Menstrual-Related Disorders

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Learning Objectives

1. Classify bleeding patterns associated with abnormal uterine bleeding and demonstrate an understanding of different evaluation techniques.
2. Based on the patient's type and severity of bleeding, construct an appropriate management plan for abnormal uterine bleeding.
3. Develop a management plan including nonpharmacologic and pharmacologic therapy for symptoms associated with premenstrual syndrome.
4. Develop a management plan including nonpharmacologic and pharmacologic therapy for symptoms associated with premenstrual dysphoric disorder.
5. Design an optimal treatment plan, based on a woman's signs and symptoms and including nonpharmacologic and pharmacologic approaches, for a woman presenting with polycystic ovary syndrome (PCOS).
6. Apply nonpharmacologic and pharmacologic approaches to improve the likelihood of conception in a woman presenting with infertility secondary to PCOS.

Premenstrual Syndrome/ Premenstrual Dysphoric Disorder

Premenstrual syndrome (PMS) is a term used to describe a constellation of more than 200 reported premenstrual complaints that typically do not cause functional impairment. Symptoms can be categorized into four domains: somatic (e.g., mastalgia, bloating, body aches, headache); affective (e.g., depression, irritability, anxiety, mood swings, feeling out of control); behavioral (e.g., reduced interest in usual activities, appetite changes, social withdrawal); and cognitive (e.g., difficulty concentrating, sleep disturbances). About 90% of women of childbearing age report experiencing premenstrual symptoms sometime in their lives; this is known as menstrual molimina. A smaller subset of women (20%) describe severe symptoms of PMS that warrant treatment, and 3% to 8% of women receive diagnoses of a severe form of PMS known as *premenstrual dysphoric disorder* (PMDD).

Etiology

The pathophysiology of PMS and PMDD is not well understood. Although no hormonal imbalance appears to exist in women with PMS or PMDD, the cyclic nature of estrogen and progesterone production is thought to trigger premenstrual symptoms. Increasing evidence supports that reduced blood concentrations and transmission of serotonin in the brain are linked to several symptoms of PMS, including poor impulse control, irritability, dysphoria, and appetite changes. Reduced concentrations of γ-aminobutyric acid, altered adrenergic receptors, and reduced opiate concentrations during the late luteal phase are also potentially associated with

Baseline Knowledge Resources

The goal of PSAP is to provide only the most recent (past 3–5 years) information or topics. Chapters do not provide an overall review. Suggested resources for background information on these topics include:

- Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit J, et al (Task Force on the Phenotype of the Polycystic Ovarian Syndrome of The Androgen Excess and PCOS Society). The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. Fertil Steril 2009;91:456–88.
- Lobo RA. Abnormal uterine bleeding: ovulatory and anovulatory dysfunctional uterine bleeding, management of acute and chronic excessive bleeding. In: Katz VL, Lentz GM, Loba RA, Gershenson DM, eds. Comprehensive Gynecology. Philadelphia: Mosby Elsevier, 2007:915–32.

Abbreviations in This Chapter

ACOG	American Congress of Obstetricians and Gynecologists
COC	Combined oral contraceptive
FSH	Follicle-stimulating hormone
GnRH	Gonadotropin-releasing hormone
LH	Luteinizing hormone
PCOS	Polycystic ovary syndrome
PMDD	Premenstrual dysphoric disorder
PMS	Premenstrual syndrome
SSRI	Selective serotonin reuptake inhibitor

the development of premenstrual symptoms. In addition, it has been postulated that lower concentrations of allopregnanolone, a progesterone metabolite with benzodiazepine-like effects, occur in the late luteal phase in women with PMS and play a role in some menstrual-related symptoms such as anxiety, irritability, and premenstrual epilepsy exacerbations.

Characteristics

Premenstrual symptoms occur cyclically during the luteal phase of the menstrual cycle and resolve quickly within a few days of the onset of menses. Women seeking medical attention usually have several symptoms from all domains; however, mood and behavioral symptoms are the most distressing. Premenstrual symptoms usually begin in the early 20s, but medical attention often is delayed for as long as 10 years after symptoms begin. Genetic factors appear to play a role because women whose mothers had PMS are more likely to develop PMS, and higher concordance rates of PMS are observed in monozygotic twins.

Diagnostic criteria for PMS set by the American Congress of Obstetricians and Gynecologists (ACOG) state that at least one affective and one somatic symptom must be prospectively charted during the 5 days before menses onset and during the three previous menstrual cycles. Symptoms must occur in the absence of pharmacotherapy, illicit drugs, or alcohol; must cease within 4 days of menses onset; and must not recur until day 12 of the next menstrual cycle. Other diagnoses, including psychiatric and nonpsychiatric disorders, should be excluded. Most other chronic conditions will be apparent throughout the menstrual cycle; however, some may worsen cyclically because of hormonal fluctuations, making the diagnosis difficult. These conditions include depression, seizures, headaches, asthma, rheumatoid arthritis, irritable bowel syndrome, and diabetes mellitus.

Premenstrual dysphoric disorder is the most severe form of PMS. Diagnostic criteria require the presence of at least five symptoms, with at least one being markedly depressed mood, anxiety, affective lability, or irritability. Often, somatic complaints accompany the mood-related symptoms. These luteal symptoms must be confirmed through daily symptom ratings during menstrual cycles. Unlike PMS, there is substantial impairment of personal functioning, generally more in social than in occupational situations. Risk factors for PMDD include age in the late 20s to mid-30s, a history of psychiatric disorders or substance abuse, and a family history of PMDD. Epidemiologic studies have not consistently demonstrated an association with parity, menstrual cycle characteristics, oral contraceptive use, or socioeconomic and lifestyle variables including smoking.

In diagnosing PMDD, a comprehensive history and physical examination are required to exclude other causes of the emotional and physical symptoms. It is important to distinguish the marked emotional symptoms observed in PMDD from those observed in other major mood or anxiety disorders because treatment may differ. Several valid and reliable diagnostic instruments are available for the prospective recording of symptoms in women with PMDD. Using these tools, the diagnosis of PMDD is confirmed if symptoms are absent during the follicular phase of the menstrual cycle, markedly increased during the luteal phase, and associated with functional impairment.

Supportive Therapies

Women with mild to moderate PMS symptoms often do not require pharmacologic treatment. However, because of its impact on social functioning, treatment is often warranted in women suffering from PMDD. First-line treatment options are primarily supportive. Second-line treatment options include selective serotonin reuptake inhibitors (SSRIs) and anxiolytics. Alternative options are various hormonal therapies and surgery.

Supportive therapies are recommended for all women experiencing PMS or PMDD symptoms, including dietary changes, exercise, cognitive behavior therapies, calcium supplementation, and complementary and alternative medicine (discussed in the Dietary Supplements chapter). These modalities may lessen mild to moderate symptoms. Dietary recommendations include premenstrual decreases in caffeine, salt, and refined sugar intake and consuming smaller, more frequent meals to help diminish irritability, insomnia, fluid retention, breast tenderness, bloating, and weight gain. Weak evidence suggests that an increase in complex carbohydrates decreases mood changes based on the theory that complex carbohydrates lead to an increase in tryptophan, a precursor to serotonin production. Exercise may increase endorphins, and it has been shown to considerably improve mood and decrease lethargy. Cognitive behavior therapy, including relaxation and sleep hygiene, may effectively treat physical and emotional symptoms and is most effective in women with severe symptoms. Alternative treatments

such as reflexology, massage therapy, biofeedback, acupuncture, and light therapy may offer improvement in symptoms such as anxiety, depression, pain, and fluid retention; however, evidence for the use of these strategies is limited and of low quality.

Pharmacologic Treatment

Antidepressants

Dysregulation of serotonergic neurotransmission appears to be part of the underlying etiology of PMDD, making SSRIs the preferred agents for the treatment of PMDD not responsive to supportive therapies. The SSRIs, with the exception of fluvoxamine, have been shown to improve the emotional and physical symptoms of PMDD and enhance psychosocial functioning, work performance, and overall quality of life.

In patients with PMDD treated with an SSRI, clinically significant improvements in irritability, depressed mood, and physical symptoms have occurred during the first menstrual cycle, unlike the 4–8 weeks generally required for improvement when major depressive disorder is treated with these agents. This rapid response may reflect drug action at a different receptor site and may be related to increased allopregnanolone concentrations. This more rapid response also allows SSRIs to be used in either continuous or intermittent regimens at the same dosage. Women with coexisting mood and anxiety disorders who develop mood symptoms outside the luteal phase, who have irregular menstrual cycles, or who experience intolerable adverse effects upon SSRI discontinuation should be considered for a continuous daily SSRI administered throughout the menstrual cycle. In addition, some studies suggest that a continuous daily SSRI results in greater improvement in somatic symptoms associated with PMDD than intermittent therapy. Fluoxetine, at a dosage of 20 mg/day, is an effective treatment for PMDD. Daily dosages of 50–150 mg of sertraline, 20–30 mg of paroxetine, 12.5–25 mg of paroxetine controlled release, 20–30 mg of citalopram, and 10–20 mg of escitalopram are also effective. A recent meta-analysis of placebo-controlled trials concluded that no SSRI appears to be more effective than another; however, no comparison data are available, and the choice of SSRI should be based on patient-specific characteristics and cost.

Patients concerned with the adverse effects or the cost associated with an SSRI may use an intermittent dosing schedule. Intermittent (or luteal phase) daily dosing is initiated on day 14 of the menstrual cycle and discontinued 1–2 days after the onset of menses. Weekly dosing with 90 mg of enteric-coated fluoxetine administered twice during the luteal phase is also effective. Because of its shorter half-life, only the controlled-release formulation of paroxetine should be used for intermittent dosing. For intermittent dosing to successfully treat PMDD symptoms, women must have regular menstrual cycles, be able to adhere to the on/off dosing schedule, and have no symptoms during the follicular phase. Semi-intermittent dosing, which involves a combination of continuous daily SSRI dosing with increased dosages during the luteal phase, is appropriate for women who experience mood symptoms throughout their menstrual cycle, with symptoms worsening during the luteal phase.

Dosing of SSRIs should be initiated at the lower end of the dosing range for the treatment of depressive disorders, and the dosage should be increased as needed. Fluoxetine at 60 mg/day resulted in increased adverse effects with no corresponding increase in effectiveness compared with 20 mg/day. Headache, fatigue, insomnia, anxiety, and sexual dysfunction were the most often reported adverse events. If treatment with one SSRI is not effective, another SSRI or serotonergic antidepressant agent may be tried.

Although SSRIs are the antidepressant class most widely evaluated for PMDD, other antidepressants have been studied, including clomipramine at a dosage of 25–75 mg/day either continuously or intermittently and venlafaxine and duloxetine at dosages of 50–200 mg/day and 60 mg/day, respectively. Antidepressants known to be ineffective in PMS and PMDD include desipramine, maprotiline, and bupropion.

Anxiolytic Agents

Premenstrual related or exacerbated anxiety is a common premenstrual complaint and can be debilitating. The use of anxiolytics in PMDD is controversial; as a result, these agents have been relegated to second- or third-line treatment options. When taken during the luteal phase of the menstrual cycle, anxiolytics can be useful in women with persistent anxiety despite the adequate trial of an SSRI.

Alprazolam is the most studied anxiolytic used in the treatment of premenstrual-related anxiety symptoms. Many studies have focused on the efficacy of alprazolam on PMS symptoms, but no large trials have examined alprazolam in women with PMDD. Nonetheless, alprazolam at doses of 0.25 mg given orally three or four times/day during the luteal phase is effective for the treatment of premenstrual depression, tension, anxiety, irritability, hostility, and social withdrawal. In addition to being associated with a risk of dependence and tolerance, alprazolam does not improve the physical or somatic symptoms associated with PMS or PMDD. Buspirone at a dosage of 20 mg/day during the luteal phase was more effective than placebo in a few PMS trials, and it has no potential for dependence or tolerance.

Hormonal Therapy

Because PMS and PMDD appear to be cyclical disorders occurring late in the luteal phase, suppression of ovulation using hormonal therapies is an alternative approach to treatment when SSRIs or other psychotropic agents are ineffective or contraindicated.

Combined Oral Contraceptives

Although combined oral contraceptives (COCs) are widely prescribed for the management of PMS, they are not consistently effective. The benefits are likely because of the estrogenic component; therefore, monophasic pills may be the most appropriate because of less hormonal fluctuations. Improvements in physical symptoms such as bloating, headache, abdominal pain, and breast tenderness may occur, but COCs can also exacerbate these symptoms in some women. Oral contraceptives do not improve mood symptoms; thus, they are an option for women with only physical PMS symptoms who are also seeking contraception.

Newer COCs containing drospirenone, a derivative of spironolactone, have been studied for their antimineralocorticoid and antiandrogenic properties. Two drospirenone-containing COCs are labeled for the treatment of PMDD. A recent systematic review of the use of drospirenone-containing COCs for PMDD reported reduced abdominal bloating and breast tenderness and improved productivity and social functioning compared with placebo after 3 months of treatment. It is unknown whether drospirenone-containing COCs are superior to other COCs. To further suppress cyclic changes and sex hormone variability, studies evaluating extended-use drospirenone-containing COCs for 42–168 days showed a greater reduction in premenstrual symptoms (e.g., edema, breast tenderness, bloating) than standard 21-day and 28-day regimens.

Gonadotropin-Releasing Hormone Analogs

The gold standard treatment for suppressing ovulation, use of gonadotropin-releasing hormone (GnRH) analogs, is referred to as *medical oophorectomy*. These synthetic analogs of naturally occurring GnRH reduce the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), interrupt normal sex hormone production, and induce anovulation. Available GnRH analogs include leuprolide, goserelin, nafarelin, and histrelin, none of which have U.S. Food and Drug Administration (FDA)-approved labeling for use in PMS or PMDD. Several studies have reported considerable reductions in psychoemotional and physical symptoms after treatment with GnRH analogs compared with placebo; most notably irritability, pain, breast tenderness, and fatigue. Variable effects on premenstrual depression can occur, but GnRH analogs appear effective in women who have ongoing dysphoric symptoms beyond the luteal phase.

Many women do not tolerate the adverse effects of GnRH analogs, particularly hypoestrogenism and the induction of menopausal symptoms, as well as depression, headache, and muscle aches. Because of reductions in bone mass, treatment with GnRH analogs should be limited to no longer than 6–9 months without adding estrogen and progesterone. The addition of estrogen and/or progesterone to GnRH analogs, known as *add-back therapy*, lessens these adverse effects; however, this may cause the return of some of the unwanted PMS symptoms.

The optimal regimen has not been established; however, data suggest that continuous daily combination therapy with conjugated estrogen (at least 0.625 mg), estradiol valerate (2 mg), or transdermal estradiol (0.05 mg) with medroxyprogesterone acetate 5–10 mg is effective for reducing bone loss associated with GnRH analogs. Long-term treatment regimens with GnRH analogs should also include adequate calcium and vitamin D intake, and baseline bone mineral density evaluation. Despite their proven efficacy, GnRH analogs should be reserved for patients who do not respond to other therapies because of the adverse effects associated with long-term use.

Danazol

Danazol, an androgenic agent that inhibits gonadotropin release and ovulation, reduces symptoms of premenstrual tension, breast pain, irritability, anxiety, lethargy, depression, mood swings, decreased libido, and abdominal swelling. Despite proven efficacy, the use of danazol is limited by serious dose-related adverse effects such as masculinization, edema, acne, abnormal liver function tests, and reduced high-density lipoprotein cholesterol. Symptoms of depression can also occur with higher dosages. To minimize adverse effects, the lowest effective dosage should be used, typically 100 mg given once or twice daily. Adequate contraception is required during therapy because some women may still ovulate, and danazol can cause virilization of a developing fetus.

Progestins

A systematic review of 14 randomized controlled trials evaluating the use of natural progesterone and synthetic progestins for PMS found no improvement in overall symptoms. Some evidence indicates that progesterone is responsible for certain PMS symptoms, such as abdominal bloating, nausea, breast discomfort, and menstrual irregularities. Therefore, progestins alone are not recommended for PMS.

Estrogens

Limited evidence suggests that estrogen therapy alleviates PMS symptoms, but some women experience worsening of symptoms with estrogen. To achieve overall symptom management, estrogen must be given continuously to suppress ovarian activity (e.g., as a transdermal patch [100–200 mcg/day]). Unopposed estrogen therapy can promote endometrial hyperplasia and carcinoma; therefore, cyclic progesterone must be added to the regimen. Progesterone, however, may induce PMS symptoms, thereby limiting the effectiveness of estrogen therapy.

Spironolactone

Spironolactone produces antimineralocorticoid and antiandrogenic effects and interferes with testosterone synthesis. Dosages of 25–200 mg/day during the luteal phase are effective at alleviating weight gain, breast tenderness, and bloating as well as decreasing negative mood and somatic symptom scores. Spironolactone can be recommended to improve these symptoms in women with PMS and PMDD. Patients taking spironolactone should be monitored periodically for hyperkalemia, particularly women who are also taking drospirenone-containing COCs.

Surgery

Most patients with PMS or PMDD will respond to medical therapy; therefore, surgery should be reserved as a treatment of last resort for severe and debilitating symptoms. In this setting, provided that the woman does not wish to have children, a total abdominal hysterectomy with bilateral oophorectomy accompanied by appropriate hormone therapy can be an extremely effective and permanent cure for PMS and PMDD. A trial of a GnRH analog as medical oophorectomy is recommended to confirm response before surgery.

Abnormal and Dysfunctional Uterine Bleeding

Abnormal uterine bleeding is one of the most common gynecologic problems, including both dysfunctional uterine bleeding (no identifiable structural uterine cause) and bleeding from structural causes (e.g., uterine fibroids and polyps, endometrial carcinoma, pregnancy complications). Many women (up to 40%) with abnormal uterine bleeding have fibroids; these women may present with abnormal bleeding, anemia, pain, and occasionally infertility.

Dysfunctional uterine bleeding can be categorized as anovulatory or ovulatory. Anovulatory dysfunctional uterine bleeding is characterized by irregular and unpredictable bleeding, particularly at the extremes of reproductive age such as perimenarche and perimenopause. Polycystic ovary syndrome (PCOS) is a common cause of anovulatory bleeding and is discussed later in this chapter. More commonly, dysfunctional uterine bleeding is ovulatory, which is characterized by heavy but regular bleeding, also known as menorrhagia. Abnormal bleeding can also result from use of various hormonal contraceptive methods.

Dysfunctional uterine bleeding can range from light to excessive and be prolonged, frequent, or random. Although dysfunctional uterine bleeding may resolve with time as the hypothalamic-pituitary-ovarian axis matures or menopause ensues, frequent or excessive uterine bleeding can lead to iron deficiency anemia, reduced quality of life, and increased health care costs. In severe cases, women may require hospitalization for fluid resuscitation, blood transfusion, or intravenous hormone therapy.

A standardized classification and naming system for abnormal uterine bleeding has not been established; this makes identifying guidelines and specific treatment strategies difficult. The following terms are used to describe specific abnormal bleeding patterns: *oligomenorrhea* is menses with intermenstrual intervals longer than 35 days; *polymenorrhea* is menses with regular intervals less than 21 days; *metrorrhagia* is irregular bleeding or bleeding between periods; *menorrhagia* is regular cycles with excessive flow (more than 80 mL) or duration (longer than 7 days); and *menometrorrhagia* is bleeding with irregular intervals and excessive flow or duration. In general, dysfunctional uterine bleeding leads to the patterns of oligomenorrhea, metrorrhagia, or menometrorrhagia.

Pathophysiology

The menstrual cycle is characterized by the regular occurrence of ovulation. In normal ovulatory cycles, estrogen concentrations increase during the follicular phase, resulting in endometrial growth and proliferation. In response to this rise in estrogen and progesterone production from the corpus luteum, the endometrium transforms and prepares for the implantation of a fertilized egg during the luteal phase. If pregnancy does not occur, the corpus luteum regresses, estrogen and progesterone concentrations rapidly decline, and the endometrium sloughs predictably in a cyclic fashion. The normal menstrual cycle averages 28 days (plus or minus 7 days), with menstrual flow occurring for an average of 4 days and resulting in 35–40 mL of blood loss.

In the 5 years after menarche, immaturity of the hypothalamic-pituitary-ovarian axis results in variable production of gonadotropins, including GnRH, FSH, and LH, and the ovarian hormones, 17β-estradiol and progesterone. Ovulation often fails because of insufficient ability to mount an LH surge in response to rising estradiol concentrations, resulting in increased cycle length. During prolonged or anovulatory cycles, the ovary produces constant, noncycling estrogen concentrations that stimulate endometrial growth. Progesterone is not available to prepare the endometrium for implantation; thus, the endometrium does not degenerate and slough as it should when progesterone support declines, like in a normal ovulatory cycle. Thus, the endometrial stroma becomes edematous with increased vascularity.

Estrogen-related endometrial proliferation without periodic shedding causes the endometrial lining to outgrow its blood supply. This fragile endometrium sheds irregularly and unpredictably, leading to erratic bleeding or heavy, prolonged menstruation. In time, menstrual cycles become more predictable and regular in most women, but they still may last 21–45 days in the first 3

years after menarche. However, if normal menses have not developed within 4 years of menarche, there is likely an underlying disease process contributing to the bleeding dysfunction.

As women approach menopause, the progressive decline in ovarian response to gonadotropins results in intermittent ovulatory failure. Initially, chronic stimulation from unopposed estrogen may lead to episodes of frequent, heavy bleeding through a mechanism similar to dysfunctional uterine bleeding in an adolescent. As ovarian function continues to decline, the ovarian follicles secrete less estradiol, and the mean length of the menstrual cycle is shortened. Insufficient endometrial proliferation caused by fluctuating estrogen concentrations may lead to infrequent light spotting or bleeding. Abnormal bleeding caused by an absence of estrogen decline and excess endometrial proliferation is sometimes referred to as *estrogen-breakthrough bleeding*, whereas bleeding from declining estrogen and insufficient endometrial proliferation is referred to as *estrogen-withdrawal bleeding*. Ovulatory dysfunctional uterine bleeding may be caused by luteal phase abnormalities or by an elevated progesterone-to-estrogen ratio as seen with progesterone-only contraceptives. Both can cause an atrophic endometrium, which without sufficient estrogen priming tends to slough.

Diagnosis

Because dysfunctional uterine bleeding is a diagnosis of exclusion, evaluation of abnormal uterine bleeding is often complicated. A woman who bleeds for longer than 1 week, bleeds more than every 3 weeks, bleeds between menses, or bleeds excessively should be advised to seek medical attention. Heavy menstrual bleeding is defined as a blood loss of 80 mL or more per menstrual cycle, but this is difficult to quantify objectively, and medical care is often sought on the basis of a perception of heavy bleeding or reduced quality of life.

The most common reason for divergence from a pattern of normal menses is pregnancy or a complication of pregnancy, such as ectopic pregnancy or threatened or incomplete abortion. After pregnancy is excluded as the cause, other anatomic conditions such as reproductive tract anomalies, trauma, cervical or endometrial polyps, adenomyosis, uterine fibroids, and infection should be considered. Other possibilities include precancerous changes or cervical or endometrial malignancies. Endocrine disorders, most notably hypo- or hyperthyroidism, can also cause menstrual changes. Coagulation disorders should be considered in women with menorrhagia. A history of postpartum bleeding or excessive bleeding during surgery, dental procedures, or trauma can be the sign of an underlying bleeding disorder. Experts estimate that the prevalence of von Willebrand disease in women with heavy menstrual bleeding is 13%. Less common reasons for abnormal bleeding include systemic disease and drugs such as hormonal contraceptives, anticoagulant and antiplatelet agents, tamoxifen, antipsychotic agents, and herbal supplements with estrogenic activity. Evaluation of lifestyle can reveal triggers of anovulation, such as weight loss, eating disorders, excessive exercise, high stress, and substance abuse.

In addition to a complete medical history and physical examination, a thorough menstrual history is the most valuable tool for differentiating anovulatory bleeding from other causes. The regularity and length of intermenstrual intervals and the volume and duration of flow should be obtained for both normal and abnormal cycles. Volume of flow is subjective, and details such as the number and type of pads during daily activities or at night, the need to wear several pads or tampons, and the number of hours each pad is worn may be helpful.

Cytologic examination of the cervix can screen for invasive cervical lesions. In addition, an ultrasound examination can be performed either transvaginally or transabdominally. Ultrasonagraphy can provide information about the uterine lining and the presence of intramural or submucosal fibroids, intrauterine polyps, and adnexal masses. A persistently thick and irregular endometrium may be indicative of endometrial carcinoma. Sonohysterography involves a pelvic ultrasound examination performed after the injection of saline into the uterus, and it has a higher sensitivity than traditional transvaginal ultrasonography.

At minimum, a pregnancy test and complete blood cell count with differential and platelet count should be performed. Laboratory tests to assess thyroid and liver function, prolactin concentration, and other hormone assays are commonly obtained; however, these tests are not routinely recommended in recent guidelines. Because underlying hematologic abnormalities are present in a significant percentage of adolescents with severe anemia associated with abnormal bleeding, obtaining coagulation studies is especially appropriate in this population. Women older than 35 who are morbidly obese, with diabetes or hypertension or with long-standing anovulation, should be evaluated for endometrial carcinoma. Additional laboratory and diagnostic tests should be obtained on the basis of individualized patient history and physical examination findings.

Severe acute uterine bleeding is defined as bleeding that requires more than one pad or tampon per hour, vital signs indicating hypovolemia, or a hemoglobin concentration less than 10 g/dL. It usually occurs in adolescents with von Willebrand disease or in adults with submucosal fibroids or those taking anticoagulants.

Treatment/Management

Abnormal uterine bleeding often requires medical or surgical treatment because overstimulation of endometrial growth results in iron deficiency anemia and risk of endometrial cancer. Therapy goals are to establish the

cause, treat any pathology present, prevent cancer, and control abnormal bleeding. Although consensus is lacking with respect to the management of abnormal uterine bleeding, treatment strategies can be categorized on the basis of severity and timing of bleeding (Table 1-1).

Hormonal therapy is the most effective medical therapy for acute bleeding. Estrogen is thought to exert early onset of capillary hemostasis by increasing the production of fibrinogen and several coagulation factors in the blood, as well as by increasing platelet aggregation and decreasing capillary permeability. Continued high-dose estrogen allows endometrial proliferation and induces the formation of progesterone receptors. These effects enhance the progestin treatment necessary to produce synchronized and controlled uterine bleeding that resembles a normal cycle.

Once the acute bleeding is controlled, long-term treatment decisions should be based on the patient's age, medical and social history, financial considerations, fertility status, and opinion of acceptable bleeding patterns. In women of childbearing age, therapy should allow predictable, manageable menstrual cycles or induce ovulation in patients who desire pregnancy. In older women who may be approaching menopause, treatment may help offset symptoms. Women whose symptoms are severe and resistant to medical therapy may choose surgical treatments such as dilation and curettage, endometrial ablation, or hysterectomy.

Because iron deficiency anemia is common in patients with dysfunctional uterine bleeding, and the diet of the average woman is often iron deficient, a daily dosage of 60–180 mg of elemental iron is an essential component

Table 1-1. Management of Abnormal Uterine Bleeding

Drug	Dosage	Comments
Acute Severe Bleeding		
Conjugated equine estrogen, followed by high-dose estrogen for 21 days	2.5 mg PO QID or 25 mg IV q4h for 12–24h	Add promethazine 25 mg/dose PO/PR/IM Q4H PRN for nausea; add medroxyprogesterone 5–10 mg/day PO to last 5–10 days of estrogen treatment to promote withdrawal bleeding
Conjugated equine estrogen	1.25 mg PO q4h for 24h; then 0.625-1.25 mg/day PO	As above
Estradiol	2 mg PO q4h for 24h; then 2 mg/day	As above
Low-dose combined oral contraceptives	1 tablet QID for 4 days; then 1 tablet TID for 3 days; then 1 tablet BID for 2 days; then 1 tablet/day for 2 weeks	As above
Ovulatory Dysfunctional Uterine Bleeding		
NSAIDs:		Begin before or at onset of menses
Mefenamic acid	250–500 mg; then 250 mg q6–8h PRN heavy menstrual bleeding	
Naproxen	250–550 mg; then 250 mg q6–8h PRN heavy menstrual bleeding	
Ibuprofen	200–800 mg; then 200–400 mg q6–8h PRN heavy menstrual bleeding	
Antifibrinolytics	500–1000 mg q6–8h PRN heavy menstrual bleeding	
Tranexamic acid		
Anovulatory Dysfunctional Uterine Bleeding		
Combined oral contraceptives	20–35 mcg/day PO ethinyl estradiol plus progestin	Monophasic or triphasic
Progestins		
Medroxyprogesterone	5–10 mg/day PO for 10–14 days initially; repeated for 5–10 days/month thereafter	
Norethindrone acetate	2.5–10 mg/day PO for 5–10 days/month	
Micronized progesterone	200 mg/day for 12 days/month	
Levonorgestrel IUS	Releases 20 mcg/day	Implanted; effective for 5 years

BID = two times/day; IM = intramuscular; IUS = intrauterine system; IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug; PO = by mouth; PR = per rectum; PRN = as needed; QID = four times/day; TID = three times/day.

of any therapeutic regimen. In many instances, the principal symptom of abnormal uterine bleeding is fatigue, in which case iron may be the only treatment necessary.

Severe Acute Bleeding

Initial management of severe acute bleeding is based on the patient's hemodynamic stability. In patients who have orthostatic hypotension, a hemoglobin concentration less than 10 g/dL, or profuse bleeding, high-dose conjugated equine estrogen should be given orally or intravenously depending on bleeding severity. Promethazine can be administered as needed for nausea associated with estrogen administration. Bleeding should stop within 24 hours; if it has not stopped after 48 hours, surgical management should be considered.

Once bleeding has stopped, patients should be changed to an oral estrogen regimen to be continued for 21 days. Many regimens have been used and are all equally effective (see Table 1-1). In addition, except for a COC, the estrogen regimens should include a progestin to induce a normal withdrawal bleed. Most commonly, medroxyprogesterone 5–10 mg/day is added to the last 5–10 days of estrogen therapy. Withdrawal bleeding typically occurs within 3–7 days after progestin discontinuation and may be heavy but will stop after a few days. On day 5 of withdrawal bleeding, patients should start normal dosing of a low-dose monophasic COC cyclically for 3–6 months to suppress endometrial development, reestablish predictable bleeding patterns, decrease menstrual flow, and lower the risk of iron deficiency anemia.

Ovulatory Dysfunctional Uterine Bleeding

Menorrhagia associated with ovulatory cycles can be treated with or without hormones. Anti-inflammatory drugs such as mefenamic acid and naproxen have been most extensively studied and are equally effective at reducing bleeding (see Table 1-1). When started on day 1 of the menstrual cycle and continued for 5 days or until bleeding stops, they reduce bleeding by 22% to 46%. Antifibrinolytics such as tranexamic acid reduce elevated concentrations of plasminogen activators and reduce bleeding by 35% to 60%. In the past, concern was raised regarding an increased risk of thrombosis; however, a systematic review showed that thrombosis rates were similar to placebo or other therapies. In addition, hormonal therapies used in the treatment of anovulatory dysfunctional uterine bleeding can be used.

Anovulatory Dysfunctional Uterine Bleeding

Anovulatory menorrhagia may require endometrial protection with a COC, a levonorgestrel intrauterine system, or cyclic oral progestins. Combined oral contraceptives can provide both cycle regulation and contraception. In patients with irregular cycles secondary to chronic anovulation, COCs help prevent the risks associated with prolonged, unopposed estrogen stimulation of the endometrium. A small study comparing COCs, mefenamic acid, naproxen, and danazol showed no significant difference in their effectiveness in treating abnormal uterine bleeding.

Despite reducing menstrual blood loss by up to 80%, adverse effects and cost limit the use of androgens such as danazol and GnRH agonists in the treatment of abnormal uterine bleeding. However, these agents may be used for short-term endometrial thinning before ablation is performed. Treatment with cyclic progestins for 5–12 days each month is preferred when COC use is contraindicated, such as in smokers older than 35 and other women at risk of thromboembolism.

Another treatment option is the levonorgestrel intrauterine system, which remains effective for 5 years, reduces menstrual blood loss by 74% to 97%, and leads to amenorrhea in many women within 12 months. Its use has resulted in similar quality-of-life scores, lower costs than hysterectomy, and efficacy superior to cyclic progestins. The levonorgestrel intrauterine system may be the best option for women who cannot take or tolerate estrogen therapy. No trials have investigated the effectiveness of the etonogestrel subdermal implant for abnormal uterine bleeding. It is known to cause unpredictable bleeding patterns ranging from amenorrhea to frequent and prolonged bleeding and therefore is not routinely recommended as a treatment for abnormal uterine bleeding.

Surgery

When medical therapy for anovulatory dysfunctional uterine bleeding is ineffective or contraindicated, surgical intervention may be required. Hysterectomy is the treatment of choice when adenocarcinoma is diagnosed. In addition, it should be considered when biopsy specimens contain atypia, and it is the only definitive treatment of abnormal uterine bleeding. Women desiring less invasive uterus-sparing surgical procedures for the treatment of abnormal uterine bleeding may be candidates for myomectomy, transcervical endometrial resection, endometrial ablation, and uterine artery embolization.

Polycystic Ovary Syndrome

Affecting 5% to 10% of women of reproductive age, PCOS is the most common cause of infertility. The heterogeneity of its presentation has precluded a universally accepted definition of PCOS. Diagnostic criteria established by the National Institutes of Health in 1990 define PCOS as hyperandrogenism and chronic anovulation in cases where secondary causes such as adult-onset congenital adrenal hyperplasia, hyperprolactinemia, and androgen-secreting neoplasms have been excluded. The 2003 Rotterdam criteria encompass a broader scope of inclusion and require the presence of at least two of the following: chronic anovulation, clinical or biochemical signs of androgen excess, and polycystic ovaries in the

absence of other metabolic disorders that could cause these abnormalities.

The onset of PCOS most often occurs during adolescence, with primary symptoms of acne, hirsutism, or irregular menses. If onset of PCOS is at a later age, the first symptom may be infertility. In addition to the physical, psychological, social, and economic consequences, studies show PCOS increases the risk of cardiovascular disease; type 2 diabetes mellitus; dyslipidemia; hypertension; and endometrial, breast, and ovarian cancers. Prevention and risk reduction for each of these long-term health problems must be part of the overall management plan.

Pathophysiology

No gene mutation or specific trigger has been identified as the cause of PCOS, and much of the pathophysiology is not fully understood. Hypotheses for possible causes of PCOS include the following: (1) an enzyme defect in ovarian and adrenal steroidogenesis, (2) dysfunction of GnRH and LH, and (3) metabolic dysfunction characterized by insulin resistance and compensatory hyperinsulinemia.

The expression and activity of steroidogenic enzymes is increased in thecal cells (epithelioid cells of the corpus luteum), resulting in high circulating testosterone concentrations. High androgen concentrations, in turn, lead to abnormal gonadotropin release by desensitizing the hypothalamus to negative feedback by progesterone. Gonadotropin abnormalities are characterized by excessive LH and normal FSH secretion, resulting in an abnormal circulating LH/FSH ratio. Peripheral insulin resistance with compensatory hyperinsulinemia

Table 1-2. Assessment of the Woman with Suspected PCOS

Evaluation Component	Specific Parameters to Be Evaluated
Medical/family history	Family history of oligomenorrhea, amenorrhea, hirsutism, or infertility
	Family history of diabetes mellitus, obesity, or cardiovascular disease
	History of menstrual irregularities: onset and duration of last menstrual period
	Onset of hirsutism: sudden or gradual onset
	Medication history: drugs that cause hirsutism (e.g., antiepileptics, exogenous androgens, corticosteroids)
	General health: diet, exercise, smoking, and alcohol use
Physical examination	Vital signs
	Height, weight, body mass index, and waist-to-hip ratio
	Signs of hyperandrogenism and insulin resistance: • Decreased breast size • Alopecia (balding) or presence of hair around the temples • Hair in places not commonly found on women (e.g., upper lip, chin, chest, back, abdomen, upper arms, thighs) • Presence and severity of acne • Acanthosis nigricans • Clitoromegaly and/or ovarian enlargement on pelvic examination
	Signs of metabolic syndrome: obesity or hypertension
Laboratory tests	Fasting glucose and insulin concentrations
	Glucose tolerance test: the ACOG recommends that all women with suspected PCOS be tested for type 2 DM and glucose intolerance with fasting and 2-hour blood glucose tests after a 75-g glucose load
	LH and FSH concentrations: LH/FSH ratio > 2 indicates premature ovarian failure
	Androgen concentrations: • Total and free testosterone concentrations • Dehydroepiandrosterone sulfate concentration • Sex hormone–binding globulin: typically suppressed in PCOS; if elevated, evaluate for tumor
	Prolactin concentration (to evaluate for pituitary tumors and Cushing syndrome)
	Thyroid-stimulating hormone (typically normal in women with PCOS)
	Fasting lipid profile: total cholesterol, LDL-C, HDL-C, and triglycerides
Diagnostic procedures	Pelvic ultrasonography (preferably transvaginal) to evaluate for polycystic ovaries
	Endometrial biopsy to evaluate for endometrial hyperplasia and cancer

ACOG = American Congress of Obstetricians and Gynecologists; DM = diabetes mellitus; FSH = follicle-stimulating hormone; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LH = luteinizing hormone; PCOS = polycystic ovary syndrome.

is similar to the decrease in insulin-mediated glucose uptake observed in women with type 2 diabetes mellitus. Hyperinsulinemia leads to decreased sex hormone–binding globulin concentrations and increased androgen production in the adrenal gland and ovaries. Insulin may also act on the hypothalamus and pituitary to abnormally stimulate appetite and gonadotropin secretion.

Although the cause of PCOS is unknown, data indicate that a primary defect in insulin activity is central to the etiology. Risk factors for PCOS include a family history of PCOS, diabetes mellitus, insulin resistance, irregular menses or anovulation, or cardiovascular disease. About 45% of siblings of women with PCOS have hyperandrogenism, which is associated with a 3-fold increase in the risk of PCOS. Premature pubarche is an indication of hyperandrogenism, and these patients should be assessed for hyperinsulinemia, which may intensify after the beginning of puberty and increase the risk of developing PCOS. Certain ethnic groups (e.g., Native Americans, Hispanics, Greeks, Australians of Aboriginal heritage) have a higher prevalence of PCOS than white or African American women.

Clinical Findings

Common clinical features of PCOS include symptoms of androgen excess and chronic anovulation. In addition, obesity, insulin resistance, dyslipidemia, and metabolic syndrome may be present. Menstrual cycle disturbances caused by chronic anovulation range from oligomenorrhea to amenorrhea and, ultimately, infertility. Women with PCOS often have ovaries of increased size with many fluid-filled sacs of underdeveloped follicles (cysts). A diagnosis of polycystic ovaries requires the presence of 12 or more follicles measuring 2–9 mm in diameter or increased ovarian volume (more than 10 mL) during the follicular phase.

Diagnosis

The diagnosis of PCOS is generally one of exclusion; recommended diagnostic procedures are listed in Table 1-2. Initially, an in-depth medical history and physical examination should be completed because signs and symptoms of hyperandrogenism and insulin resistance can help identify women with PCOS; There is no single test that determines the diagnosis of PCOS: laboratory evaluation is used to exclude other underlying conditions and to create a biochemical profile to aid in the diagnosis of PCOS. Ultrasonography cannot result in a definitive diagnosis because polycystic ovaries can be associated with other conditions.

Treatment

Treatment goals for PCOS include ovulation induction and restoration of reproductive function for women who desire pregnancy, normalization of the endometrium, suppression of hyperandrogenism and associated symptoms, reduction in insulin resistance, and prevention of long-term risks. Pharmacologic agents used to manage symptoms are listed in Table 1-3.

Nonpharmacologic Treatment

Patient and family education regarding PCOS and lifestyle changes is important in PCOS treatment. Lifestyle modifications include a reduced-fat, high-fiber, and low glycemic index diet; and regular aerobic exercise (walking for 20 minutes four times/week) to achieve weight loss and reduce insulin resistance. A loss of even 7% of body weight can increase sex hormone–binding globulin concentrations, reduce testosterone and androgen

Table 1-3. Pharmacologic Management of PCOS

Drug	Dosage	Targeted Symptoms
Combined oral contraceptives	1 active tablet/day PO	Menstrual cycle irregularity, hirsutism, acne
Antiandrogens		
Spironolactone	25–100 mg PO BID	Hirsutism, acne
Flutamide	250 mg/day PO	
Finasteride	2.5–5 mg/day PO	
Insulin-sensitizing agents		
Metformin	500–1000 mg PO BID	Hirsutism, acne, menstrual cycle irregularity, anovulation, insulin resistance, infertility
Pioglitazone	45 mg/day PO	
Rosiglitazone	4 mg/day PO	
Antiestrogen		
Clomiphene	50–100 mg/day PO for 5 days at beginning of menstrual cycle	Hirsutism, acne, menstrual cycle irregularity, anovulation, insulin resistance, infertility

BID = two times/day; PCOS = polycystic ovary syndrome; PO = by mouth.

concentrations, and improve menstrual function and conception rates. Nonpharmacologic options for the treatment of hirsutism include bleaching, plucking, shaving, electrolysis, and laser therapy.

Pharmacologic Treatment

Combined Oral Contraceptives

Combined oral contraceptives are considered first-line therapy for the long-term management of PCOS, but responses to COCs vary. The estrogenic component of COCs suppresses pituitary LH secretion and increases circulating sex hormone–binding globulin concentrations, leading to restored menstrual cycle regularity and suppression of ovarian androgen production and associated symptoms (particularly hirsutism and acne). In addition, COCs help protect the endometrium from unopposed estrogen stimulation.

Even though COCs are widely used and their efficacy is well established, no oral contraceptive has FDA-approved labeling specifically for hirsutism treatment. Although all COCs lessen acne severity to some extent, the combinations norgestimate/ethinyl estradiol, ethinyl estradiol/norethindrone acetate, and ethinyl estradiol/drospirenone have FDA-approved labeling for this indication. Because most progestins possess variable androgenic effects, COCs containing nonandrogenic progestins (e.g., norgestimate, desogestrel, drospirenone) may be preferred. Further studies are needed to determine whether certain oral contraceptives are better than others for women with PCOS. The potential for adverse effects on insulin resistance, glucose tolerance, and coagulopathy are of particular concern with the use of COCs in women with PCOS.

Antiandrogens

When given at high dosages, spironolactone blocks androgenic effects at the follicle. It is the most widely used antiandrogenic agent in the United States and is highly effective for the treatment of hirsutism, producing a 40% to 80% reduction in hair growth. However, spironolactone does not have FDA-approved labeling for this indication.

The activities of spironolactone and COCs for the treatment of hirsutism and acne appear to be synergistic. If used in combination with a drospirenone-containing COC, serum potassium concentrations should be monitored routinely. Flutamide is also effective for the treatment of hirsutism and acne by reducing circulating androgen concentrations, reducing overall ovarian size, and restoring menstrual cycles. Its efficacy for the treatment of hirsutism and acne is similar to that of spironolactone, but the high risk of hepatotoxicity limits its use.

Cyproterone, a progestin that competitively inhibits the binding of testosterone to the androgen receptor, is effective for the treatment of hirsutism and is often combined with COCs to enhance its effect and prevent uterine bleeding. Cyproterone may be teratogenic and cause hepatotoxicity, and it is not currently available in the United States. Finasteride inhibits 5-alpha-reductase, the enzyme responsible for the conversion of testosterone to its active metabolite in the hair follicle. Finasteride can also be used to treat hirsutism and acne.

Ketoconazole, an antifungal agent, inhibits androgen biosynthesis in a dose-dependent manner; however, because of the risk of hepatotoxicity, it is considered an alternative only if a patient cannot tolerate other drugs. Antiandrogens may be teratogenic; so they must be prescribed in conjunction with COCs in women who may become pregnant. In addition, COCs can prevent irregular bleeding, which is often an adverse effect of antiandrogens.

Insulin-Sensitizing Agents

Insulin-sensitizing agents are effective in improving the underlying metabolic dysfunction associated with insulin resistance by increasing insulin sensitivity, inhibiting gluconeogenesis, and reducing androgen synthesis. An increase in ovulation, resumption and normalization of the menstrual cycle, reduced waist-to-hip ratio, and decreased androgen concentrations are benefits of insulin-sensitizing agents in women with PCOS. Whether insulin-sensitizing agents reduce the risk of developing type 2 diabetes mellitus in women with PCOS has not been established. These agents act synergistically with clomiphene to regulate the menstrual cycle and ovulation, thereby improving reproductive function.

Metformin does not have FDA-approved labeling for use in PCOS; however, it has been widely studied and is considered first-line therapy for insulin resistance and glucose intolerance associated with PCOS. Metformin has less pronounced effects on hirsutism than COCs or antiandrogens and is often combined with antiandrogens and COCs for added effectiveness. It appears that women with PCOS benefit from metformin administration regardless of whether they show signs of insulin resistance. Metformin is usually initiated at low dosages and increased gradually as needed. Long-term safety and efficacy have not been shown, but metformin appears to improve cardiovascular risk factors.

Pioglitazone and rosiglitazone have not been as extensively studied as metformin but have been shown to be effective in reducing ovarian androgen production and improving ovulation. One randomized controlled clinical trial found pioglitazone to be as effective as metformin in improving insulin resistance and hypoandrogenism in women with PCOS. However, the pioglitazone-treated group reported increases in body mass index and waist-to-hip ratio and only a modest effect on hirsutism. Similar results have been seen with rosiglitazone. Studies evaluating the use of acarbose in PCOS indicate improvements in hirsutism, acne, and obesity; however, adverse effects, specifically gastrointestinal effects, limit its use.

Infertility Treatment

Women with PCOS who wish to conceive must discontinue COCs and antiandrogens. Weight loss and exercise are considered first-line therapies for overweight women with infertility. If conception is not achieved, agents that induce ovulation can be employed. The first-line agent for anovulatory infertility in women with PCOS is clomiphene. Clomiphene restores menstrual cycle regularity, prevents endometrial hyperplasia, and induces ovulation by inhibiting estrogen's action on the hypothalamus, which in turn stimulates the release of pituitary LH and FSH. With clomiphene, 80% of women will ovulate, and 50% will conceive within the first six ovulatory cycles.

If conception is not achieved after six cycles, the addition of metformin may increase ovulation rates. Metformin alone has been shown to induce ovulation in women with PCOS but with a lower rate of live births than observed with clomiphene alone. One study showed that women treated with metformin plus clomiphene had an ovulation rate of 89% versus 8% for those treated with placebo. However, the synergistic action in restoring ovulation and achieving pregnancy of the two-agent combination has been challenged by two recent studies that found no additional benefit in pregnancy or live birthrates compared with clomiphene alone.

Limited evidence supports the use of tamoxifen, acarbose, or the aromatase inhibitor letrozole to improve ovulation rates in women with PCOS; these agents can be considered in cases of clomiphene-resistant PCOS. Laparoscopic electrocautery of the ovaries is effective for ovulation induction and is indicated for patients who are treatment resistant or who cannot tolerate the adverse effects of ovulation-inducing drugs.

Miscellaneous Agents

Medroxyprogesterone (10 mg/day) given orally for 7–10 days can be used every 1–3 months to induce menses, normalize endometrial growth, reduce endometrial hyperplasia, and restore menstrual cycle regularity in women with PCOS. Medroxyprogesterone does not affect androgen concentrations.

Topical use of eflornithine for hirsutism slows hair growth by inhibiting ornithine decarboxylase, the enzyme in the hair follicle that stimulates hair growth, but eflornithine does not remove hair. Eflornithine is well tolerated and has proven efficacy for treatment of unwanted facial hair in women after 6 months of continued use, but it has not been studied in women with PCOS.

In women with PCOS whose adrenal testosterone and dehydroepiandrosterone production is not adequately suppressed by COCs or spironolactone, low doses of glucocorticosteroids (e.g., prednisone, dexamethasone) can be used to suppress corticotropin and subsequent adrenal androgen production. These agents may help in the establishment of ovulatory cycles; however, prolonged use is not advised because of the long-term risks of glucose intolerance, insulin resistance, osteopenia, and weight gain.

The GnRH analogs can be used for severe ovarian hyperandrogenism because they cause almost complete suppression of ovarian function. As discussed in the section on endometriosis, the adverse effect profile of GnRH agonists limits their use.

Role of the Pharmacist

Many women see their pharmacist more often than any other heath care professional, allowing pharmacists to play an important role in optimizing drug therapy in menstrual-related disorders. By recognizing symptoms associated with abnormal uterine bleeding, PMS, PMDD, or PCOS, the pharmacist can facilitate early diagnosis and encourage risk prevention. By recognizing the benefits of various therapeutic strategies, such as SSRIs for PMDD, or identifying the nontraditional use of agents, such as metformin and thiazolidinediones in PCOS, the pharmacist can focus counseling on appropriate drug use and improve patient adherence.

As with all prescriptions, pharmacists should screen the patient's medication profile for potential drug interactions and provide patients with information regarding proper administration, potential adverse effects, and expected outcomes. Pharmacists who provide patient care services such as blood pressure monitoring, cholesterol screening, diabetes screening, or weight management can help monitor women for the development of metabolic syndrome, cardiovascular risk factors, and other long-term consequences associated with menstrual-related disorders and their treatment.

Annotated Bibliography

1. Braverman PK. Premenstrual syndrome and premenstrual dysphoric disorder. J Pediatr Adolesc Gynecol 2007;20:3–12.

   This review article describes the definitions of PMS and PMDD as well as the diagnostic criteria set by ACOG and the American Psychiatric Association. The importance of prospectively reporting symptoms is discussed, and several examples of assessment tools are provided. Risk factors, pathophysiology, and clinical manifestations are also reviewed. The article provides a comprehensive overview of many nonpharmacologic management options including lifestyle changes, education, stress management, cognitive behavior therapy, dietary modifications, and exercise. The article also extensively reviews pharmacologic options including minerals, vitamins, and herbal preparations; medications to suppress ovulation; medications to suppress somatic symptoms; antidepressants; and anxiolytics. The review concludes with a step-wise approach to the treatment of PMS/PMDD based on specific symptom presentation and severity.

2. Munro MG. Medical management of abnormal uterine bleeding. Obstet Gynecol Clin North Am 2000;27:287–304.

This article, written by a leading expert in gynecology, discusses the medical management of abnormal and dysfunctional uterine bleeding and includes a variety of treatment options. By providing an understanding of the biology of menstruation and the pathogenesis of mechanisms involved in uterine bleeding, the author provides the rationale for appropriate application of treatment. More specifically, the author describes the distinguishing features of abnormal bleeding that are associated with ovulation compared with bleeding that is anovulatory. This article clearly defines mild, moderate, and severe disorders and makes treatment recommendations based on the specific type and cause of the abnormal bleeding. The author notes that there is a role for surgery in some patients; however, medical management has great potential for most women with abnormal and dysfunctional uterine bleeding.

3. ACOG Practice Bulletin. Management of anovulatory bleeding. No. 14; March 2000. Int J Gynecol Obstet 2001;72:263–71.

This practice bulletin was developed by the ACOG Committee on Practice Bulletins to provide management guidelines for the treatment of patients with menstrual irregularities associated with anovulation, a form of dysfunctional uterine bleeding. General information on the nomenclature and underling pathophysiology of anovulatory bleeding is provided. The diagnosis of anovulatory bleeding is one of exclusion, and the authors suggest several medical problems to be excluded before the diagnosis can be established, as well as recommend specific laboratory assessments on the basis of patient characteristics. Clinical considerations based on patient age and fertility status, the rationale for various treatment modalities, and pharmacotherapeutic and surgical options are included. Specific evidence-based treatment recommendations are referenced. A limitation to the information is that this bulletin has not been updated since 2000.

4. ACOG Practice Bulletin. Polycystic ovary syndrome. No. 108; October 2009. Obstet Gynecol 2009;114:936–49.

Designed to aid practitioners in making decisions regarding the appropriate care of patients with PCOS, this ACOG Practice Bulletin provides general information on the etiology, clinical manifestations, differential diagnosis, and diagnostic criteria for PCOS. Clinical considerations and recommendations for the treatment of PCOS and its associated infertility are presented. This document emphasizes that PCOS is a heterogeneous syndrome with an unknown etiology. There is no single diagnostic test for PCOS, and treatment should focus on the metabolic sequelae. Recommendations are referenced and based on levels of scientific evidence. A strength of this bulletin is that these are the most up-to-date published guidelines for the diagnosis and clinical management of PCOS.

5. University of Texas, School of Nursing, Family Nurse Practitioner Program. Diagnosis and management of polycystic ovarian syndrome. Austin: University of Texas, School of Nursing, May 2006. Available at *www.guideline.gov/summary/summary.aspx?doc_id=9438&nbr=005059&string=PCOS*. Accessed June 3, 2010.

Developed by the Family Nurse Practioner Program at the University of Texas School of Nursing, these guidelines for the management of PCOS provide recommendations on objective symptom assessment, diagnostic procedures, laboratory evaluations, criteria for diagnosis, differential diagnoses, nonpharmacologic and pharmacologic treatment, surgical procedures, and follow-up procedures. In addition, these guidelines provide information regarding patient resources and support groups for women with PCOS. Information is provided in an outline format, is referenced, and is evaluated for quality of evidence and strength of recommendation. Definitions for quality of evidence and strength of recommendation are provided. Methods used to collect, select, and analyze evidence used in the development of these guidelines are described.

6. Norman RJ, Dewailly D, Legro RS, Hickey TE. Polycystic ovary syndrome. Lancet 2007;370:685–97.

This review article provides comprehensive, up-to-date information on the classification, epidemiology, clinical features, diagnosis, risk factors, causes, and management of PCOS. The article clearly defines the role of hyperandrogenism, chronic anovulation, and gonadotropin and insulin abnormalities in the pathogenesis of PCOS. Primary literature is discussed and evaluated. Furthermore, there is a discussion regarding the health implications of PCOS and issues for family members. The authors note that future priorities for PCOS research include the development of evidence-based criteria for diagnosis, the updating of evidence-based criteria for treatment, and the determination of the causes and prevention of long-term consequences associated with PCOS.

7. The Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Consensus on infertility treatment related to polycystic ovary syndrome. Hum Reprod 2008;23:462–77.

This article addresses the therapeutic challenges of infertility treatment in women with PCOS. This international workshop, endorsed by the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine, evaluated the safety and efficacy of treatment of women with PCOS presenting with infertility on the basis of current available evidence. Studies involving lifestyle modifications such as diet and exercise are discussed. Study data are provided on patient populations, doses, monitoring parameters, efficacy, treatment duration, and adverse effects of drug therapy, including clomiphene, insulin-sensitizing agents, gonadotropin and GnRH analogs, and combination

therapies. In addition, this article reviews the efficacy and safety of procedures such as laparoscopic ovarian surgery and assisted reproductive techniques. Summary points are provided for each nonpharmacologic and pharmacologic treatment approach evaluated. Overall conclusions reached by the PCOS Consensus Workshop Group provide evidence-based recommendations.

8. Jarvis CI, Lynch AM, Morin AK. Management strategies for premenstrual syndrome/premenstrual dysphoric disorder. Ann Pharmacother 2008;42:967–78.

   This comprehensive review article written by clinical pharmacy faculty members evaluates the current nonpharmacologic and pharmacologic treatment options for the symptoms of PMS and PMDD. A discussion of the clinical presentation and diagnostic criteria of both PMS and PMDD provides practitioners with information on how to distinguish between the two disorders. A comprehensive and detailed review is provided of the evidence for many treatment options, from lifestyle modification and vitamin supplementation to antidepressants and hormonal agents. For each treatment option, its place in therapy and rating of available evidence is provided. This article represents the most comprehensive review of PMS and PMDD treatment options published to date.

9. Singh RH, Blumenthal P. Hormonal management of abnormal uterine bleeding. Clin Obstet Gynecol 2005;48:337–52.

   This review article aims to guide the selection and use of the hormonal treatment options to treat abnormal uterine bleeding. The article highlights that medical management of abnormal uterine bleeding is supported by strong evidence and may delay or prevent the need for surgical management. A comprehensive review of the literature related to hormonal modalities (e.g., oral and intrauterine progestins, estrogens, COCs, danazol, GnRH analogs) is provided for both ovulatory and anovulatory bleeding. Where available, data comparing these hormonal options with each other, nonhormonal options, ablation procedures, and surgery are provided. In addition, key recommendations are provided for each option, explaining its role in the treatment of abnormal uterine bleeding.

10. Telner DE, Jakubovicz D. Approach to diagnosis and management of abnormal uterine bleeding. Can Fam Physician 2007;53:58–64.

    This evidence-based review article provides an in-depth yet easy-to-understand overview of the evaluation and treatment of abnormal uterine bleeding in a primary care setting. Using a case-based format, the review provides a clear description of several key areas, including how to differentiate the types of abnormal uterine bleeding, drugs that can cause abnormal uterine bleeding, suggested diagnostic investigation based on clinical suspicion, and treatment options. Suggestions for when women with abnormal uterine bleeding should be referred for specialist evaluation are provided. A summary of the evidence for anti-inflammatory and antifibrinolytic agents, COCs, progestins, GnRH agonists, androgens, and surgery is provided. In addition, the therapeutic approaches for both pre- and postmenopausal women are outlined, allowing patient-specific application.

Self-Assessment Questions

Questions 1 and 2 pertain to the following case.
O.K., a 32-year-old woman, presents to her primary care provider with the complaints of feeling tired, depressed, and anxious. On questioning, she states that she feels this way only during the 2 weeks before the onset of menses. She also experiences chocolate cravings, mood swings, weight gain, bloating, breast tenderness, backaches, headaches, insomnia, and an inability to concentrate on her work during this time. O.K. becomes extremely irritable and feels that she cannot control her anger toward others, including her family and co-workers. She states that after the onset of her menses she feels "back to normal." She has a medical history of postpartum depression after the birth of her second child. She smokes one pack of cigarettes daily, drinks alcohol socially, and consumes 2–3 cups of coffee each day. She has no known drug allergies and takes no drug therapy. After careful assessment, O.K.'s physician gives her a diagnosis of premenstrual dysphoric disorder (PMDD).

1. **Which one of the following presenting characteristics best supports the diagnosis of PMDD in O.K.?**

   A. Weight gain and bloating during the luteal phse.
   B. Mood-related symptoms present only during the luteal phase.
   C. Symptoms that remit after the onset of menses.
   D. History of cigarette smoking.

2. **Which one of the following treatment options would be most appropriate for O.K.'s premenstrual symptoms?**

   A. Ethinyl estradiol 0.02 mg/levonorgestrel 0.1 mg/day orally.
   B. Naproxen 250 mg every 6–8 hours orally.
   C. Citalopram 20 mg daily orally.
   D. Buproprion 150 mg twice daily orally.

Questions 3–7 pertain to the following case.
A.J., a 16-year-old girl, is brought to the medical center after fainting in math class. She experienced menarche at age 13, and since then her periods have been irregular. Recently, her cycles have been associated with heavy flow (soaking 8–10 pads/day) every 3–4 weeks. She has never been sexually active. On questioning, A.J. says she twice felt she was going to "pass out" during a recent soccer practice. Currently, she is having a heavy menstrual period that began 3 days ago. Her hemoglobin concentration is 7.5 g/dL, and a pregnancy test is negative.

3. **Which one of the following diagnostic tests is most appropriate in evaluating A.J.'s abnormal uterine bleeding?**

   A. Prolactin concentration.
   B. Partial thromboplastin time.
   C. Endometrial biopsy.
   D. Blood glucose concentration.

4. **Which one of the following terms best describes A.J.'s bleeding pattern?**

   A. Polymenorrhea.
   B. Oligomenorrhea.
   C. Menometrorrhagia.
   D. Menorrhagia.

5. **Which one of the following is the best initial therapy for A.J.'s abnormal uterine bleeding?**

   A. Oral progestin for 5–10 days.
   B. Intravenous estrogen for 12–24 hours.
   C. Typical daily dosing of a combined oral contraceptive (COC).
   D. Levonorgestrel intrauterine system.

6. After an in-depth assessment, A.J. is given a diagnosis of dysfunctional anovulatory bleeding without any underlying structural uterine abnormality. **Which one of the following treatment options is best to prevent A.J. from having further heavy bleeding?**

   A. Medroxyprogesterone 5 mg/day orally for 5 days/month.
   B. Ethinyl estradiol plus progestin-containing COC orally daily.
   C. Mefenamic acid 250 mg orally every 6 hours as needed for heavy bleeding.
   D. Tranexamic acid 500 mg orally every 6 hours as needed for heavy bleeding.

7. W**hich one of the following adjunctive therapies is most appropriate to add to A.J.'s treatment regimen?**

   A. Ferrous sulfate.
   B. Ferrous sulfate plus danazol.
   C. Ferrous sulfate plus histrelin.
   D. Etonogestrel implant.

Questions 8 and 9 pertain to the following case.
N.M. is a 36-year-old woman with a diagnosis of PMDD characterized by severe mood-related symptoms. She has a history of migraines, diet-controlled diabetes, and hypertension. Her current drugs include sumatriptan and

hydrochlorothiazide. N.M. smokes one pack of cigarettes daily and consumes 5–6 cups of coffee daily.

8. **Which one of the following drug regimens is best for the initial management of N.M.'s symptoms?**

   A. Bupropion 150 mg orally two times/day continuously throughout the menstrual cycle.
   B. Paroxetine 20 mg/day orally dosed intermittently during the luteal phase.
   C. Citalopram 20 mg/day orally dosed continuously throughout the menstrual cycle.
   D. Fluoxetine 60 mg/day orally dosed intermittently during the luteal phase.

9. After four menstrual cycles with her initial drug regimen, N.M.'s symptoms have improved, but depressed mood is still affecting her relationships at work and home. **Which one of the following is the best approach to her therapy?**

   A. Mestranol 0.05 mcg/norethindrone 1 mg daily.
   B. Ethinyl estradiol 0.03 mg/drospirenone 3 mg daily.
   C. Danazol 100 mg/day.
   D. Levonorgestrel intrauterine device.

10. Your patient is a 33-year-old woman with a history of severe mood-related symptoms of PMDD unresponsive to several treatment modalities, including two different antidepressants and COCs. The medical care team is considering future treatment options to better control her symptoms. **Which one of the following treatment options is most appropriate for the treatment of this patient's PMDD?**

    A. Alprazolam 0.5 mg orally three times/day.
    B. Estradiol 100 mcg/24 hours transdermally weekly.
    C. Goserelin 3.6 mg/month subcutaneously.
    D. Medroxyprogesterone acetate 150 mg intramuscularly every 3 months.

11. Your patient is a 21-year-old college student who complains of bloating, headaches, and breast tenderness for a few days before her menses each month. She states that these symptoms usually keep her from going to class and work at least 1 day each month. She says ibuprofen helps with the headaches but not the other symptoms. **Which one of the following treatment options is best for the management of this patient's symptoms?**

    A. Lorazepam.
    B. Ethinyl estradiol 0.02 mg/levonorgestrel 0.1 mg daily.
    C. Sertraline.
    D. Spironolactone.

12. A 24-year-old woman with a medical history significant for depression and alcohol abuse presents to her physician for her annual physical examination. Her body mass index (BMI) is 30.2 kg/m^2, and she exhibits signs and symptoms of hirsutism and glucose intolerance. After a series of tests, the patient is given a diagnosis of polycystic ovary syndrome (PCOS), and her physician wants to begin pharmacotherapy. Her laboratory values are as follows: sodium, 140 mEq/L; potassium, 3.8 mEq/L; chloride, 122 mEq/L; blood urea nitrogen, 17 mg/dL; creatinine, 1.5 mg/dL; aspartate aminotransferase, 15 international units/L; alanine aminotransferase, 23 international units/L; alkaline phosphatase, 51 international units/L; white blood cells, 5×10^3 cells/mm^3; and platelets, 250,000/mm^3. **Which one of the following is the best treatment of this patient's PCOS symptoms?**

    A. Acarbose and a COC.
    B. Pioglitazone and a COC.
    C. Metformin and spironolactone.
    D. Clomiphene and spironolactone.

Questions 13–16 pertain to the following case.
J.D. is a 16-year-old girl who presents to her primary care physician's office for an annual physical examination. The physician notes oily skin, acne, and excessive facial hair growth. J.D.'s BMI is 24.8 kg/m^2, and her menstrual cycles occur at regular 28-day to 30-day intervals. She requests treatment of her acne and facial hair but does not want to use an oral contraceptive because she does not think her mother will approve.

13. **Which one of the following is the best choice for J.D.'s treatment?**

    A. Flutamide 250 mg/day orally.
    B. Eflornithine topically applied as directed.
    C. Spironolactone 25 mg orally two times/day.
    D. Clomiphene 50 mg/day orally for 5 days at the beginning of each menstrual cycle.

14. **In addition to her presenting symptoms, which one of the following, if present in J.D., would be most likely to lead to a diagnosis of PCOS, according to the 2003 Rotterdam criteria?**

    A. Infertility.
    B. Weight gain.
    C. Chronic anovulation.
    D. Glucose intolerance.

15. Two years later, J.D. is 18 and returns to see her physician. In addition to her previous symptoms, she now has light brown patches of skin on her neck and

under her arms. Her BMI is 25.5 kg/m^2, her blood pressure is 135/98 mm Hg, and her menstrual cycles are irregular. She has experienced menses only four times in the past 12 months. **Based on these new symptoms, which one of the following drugs is most appropriate to treat J.D.?**

A. A COC.
B. Danazol.
C. Clomiphene.
D. Metformin.

16. Six months later, J.D. returns to her physician for a follow-up visit. Despite additional drug therapy, her menstrual cycle continues to be irregular. **Which one of the following is the best choice to restore menstrual cycle regularity in J.D.?**

A. Dexamethasone.
B. Goserelin.
C. Medroxyprogesterone.
D. Finasteride.

Questions 17 and 18 pertain to the following case.
K.W., a 27-year-old woman diagnosed 6 years ago with PCOS, presents to the fertility clinic. She stopped taking a COC 3 months ago but has not been able to conceive. K.W. currently takes metformin, and her PCOS symptoms appear to be well controlled. On physical examination, her blood pressure is 118/76 mm Hg, pulse rate is 88 beats/minute, and BMI is 30.8 kg/m^2. Her fasting lipid profile is within normal limits. Her menstrual cycle occurs at regular monthly intervals.

17. **Which one of the following is the most appropriate first-line approach to help improve fertility in K.W.?**

A. Encourage weight loss and exercise.
B. Undergo laparoscopic electrocautery of the ovaries.
C. Start medroxyprogesterone 10 mg/day orally.
D. Start clomiphene 50 mg orally two times/day.

18. Six months later, K.W. returns to the fertility clinic. There is no change in her physical examination parameters, but she states that her menstrual cycle is no longer regular. She has had two menstrual cycles in the past 4 months. **Which one of the following is the most appropriate recommendation to help improve fertility in K.W.?**

A. Continue metformin; start spironolactone.
B. Continue metformin; start clomiphene.
C. Discontinue metformin; start rosiglitazone.
D. Discontinue metformin; start acarbose.

Questions 19 and 20 pertain to the following case.
L.L. is a 29-year-old woman who presents to her physician's office for her annual physical examination. She was given a diagnosis of PCOS 10 years ago, and her symptoms have been well controlled with diet and exercise. L.L. has two daughters, ages 3 years and 8 months, and does not wish to have any more children. At this visit, the physician notes an increase in L.L.'s facial and chest hair. Her BMI is 23.5 kg/m^2, and all laboratory values are within normal limits.

19. **Which one of the following is most appropriate to recommend for the treatment of L.L.'s hirsutism?**

A. Spironolactone.
B. Flutamide.
C. Cyproterone.
D. A COC.

20. The pharmacist plans to counsel L.L. about taking metformin. **Which one of the following benefits to her health is she most likely to experience?**

A. Improved glucose tolerance, decreased risk of developing type 2 diabetes mellitus, and normalization of her menstrual cycle.
B. Decreased waist-to-hip ratio, decreased risk of developing endometrial cancer, and decrease in androgen concentrations.
C. Decreased risk of developing type 2 diabetes mellitus, decreased risk of developing endometrial cancer, and decreased need for contraception.
D. Normalization of her menstrual cycle, improved glucose tolerance, and decreased waist-to-hip ratio.