake may also help reduce renal adverse effects. Choice of one agent over another may be based on cost, convenience, and patient preference. All NSAIDs should be dosed on an individual basis and are most effective if started 1 to 2 days prior to the onset of menses and continued through the first 2 to 3 days of menstrual bleeding. According to some research, NSAID therapy should begin at the onset of menses or perhaps even the day before and continued around the clock instead of waiting until symptom onset; however, the data substantiating this are weak. Acetaminophen is inferior to NSAID use in the treatment of this disorder. Opioid should be avoided for dysmenorrhea pain management as adolescents can develop dependence in as few as 7 days, leading to physical withdrawal symptoms. If an NSAID or celecoxib use is contraindicated or not desired, hormonal agents should be considered.

Overall, the CHCs improve dysmenorrhea by inhibiting endometrial tissue proliferation which reduces endometrial-derived prostaglandins and leukotrienes that cause the pelvic pain. Significant improvements in mild, moderate, and severe dysmenorrhea have been noted with CHCs. Although one study suggested that a CHC containing a potent progestin (eg, levonorgestrel) may be more beneficial, other studies using CHCs with other progestins suggest that pain reduction is not limited to levonorgestrel-containing regimens. Compared with cyclic regimens, continuous CHC regimens may result in more rapid pain reduction. However, both cyclic and continuous regimens have been used successfully.

Long-acting progesterones, such as depot MPA and the LNG-IUS, can be considered for dysmenorrhea treatment. Their efficacy is secondary to their ability to render most patients amenorrheic within 6 to 12 months of use. Because the pelvic pain of dysmenorrhea is related to the prostaglandins released during menses, in the setting of amenorrhea the underlying cause of dysmenorrhea is removed.

Several factors influence the choice of first-line treatment for dysmenorrhea. If contraception is desired, then a hormonal option may be considered taking into account cost, adherence issues, and adverse effects. If contraception is not desired, then NSAID use would be desirable from both cost and convenience standpoints. If NSAIDs are not tolerated, celecoxib could be recommended. In patients for whom hormonal contraception, NSAIDs, or celecoxib is not an option, topical heat should be considered.

Adolescents

According to the ACOG, adolescents are particularly at risk of receiving delayed medical care for symptoms of dysmenorrhea. Because NSAIDs impact prostaglandin production specifically, they are recommended as the initial treatment choice for adolescents with primary dysmenorrhea. Adolescent patients are more likely to engage in self-directed treatment use of NSAIDs and, therefore, are at higher risk of subtherapeutic treatment. Early diagnosis, treatment, and education are essential in this population. In adolescent patients desiring contraception, or in whom NSAIDs do not provide adequate relief, hormonal contraceptives can be used alone, or in combination with NSAIDs. Prolonged use of depot MPA may lead to significant loss of bone mineral density (BMD) loss which may not be completely reversible after depot MPA discontinuation. Adolescence is a critical period for BMD accrual. Hence, depot MPA may not be the first choice in this population. Table 106-4 identifies the significant pharmacologic properties of agents used to treat dysmenorrhea that require monitoring.

Evaluation of Therapeutic Outcomes

Table 106-4 lists the expected outcomes and specific monitoring parameters for the treatment modalities used in the management of dysmenorrhea.

ABNORMAL UTERINE BLEEDING WITH OVULATORY DYSFUNCTION

Epidemiology

7 AUB-O is caused by oligo- or anovulation, leading to irregular, HMB due to chronic unopposed estrogen on the endometrium. While it does encompass bleeding patterns such as HMB and amenorrhea, this section will focus specifically on AUB-O as it relates to oligo-anovulation.

The estimated annual prevalence of menstrual irregularities is 53 per 1,000 females. In reproductive-age females, PCOS is one of the most common causes of AUB-O, with a prevalence range of 8% to 13%. In perimenopausal individuals, bleeding changes are due to normal menopausal transition, with the average age of menopause being 51 years in developed countries. In North America, the mean duration of menopausal transition is 4 years, and during this time period menstrual irregularity is commonly observed.

Etiology

When considering the etiology of AUB-O, the patient's age must be considered. As previously discussed, all patients presenting with abnormal bleeding should be evaluated for pregnancy. In adolescents though, anovulation is the most common cause of AUB-O. During the first 12 to 18 months after menarche, immaturity of the HPO axis is frequently the cause of AUB-O. By the third year after the onset of menstruation, 60% to 80% of cycles are regular. If regular menstrual cycles have not been established within 5 years of menarche, further evaluation for the cause, such as PCOS, should be considered. When irregular menses is associated with significant bleeding, an inherited bleeding disorder should be considered as a cause, especially in adolescence. Individuals experiencing AUB-O in their reproductive years should be evaluated for pathologic causes, including PCOS, thyroid dysfunction, hyperprolactinemia, primary pituitary disease, premature ovarian failure, hypothalamic dysfunction, disordered eating, adrenal disease,

and androgen-producing tumors. Individuals in their perimenopausal years may experience “physiologic” anovulatory cycles because of intermittently declining estrogen levels. Regardless of age, evaluation for endometrial hyperplasia and/or endometrial cancer should be considered when a patient experiences excessive bleeding with irregular menses. When considering the etiology of AUB-O, more than one condition may coexist (eg, PCOS and hypothyroidism), each contributing to the constellation of symptoms.

Pathophysiology

Normal menstrual cycles occur through a complex interaction of the hypothalamus, pituitary gland, ovaries, and endometrium (see Fig. 106-1). In an ovulatory cycle, the ovary produces a mature, estrogen-secreting follicle in response to FSH release from the pituitary. The endometrium proliferates under the influence of this estrogen production. At a critical level of estrogen concentration, the pituitary responds by producing an “LH surge,” which creates a cascade of ovarian events, culminating in ovulation. Upon oocyte release, the follicle becomes a progesterone-producing corpus luteum. The endometrium “organizes” into secretory endometrium in the presence of adequate progesterone, preparing itself for a possible pregnancy. If conception and implantation do not occur, corpus luteum involution causes a decline in estrogen and progesterone leading to predictable, organized menstrual flow as the endometrium sloughs.

If ovulation does not occur, progesterone is not produced, and the endometrium will continue to proliferate in an “unorganized” fashion under the influence of continued estrogen production. Eventually, the endometrium will become so thick that it can no longer be supported by continued estrogen production. This results in unorganized, sporadic sloughing of the endometrium, characteristic of the unpredictable and heavy bleeding associated with AUB-O.

Overall, AUB-O has various etiologies, which will require a careful history and examination along with laboratory assessments to elucidate. For example, in adolescence, HPO axis immaturity contributes to the absence of the LH surge required for ovulation. In patients with anorexia, the hypothalamus loses much of its pulsatile GnRH release, leading to low levels of FSH and LH, and in certain cases enough for estrogen production but not enough to induce ovulation. Oocyte decline and abnormal follicular development contribute to anovulatory cycles common among individuals in the perimenopause transition.

In females of reproductive age, PCOS is one of the most common causes of AUB-O. Generally, PCOS can present as AUB-O, and symptoms include amenorrhea, oligomenorrhea, intermenstrual bleeding, and HMB. Although its exact definition continues to evolve, it is a disorder of androgen excess accompanied by ovulatory dysfunction and/or polycystic ovarian morphology. Insulin resistance is often present, and PCOS is a risk factor for metabolic syndrome, type 2 diabetes, dyslipidemia, hypertension, and possibly cardiovascular disease. Besides PCOS, common causes of AUB-O in reproductive-age females include hyperprolactinemia, hypothalamic amenorrhea, also known as hypogonadotropic hypogonadism, primary ovarian insufficiency, and thyroid dysfunction.

The criteria for diagnosing PCOS in adolescents are controversial as the pathologic features used for the diagnosis in adults, specifically acne and irregular menses, may be normal pubertal occurrences. Adolescent hyperandrogenism (as opposed to adult hyperandrogenism) may be a natural consequence of the lack of synchronicity within the HPO axis during prolonged anovulatory cycles that are typical during puberty. Additionally, there is a high background prevalence of polycystic ovarian morphology in this population. Menstrual irregularity for over 2 years and accurate assessment of hyperandrogenic as well as metabolic features, in addition to reduced reliance on ultrasound diagnosis of polycystic ovarian morphology, may be suitable strategies for PCOS diagnosis in the adolescent population. More research is needed to definitively identify the appropriate diagnosis of PCOS among adolescents so that appropriate treatment(s) can be recommended.

Abnormal Uterine Bleeding with Ovulatory Dysfunction Clinical Presentation

CLINICAL PRESENTATION: Abnormal Uterine Bleeding with Ovulatory Dysfunction

General

- Patients typically will not be in acute distress.

Symptoms

- Irregular, heavy, or prolonged uterine bleeding
- Perimenopausal symptoms (eg, hot flashes, night sweats, and vaginal dryness) in ovarian insufficiency or menopausal transition

Signs

- Acne, hirsutism, and obesity in PCOS

Laboratory Tests

- Pregnancy testing
- If PCOS is suspected, consider free or total testosterone, fasting glucose, fasting lipid panel
- If perimenopause is suspected, measure FSH
- TSH

Other Diagnostic Tests

- Endometrial biopsy for patients with risk factors for endometrial hyperplasia or malignancy
- Pelvic ultrasound to evaluate for polycystic ovaries

Treatment

Desired Outcomes

The optimal therapy for AUB-O depends upon the underlying cause(s), and the treatment options for AUB-O are wide and varied. When applicable, control of excessive bleeding in the short term is paramount. Longer-term goals of therapy include restoring the natural cycle of orderly endometrial growth and shedding, preventing endometrial hyperplasia, addressing fertility concerns, decreasing the risk of osteopenia in cases of ovarian insufficiency, and improving the overall quality of life. Table 106-3 identifies the agents used to manage AUB-O and their recommended doses. Medical treatment, as opposed to surgical management, to resolve AUB-O should be initiated, as AUB-O is primarily an endocrinologic abnormality.

Nonpharmacologic Therapy

Nonpharmacologic treatment options for AUB-O depend on the underlying cause. In a female of reproductive age with PCOS, weight loss of 5% to 10% may result in improved menstrual regularity and ovulatory function, reduced hirsutism, increased insulin sensitivity, and improved response to fertility treatments. Further, sustained weight loss has resulted in a return to ovulatory cycles in those without PCOS who experienced anovulatory cycles. In patients with AUB-O who have completed childbearing or who have not responded to medical management, endometrial ablation or resection and hysterectomy are surgical options. In the short term, ablation results in less morbidity and shorter recovery periods compared to other surgical interventions. However, patients should be counseled about the risks regarding the ability to detect and diagnose endometrial cancer in the future. Importantly, procedure choice involves shared decision-making with the patient.

Pharmacologic Therapy

Hormonal contraceptives prevent recurrent AUB-O by providing a progestin and suppressing ovarian hormones. The CHCs are also useful for cycle regulation, leading to predictable menstrual cycles. In individuals with contraindication(s) to estrogen or in whom the adverse medication effects are unacceptable, progesterone-only products are an option. They should be strongly considered for patients experiencing HMB associated with anovulatory cycles. Depot and intermittent oral MPA provide endometrial protection through endometrial suppression. Another progesterone option is placement of the LNG-IUS, particularly if pregnancy is not desired. Studied specifically in females over 30 years of age, use of the LNG-IUS resulted in a greater than 95% reduction in menstrual blood loss by 2 years. Patient satisfaction rates were greater than 80%, with 74% agreeing to recommend it to others.

For individuals with PCOS who have high androgen levels and its related signs (eg, hirsutism), CHCs also increase sex hormone-binding globulin (SHBG) which binds androgens and reduces their circulating free concentrations. The 2018 international PCOS guideline recommends that CHCs alone should be recommended in adults and adolescents with PCOS for management of irregular menstrual cycles and clinical hyperandrogenism. For patients with PCOS, CHCs containing less than or equal to 35 mcg of ethinyl estradiol and a progesterone that exhibits minimal androgenic effects (eg, norgestimate and desogestrel) or with antiandrogenic effects (eg, drospirenone) may be desirable.

The 2018 international PCOS guidelines also recommend that metformin should be considered in adults and adolescents with PCOS for management of metabolic features when lifestyle changes do not achieve desired goals. Although metformin improves insulin sensitivity and can reduce circulating androgen concentrations and improve ovulation rates, CHCs are more effective in cycle regulation and decreasing androgens. The 2018 international PCOS guidelines recommend that metformin can be used in combination with CHCs for treatment of hyperandrogenic-related alopecia or hirsutism if at least 6 months of CHCs and cosmetic therapy do not adequately improve symptoms. While not typically an issue among the relatively young population of patients treated with metformin for PCOS, one must be cognizant of the risk of lactic acidosis in metformin users with renal impairment. As such, this medication should be avoided in individuals with serum creatinine greater than 1.4 mg/dL (124 µmol/L). In addition, metformin may lead to spontaneous ovulation, and birth control should be advised in patients with PCOS not desiring pregnancy.

Hormonal contraceptives containing antiandrogenic progesterones are very effective in managing the acne and hirsutism that accompany PCOS, as they suppress ovarian androgen production and increase SHBG, thus reducing free testosterone concentrations. Controversy regarding their use in PCOS exists secondary to their potential adverse effects on insulin resistance and glucose tolerance. An increase in high-sensitivity C-reactive protein and an increase in homocysteine levels, both indicators of cardiovascular risk, have been observed with the use of CHCs. Another trial found a reduction in brachial artery flow-mediated dilatation and an increase in carotid intima-media thickness, both indicators of endothelial dysfunction, following therapy with oral CHCs containing ethinyl estradiol and cyproterone acetate in patients with PCOS. Additional, longer-term clinical trials will clarify whether the benefits of these agents outweigh the risks. Cardiovascular risk calculators should be employed as an adjunct to guidelines suggesting the use of oral CHCs in this patient population.

If the treatment goal is fertility, letrozole should be considered the first-line treatment for ovulation induction in individuals with PCOS with anovulatory infertility and no other infertility factors. Letrozole has been found to lead to significantly more ovulatory cycles, pregnancies, and live births compared to clomiphene in patients with PCOS. It is dosed at 2.5 mg daily for 5 days beginning on cycle day 3 after induced withdrawal bleeding with a progesterone such as MPA 10 mg daily orally for 10 days. If ovulation does not occur, doses can be increased in subsequent cycles to a maximum of 7.5 mg daily in up to 5 cycles. As an alternative ovulation induction agent, clomiphene citrate is administered in a similar manner, initiated at 50 mg daily, with dose increase in subsequent cycles to a maximum of 150 mg daily.

Glucagon-like peptide (GLP-1) agonists such as liraglutide and semaglutide have an emerging role in the treatment of PCOS due to their benefits on weight loss as well as their ability to improve insulin resistance. It is important to ensure the patient taking GLP-1 receptor agonists has effective contraception, as pregnancy safety data are lacking. The cost of these medications as well as potential side effects and potential need for long-term use to avoid weight regain should all be discussed with the patient.

Overall, the treatment(s) of choice depends on accurate etiologic diagnosis as well as identification of the desired treatment outcome(s). Hormonal contraceptives are the first-choice treatment in individuals with AUB-O who do not desire pregnancy. In those with PCOS, CHCs are first-line pharmacologic agents for cycle control and minimizing the androgenic signs and symptoms of PCOS, while metformin is primarily used for metabolic improvement when lifestyle interventions do not yield adequate improvements. Letrozole is used for ovulation induction in PCOS. Table 106-4 lists the important pharmacologic properties of agents used to treat AUB-O that require monitoring.

Perimenopause

Anovulatory cycles are common in the perimenarchal reproductive years. Ovulation typically is established 1 year or more following menarche. If excessive bleeding occurs, the patient should be evaluated for bleeding disorders, as HMB since menarche may indicate an undetected coagulopathy. If identified, the specific bleeding disorders should be treated. Acute severe bleeding can be managed with intravenous CEE, high-dose CHCs, or high-dose oral progestins.

Evaluation of Therapeutic Outcomes

Table 106-4 lists the expected outcomes and specific monitoring parameters for the treatment modalities used to manage AUB-O.

CONCLUSION

Problems related to the menstrual cycle are very common in females of reproductive age. The most frequently encountered menstruation-related difficulties include amenorrhea; HMB; AUB-O, including PCOS; dysmenorrhea; and PMS and PMDD. The diagnosis of various menstruation-related disorders begins with a thorough history of the patient's menstrual patterns and co-occurring symptoms. Problems related to the menstrual cycle negatively affect quality of life, reproductive potential, and may have long-term detrimental health effects.

KEY RESOURCES

KEY RESOURCES

Gordon CM, Ackerman KE, Berga SL, et al. Functional hypothalamic amenorrhea: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2017;102(5):1413-39.

These are evidence-based guidelines for the treatment of FHA written by a panel of experts from the Endocrine Society and cosponsoring associations (The American Society of Reproductive Medicine, the European Society of Endocrinology, and the Pediatric Endocrine Society).

Management of premenstrual disorders: ACOG Clinical Practice Guideline No. 7. Obstet Gynecol 2023;142(6):1516-33. DOI:10.1097/AOG.0000000000005426.

This guideline provides current evidence-based treatment recommendations for premenstrual disorders and reviews the multimodal approach that is often needed to treat patients. Recommendations are categorized by evidence quality and strength.

Singh S, Pal N, Shubham S, et al. Polycystic ovary syndrome: etiology, current management, and future therapeutics. J Clin Med 2023;12(4):1454. DOI:10.3390/jcm12041454.

This article provides a review of the risk factors potentially involved in the prevalence and etiology of PCOS along with discussion regarding proposed treatment targets.

Teede HJ, Tay CT, Laven JJE, et al. Recommendations from the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome. J Clin Endocrinol Metab 2023;108(10):2447-69. DOI:10.1210/clinem/dgad463.

This is the most recent update to the 2018 International Evidence-based Guideline for the Assessment and Management of PCOS. Over 250 recommendations provide evidence-based treatment and improve outcomes. There is a focus on educating the healthcare team and ensuring the patient is involved in their care as related to treatment decisions.

ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists

AUB-O	abnormal uterine bleeding with ovulatory dysfunction
CEE	conjugated equine estrogen
CHC	combined hormonal contraceptive
COX-2	cyclo-oxygenase-2
FHA	functional hypothalamic amenorrhea
FSH	follicle-stimulating hormone
GLP-1	glucagon-like peptide
GnRH	gonadotropin-releasing hormone
HC	hormonal contraceptive
HMB	heavy menstrual bleeding
HPA	hypothalamic–pituitary–adrenal
HPO	hypothalamic–pituitary–ovarian
IUSs	intrauterine systems
hCG	human chorionic gonadotropin
LH	luteinizing hormone
LNG-IUS	levonorgestrel-releasing intrauterine system
MPA	medroxyprogesterone acetate
NSAID	nonsteroidal anti-inflammatory drug
PCOS	polycystic ovary syndrome
PMDD	premenstrual dysphoric disorder
PMS	premenstrual syndrome
SHBG	sex hormone-binding globulin
SNRI	serotonin–norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TRH	thyrotropin-releasing hormone
TSH	thyroid-stimulating hormone

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SELF-ASSESSMENT QUESTIONS

1. JT is a 17-year-old who complains of amenorrhea for 6 months. She experienced menarche at the age of 14 years. A pregnancy test is performed and found to be negative. This patient is a distance runner who describes her appetite as "healthy." Her BMI is 21 kg/m^2. What is the next step in evaluating this complaint?

   A. Check her serum prolactin concentration.

   B. Check her thyroid-stimulating hormone (TSH) concentration.

   C. Quantify her level of exercise.

   D. Evaluate whether she may have anorexia.

2. Regardless of the etiology of amenorrhea, which of the following lifestyle interventions is most appropriate?

   A. Increase the dietary intake of folate and vitamin E.

   B. Increase the dietary intake of calcium and vitamin D.

   C. Decrease the intake of alcohol.

   D. Decrease the level of exercise.

3. KS is a 36-year-old patient who has not had a period for 8 months. She is not pregnant and has a serum prolactin concentration twice the upper limit of normal. There are no symptoms of polycystic ovary syndrome (PCOS). Which of the following is most appropriate for KS now?

   A. An oral contraceptive containing 30 mcg ethinyl estradiol plus levonorgestrel

   B. Bromocriptine 2.5 mg by mouth three times daily

   C. Medroxyprogesterone acetate (MPA) 10 mg by mouth for 10 days

   D. Metformin 1,000 mg by mouth twice daily

4. BJ is a 14-year-old female who started having menses 7 months ago. Her menses is irregular, with cycle length ranging from 32 days to 75 days. What is the best cause of action now?

   A. Evaluate BJ for hypothyroidism.

   B. Evaluate BJ for polycystic ovary syndrome (PCOS).

   C. Evaluate BJ for bleeding disorders.

   D. Educate BJ that her menstrual irregularity is expected.

5. Which of the following statements is true regarding the levonorgestrel-releasing intrauterine system (LNG-IUS) in an individual with HMB?

   A. It should never be used in nulliparous females.

   B. It reduces menstrual flow by a maximum of 25%.

   C. It is a therapeutic option for any individual at low risk for sexually transmitted infections.

   D. Its use increases the need for hysterectomy.

6. In patients with PCOS whose primary concern is menstrual irregularity, who is not attempting pregnancy, which of the following is the initial

therapeutic option after a trial of applicable lifestyle intervention?

A. Metformin

B. A combination oral contraceptive containing ethinyl estradiol and drospirenone

C. LNG-IUS

D. Letrozole

7. BB is a 32-year-old patient who initially presented with complaints of irregular menses and excess hair growth around the jawline. She was diagnosed with PCOS and was started on an oral contraceptive and lifestyle modification. Today at her 6-month follow-up appointment, her BMI is 35 kg/m^2 with a waist circumference of 40 in. (102 cm). A 2-hour oral glucose tolerance test suggests impaired glucose tolerance. Which of the following is the most appropriate option for BB now?

A. Continue her oral contraceptive.

B. Discontinue her oral contraceptive and initiate a LNG-IUS.

C. Discontinue her oral contraceptive and initiate letrozole.

D. Add metformin.

8. Hyperkalemia is most likely to result from which of the following products used in the management of PCOS?

A. A combination oral contraceptive containing ethinyl estradiol and drospirenone

B. A combination oral contraceptive containing ethinyl estradiol and levonorgestrel

C. Metformin 850 mg by mouth twice daily

D. Injectable medroxyprogesterone acetate (MPA), 150 mg dose every 12 weeks

9. JK has PCOS that was previously treated with a combined oral contraceptive. She discontinued oral contraceptive use 14 months ago to attempt pregnancy. During these 14 months, there have been two menstrual periods, both with heavy bleeding. A pregnancy test today is negative. Which of the following is the most appropriate treatment?

A. Clomiphene 50 mg daily orally for 5 days

B. MPA 10 mg daily orally for 10 days

C. MPA 10 mg daily orally for 10 days, followed by letrozole 2.5 mg orally daily for 5 days beginning on cycle day 3 after induced withdrawal bleeding

D. MPA 10 mg daily orally for 10 days, followed by metformin 550 mg orally daily and titrated to 2,000 mg total daily dose

10. Excessive anovulatory bleeding in the adolescent population should result in an evaluation for:

A. Hypoprothrombinemia

B. Hyperandrogenism

C. Hypoestrogenism

D. Hypothyroidism

11. Which of the following agents is most appropriate for the management of dysmenorrhea in an adolescent who is not sexually active?

A. Depot MPA 150 mg intramuscularly every 12 weeks

B. Ibuprofen 800 mg by mouth three times daily during menses

C. LNG-IUS releasing 20-mcg levonorgestrel daily

D. Oral contraceptive with 35-mcg ethinyl estradiol plus norgestimate daily

12. The most cost-effective treatment for heavy menstrual bleeding is:

A. A combination oral contraceptive

B. LNG-IUS

C. Oral MPA

D. Depot MPA

13. Which of the following nonpharmacologic options is effective for the treatment of dysmenorrhea?

A. High protein diet

B. Topical ice packs

C. Reduced exercise

D. Topical heat

14. Dysmenorrhea is experienced by as many as _____% of females of childbearing age.

A. 20

B. 40

C. 70

D. 90

15. CO is a 30-year-old patient diagnosed with PMDD after charting symptoms for two cycles and attempting nonpharmacologic interventions for her symptoms without much relief. This patient is married and does not wish to use any form of birth control. Which of the following agents would be most appropriate for managing CO's PMDD?

A. Continuous treatment with paroxetine

B. Luteal phase treatment with fluoxetine

C. Luteal phase treatment with sertraline

D. 90-mcg levonorgestrel and 20-mcg ethinyl estradiol dosed continuously for 12 months

ANSWERS

1. **C.** Given that JT is a distance runner, and reported a healthy appetite, the most likely cause of amenorrhea is excess physical activity. Although hyperprolactinemia and hypothyroidism could be a possibility, they are not the most probable cause given the patient's history (see subsection "Pathophysiology" under section "Amenorrhea").

2. **D.** Among the choices presented, only physical exercise has been associated with amenorrhea (see subsections "Nonpharmacologic Therapy" and

"Pharmacologic Therapy" under section "Amenorrhea").

3. **B.** The initial treatment of hyperprolactinemia is bromocriptine. Although an oral contraceptive and cyclical medroxyprogesterone acetate (MPA) can produce predictable menses, they do not address high prolactin levels (see subsection "Pharmacologic Therapy" under section "Amenorrhea"; also Table 106-3 for amenorrhea related to hyperprolactinemia).

4. **D.** During the first 12 to 18 months after menarche, immaturity of the hypothalamic–pituitary–ovarian axis is frequently the cause of ovulatory abnormal uterine bleeding. By the third year after the onset of menstruation, 60% to 80% of cycles are regular. If regular menstrual cycles have not been established within 5 years of menarche, further evaluation for the cause, such as polycystic ovary syndrome (PCOS), should be considered (see subsection "Etiology" under section "Abnormal Uterine Bleeding with Ovulatory Dysfunction").

5. **C.** Although historically it was believed that intrauterine devices (IUS) use should be avoided in nulliparous females, guidelines from the American College of Obstetricians and Gynecologists indicate that both nulliparous and multiparous individuals at low risk of sexually transmitted illnesses are good candidates for IUS use. IUSs are not associated with an increased risk of uterine pathology necessitating a hysterectomy (see "Special Populations and Adolescents" under section "Heavy Menstrual Bleeding").

6. **B.** The 2018 international PCOS guideline recommends that combined hormonal contraceptives (CHCs) alone should be recommended in adults and adolescents with PCOS for management of irregular menstrual cycles and clinical hyperandrogenism. For those with PCOS, CHCs containing less than or equal to 35 mcg of ethinyl estradiol and a progesterone that exhibits minimal androgenic effects (eg, norgestimate and desogestrel) or with antiandrogenic effects (eg, drospirenone) is desirable (see subsection "Pharmacologic Therapy" under section "Abnormal Uterine Bleeding with Ovulatory Dysfunction").

7. **D.** The 2018 international PCOS guidelines recommend that metformin should be considered in adults and adolescents with PCOS for management of metabolic features when lifestyle changes do not achieve desired goals. Given the patient's impaired glucose tolerance, the addition of metformin is the most appropriate choice (see subsection "Pharmacologic Therapy" under section "Abnormal Uterine Bleeding with Ovulatory Dysfunction").

8. **A.** Of the options listed, only drospirenone carries a risk of hyperkalemia (see Table 106-4, drospirenone-containing CHC).

9. **D.** The 2018 international PCOS guidelines recommend that if the treatment goal is fertility, in individuals with PCOS with anovulatory infertility and no other infertility factors, letrozole should be considered first-line treatment for ovulation induction. Letrozole should be started at 2.5 mg orally daily for 5 days beginning on cycle day 3 after induced withdrawal bleeding with a progesterone such as MPA. Although clomiphene also induces ovulation and improves pregnancy and live birth rates compared to metformin, it is less efficacious than letrozole in a double-blind controlled clinical trial (see subsection "Pharmacologic Therapy" under section "Abnormal Uterine Bleeding with Ovulatory Dysfunction").

10. **A.** Anovulatory cycles are common in the perimenarchal reproductive years. Recommendations indicate that heavy menstrual bleeding following menarche can be highly indicative of an undetected coagulopathy as opposed to a menstrual abnormality related to hormonal irregularities (see subsection "Perimenopause" under section "Abnormal Uterine Bleeding with Ovulatory Dysfunction").

11. **B.** Treatment choice for dysmenorrhea is influenced by the patient's level of sexual activity and/or their desire for contraception. In this case, as contraception is neither desired nor needed, the nonhormonal option of a nonsteroidal anti-inflammatory agent, ibuprofen, is desirable (see subsection "Desired outcomes" under section "Dysmenorrhea" and Table 106-3).

12. **B.** Among all hormonal agents available to manage heavy menstrual bleeding, all cost-effectiveness data support the LNG-IUS above all other options (see subsection "Pharmacologic Therapy" under section "Heavy Menstrual Bleeding").

13. **D.** The nonpharmacologic options shown to be effective in managing dysmenorrhea include low-fat vegetarian diet (NOT high protein), exercise (NOT reduced exercise), acupuncture, and topical heat. Topical ice packs have NOT been shown effective in managing dysmenorrhea (see subsection "Nonpharmacologic Therapy" under section "Dysmenorrhea").

14. **D.** The answer is 90% and the intent of asking this question is to raise awareness of the extreme prevalence of this disorder that so negatively impacts the quality of life of so many individuals (see subsection "Epidemiology" under section "Dysmenorrhea").

15. **C.** The SSRIs are considered the first-line treatments for PMDD. Evidence comparing luteal phase versus continuous dosing shows equal efficacy between the two dosing regimens. From a medication adverse effect standpoint, the luteal phase dosing is associated with LESS of a negative impact on libido when compared to continuous dosing. Birth defects have been noted to occur 2 to 3.5 times more frequently with paroxetine and fluoxetine. Further, this patient does NOT desire the use of any form of contraception (see subsection "Pharmacologic Therapy" under section "Premenstrual Syndrome and Premenstrual Dysphoric Disorder").