Vaginal and Uterine Bleeding

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- Complete the questions at the end of the course.
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Faculty

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Faculty Disclosure

Contributing faculty, Julie Quinn, MD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for gynecologists, primary care physicians, surgical professionals, and other primary care health providers, including physician assistants and nurses, involved in the care of women.

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Course Objective

The purpose of this course is to outline the many different causes of vaginal and uterine bleeding, describe the FIGO classification system, and discuss diagnostic techniques and treatment options for various causes of bleeding, allowing for improvements in the care of women who present with abnormal vaginal or uterine bleeding.

Learning Objectives

Upon completion of this course, you should be able to:

1. Describe different etiologies of vaginal bleeding in different age groups.
2. Outline treatment options for various causes of vaginal bleeding.
3. Describe the diagnosis of and FIGO classification system for abnormal uterine bleeding.
4. Evaluate the pathophysiology of various types of abnormal uterine bleeding and appropriate treatment modalities.
5. Discuss the identification and treatment of abnormal uterine bleeding in special populations.

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Vaginal bleeding is a common complaint in patients seeking care from their primary care provider, obstetrician/gynecologist, or urgent care/emergency department provider [1]. Distinguishing normal from abnormal bleeding is important in determining the best course of management, as is distinguishing the type of bleeding. Normal versus abnormal bleeding will, of course, depend on the patient's age and menstrual status (i.e., prepubertal, reproductive age, or postmenopausal).

VAGINAL BLEEDING

SOURCES BY AGE

Prepubertal

Prepubertal girls lack estrogenization of the vagina and may have poor hygiene, both of which can predispose them to vulvovaginal issues [2]. Prepubertal or pediatric cases of vaginal bleeding are most often caused by either a foreign body (usually toilet paper) or a vulvovaginal irritation or infection [3]. In some cases, the presence of a foreign body will result in a bloody, foul-smelling vaginal discharge. There may be a reactive, irritated area of vaginal mucosa even if the foreign body is no longer retained [2].

Vaginal *Streptococcus pyogenes* (group A, beta-hemolytic streptococci) can result in vaginal bleeding and may or may not be associated with a nasopharyngeal, perianal, or skin infection. Inspection of the vulva and perianal skin can show a beefy, bright red appearance [3]. *Shigella* infection can also cause a bloody vaginal discharge that is not necessarily associated with diarrhea [2]. *Candida albicans* infections are rare in prepubertal girls, given their poorly estrogenized tissues; however, it should be considered if the patient in question has recently taken antibiotics or is diabetic, immunosuppressed, or still in diapers [3].

Various dermatologic conditions can also cause bleeding from the vulva. Seborrheic dermatitis can produce bleeding fissures within the labial folds, and psoriasis, lichen sclerosus, or contact dermatitis can cause the child to rub the involved skin, which can produce bleeding [2; 3]. An irritative dermatitis can result from soaps, tight clothing, or poor hygiene. Pinworm infection is another very common cause of excoriations leading to bleeding [3].

Lesions such as condyloma or hemangioma can cause bleeding; these should be evident on physical examination. Tumors are a rare cause of pediatric vaginal bleeding, with the most common vaginal tumors in this age group being embryonal rhabdomyosarcoma (sarcoma botryoides) and adenocarcinoma of the vagina [2]. Anatomic considerations, such as vaginal polyps and urethral prolapse, should be taken into consideration if the more common causes are not discovered [3].

A thorough history should be taken from both the child and the parent, including exposure to medications or foreign bodies. A thorough pediatric gynecologic exam is indicated in certain cases. Exposure to medications, such as a caregiver's oral contraceptive pills or estrogen creams, should be investigated [3].

Of course, precocious puberty and the possibility of sexual abuse must be taken into account. Precocious puberty involving uterine bleeding will be discussed later in this course. Sexual abuse may or may not have physical findings, such as evident trauma to the introitus/hymen and vulva. Behavioral changes and somatic symptoms can indicate abuse as well [3]. An exam by a compassionate and experienced clinician is required, and vaginal cultures to rule out sexually transmitted infections (STIs) should be performed in any prepubertal girl evaluated for vulvovaginitis [2].

High-pressure water injuries (as incurred on a water slide) or straddle injuries can cause traumatic injury to the vagina or vulva [3]. If there is evidence of a penetrating injury, an exam under anesthesia may be needed to ensure that there is no involvement of bladder, bowel, or peritoneal cavity [2].

It should be noted that newborns may experience bleeding as they withdraw from maternal estrogen. This is normal and not worrisome, occurring in about 10% of newborns [2].

Reproductive Age

In reproductive-age women, trauma to the vulva (e.g., straddle injury, sexual trauma) can certainly produce vaginal or vulvar bleeding. A thorough pelvic examination is in order.

The only vulvar lesion of an STI that bleeds easily is the ulcer of granuloma inguinale (donovanosis), caused by *Klebsiella granulomatis* (previously known as *Calymmatobacterium granulomatis*). Other ulcerating STIs, such as herpes simplex and syphilis, do not often have bleeding as a primary complaint; however, any bleeding lesion must be evaluated and tested [2]. Gonorrheal infections (*Neisseria gonorrhoeae*) can produce abnormal vaginal bleeding. Bleeding is usually not seen with chlamydial infections (*Chlamydia trachomatis*), but any patient with unusual bleeding should be evaluated for cervicitis [2].

Malignant lesions are also a concern in women of childbearing age. Cervical intraepithelial neoplasia (CIN) and cervical carcinoma can present with bleeding, particularly postcoital bleeding [4]. The median age for diagnosis of cervical cancer is 50 years, and the incidence rate is nearly twice as high for women older than 50 years of age as younger women [22]. However, the prevalence of CIN is highest among women in their 20s and 30s [30].

Postmenopausal

The first concern with postmenopausal bleeding is to rule out uterine adenocarcinoma, as will be addressed later in this course. One of the most common causes of vaginal or vulvar bleeding in a postmenopausal woman is simply atrophy of the vulvovaginal tissues, resulting in bleeding with manipulation or sex. Pruritus is another common complaint in postmenopausal women whose vulvar tissues are lacking in estrogen support [2]. All women with vulvar bleeding should be evaluated for vulvar intraepithelial neoplasia, vaginal intraepithelial neoplasia, carcinoma, and benign skin lesions such as lichen sclerosus and lichen planus. A vulvar biopsy is usually necessary and is considered the gold standard to obtain a precise diagnosis [2].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the American College of Radiology, initial imaging study in both premenopausal and postmenopausal women with vaginal bleeding should be a combined transabdominal and transvaginal approach. Transabdominal ultrasound is most helpful in the case of a significantly enlarged uterus or uterine tumor, in which the limited field-of-view of transvaginal ultrasound cannot image all portions of the uterus or uterine tumor.

(https://acsearch.acr.org/docs/69458/Narrative. Last accessed August 20, 2021.)

Strength of Recommendation: 9 (Usually appropriate)

TREATMENT

Prepubertal

Treatment of any pertinent infection or dermatologic condition should resolve vaginal bleeding in prepubertal patients. Group A streptococcus is treated with penicillin VK, *Shigella* with trimethoprim/sulfamethoxazole, *Candida* with an antifungal cream, pinworm with oral mebendazole, and gonorrhea with ceftriaxone, adding azithromycin to cover for antibiotic resistant strains and chlamydia if the child is 8 years of age or older [2; 31].

Improving hygiene and avoiding irritants will resolve most cases of irritative vulvovaginitis. Lichen sclerosus is treated by removing irritants, using a soothing ointment to protect and heal affected skin, avoiding bicycle riding and other straddle sports, and short-term steroid ointment for persistent cases. Cases that resist these treatments will usually improve or resolve at puberty [2].

Any injuries requiring suturing may be repaired under anesthesia. If present, vaginal polyps should be removed. Hemangiomas usually resolve at puberty, although cavernous hemangiomas should be removed to prevent excessive bleeding [2].

Reproductive Age

Any injury to vulvar or vaginal tissues should be repaired, if appropriate, and an estrogen cream can be used topically during the healing process. Any STI or bacterial imbalance, such as bacterial vaginosis, should be treated with the appropriate antibiotics (i.e., metronidazole as first-line treatment) [31]. If bleeding persists, a biopsy should be performed to evaluate for dysplasia and to obtain a definitive diagnosis [2].

Postmenopausal

The most effective treatment for bleeding resulting from vulvovaginal atrophy is local estrogen replacement. Estrogen may be applied topically as a cream or inserted vaginally as a suppository or ring. Soothing ointments, available over the counter, may be used if the woman does not desire local hormonal treatment. Certain dermatoses, such as lichen sclerosus or lichen planus, may require treatment with a high-potency topical steroid ointment [2].

EVIDENCE-BASED PRACTICE RECOMMENDATION

For women with moderate to severe dyspareunia associated with genitourinary syndrome of menopause with concurrent vasomotor symptoms, The North American Menopause Society asserts that transdermal and oral hormone therapy are effective options. Symptom reduction may take one to three months, and continued therapy is generally required because symptoms are likely to recur on cessation of treatment.

(https://www.menopause.org/docs/default-source/default-document-library/2020-gsm-ps.pdf. Last accessed August 20, 2021.)

Level of Evidence: Consensus Statement/Expert Opinion

AN OVERVIEW OF UTERINE BLEEDING

DIAGNOSIS

A thorough history for patients with uterine bleeding should cover the amount and timing of the bleeding as well as any co-existing symptoms that could be related to structural or hormonal abnormalities. Any comorbid medical conditions should be noted. It is important to include the impact of the bleeding on the patient's quality of life [1]. A thorough physical examination is in order to evaluate for signs of anemia and other medical disorders and to evaluate the shape and size of the uterus (via bimanual examination).

Laboratory Analysis

A complete blood count should be performed, along with other testing if symptoms recommend it. A serum ferritin is not routinely recommended unless there is a concern that the patient's anemia is not of iron-deficiency origin. If there are other symptoms of thyroid disease, a test of thyroid-stimulating hormone (TSH) level is in order. If symptoms of menopause are present, follicle-stimulating hormone (FSH) can be checked. Heavy bleeding that has been present since menarche or a personal or family history suggesting a bleeding dyscrasia necessitates testing for von Willebrand disease and other bleeding disorders [32].

If ovulatory dysfunction/anovulation is suspected, timed tests for serum progesterone levels can confirm this. Progesterone is traditionally checked on day 21 of the cycle or whichever day represents the mid-luteal stage of the cycle [7]. Other specific laboratory tests are dependent on likely etiology.

Biopsy

Endometrial curettage can be performed at the time of hysteroscopy or on its own to evaluate for any histologic pathology. However, it is not recommended as a treatment for heavy bleeding [1]. Office endometrial biopsy has been shown to be as effective

as curettage in evaluation for histologic pathology [9]. This is performed in the office by passing a thin, plastic tube (Pipelle) through the cervix, advancing to the uterine fundus and inducing a vacuum in the Pipelle to collect tissue samples from the uterine sidewalls. In addition to evaluation for hyperplasia, the office endometrial biopsy can be examined to determine whether ovulation has occurred [7].

Imaging Techniques

If the uterus is palpable abdominally or there is evidence on physical exam of a pelvic mass, then imaging should be carried out, beginning with transvaginal ultrasonography. Imaging is also necessary when pharmaceutical treatment fails to resolve abnormal bleeding [1].

Ultrasonography is the first-line imaging technique for viewing any structural pathology of the uterus and ovaries [7]. Sonohysterography (or saline infusion hysterography) involves the installation of saline into the uterine cavity, followed by ultrasound exam. This helps to elucidate any intracavitary structural elements, such as polyps or fibroids [7]. Magnetic resonance imaging (MRI) may be required to distinguish a rapidly enlarging leiomyoma from a sarcoma [10].

Hysterosalpingography evaluates the patency of the uterine (Fallopian) tubes by installation of a radioopaque dye through the cervix into the uterine cavity; an x-ray is then taken. Anomalies of uterine cavity shape, such as septae, can be visualized this way.

Hysteroscopy can be used to evaluate for intracavitary pathology such as septae, polyps, and fibroids. This technique can be therapeutic as well as diagnostic [1].

CLASSIFICATION

In 2011, the International Federation of Gynecology and Obstetrics (FIGO) proposed a classification system for abnormal uterine bleeding (AUB) in order to have a "consistent and universally accepted" method for communicating the various causes of this disorder. They noted the wide variety of causes for AUB and the inconsistency of nomenclature impeding communication and comparative research. An individual patient may have more than one etiology of bleeding, which further complicates diagnosis and treatment [7]. Their goal was "to develop a nomenclature and classification system that fits research/educational requirements and clinical needs, but is also practicable" [7].

FIGO recommends abandoning the term "dysfunctional uterine bleeding" entirely and has developed revised terminology for describing the nature of the abnormal bleeding [7]. The new system is based on the mnemonic PALM-COEIN:

- **P**olyp
- **A**denomyosis
- **L**eiomyoma
- **M**alignancy and hyperplasia
- **C**oagulopathy
- **O**vulatory dysfunction
- **E**ndometrial
- **I**atrogenic
- **N**ot yet classified

The first four letters, PALM, represent objective structural or histologic causes of bleeding.

Each letter in the mnemonic is followed by a zero or a one, indicating the absence or presence of that disorder. For example, a patient with a polyp would be classified AUB P_1 A_0 L_0 M_0 - C_0 O_0 E_0 I_0 N_0, or more simply, AUB-P_1.

Leiomyomata are further subclassified, describing whether fibroids are submucosal (SM) versus others (O), as submucosal fibroids are thought to be more likely to contribute to AUB. A tertiary classification further describes their location. SM0 describes an intracavitary lesion; SM1 is <50% intramural, and SM2 is >50% intramural. O3 is 100% intramural but does contact the endometrium. O4 is purely intramural, O5 is subserosal >50% intramural, O6 is subserosal <50% intramural, O7 is subserosal pedunculated, and O8 requires specification of the location (cervical, for example). Fibroids that involve

both the endometrium and serosa are given a hybrid number (2-5, for example). Because this tertiary description would likely require use of MRI for evaluation, it is usually left off [16]. Thus, a patient with abnormal bleeding and a known submucosal fibroid would be classified AUB P_0 A_0 $L_{1(SM)}$ M_0 - C_0 O_0 E_0 I_0 N_0, or more simply, AUB-$L_{1(SM)}$.

In addition, the committee recommended that any AUB that has been present for the majority of the prior six months be classified as chronic AUB not requiring immediate intervention. Acute AUB, however, does require immediate intervention. Acute AUB may be superimposed on pre-existing chronic bleeding [7].

The PALM-COEIN rubric can help to organize investigation into the cause of AUB. Naturally, the first step is to distinguish normal bleeding from abnormal [5]. Many patients will describe their bleeding as excessive or abnormal when it actually falls within normal parameters. Resetting expectations may be all that is needed, although appropriate treatment to improve quality of life is an option. Normal ranges of bleeding should be discussed with the woman, but if she feels that her bleeding is too heavy, despite having a normal blood count, it should be remembered that perceived heavy menstrual bleeding can have a profound impact on quality of life [1].

FIGO and the American College of Obstetricians and Gynecologists (ACOG) have recommended discarding the traditional descriptors of AUB, but it is helpful to discuss them in order to have a standardized frame of reference. The recommended changes follow the traditional definitions.

Menorrhagia (replaced with "heavy menstrual bleeding") is defined as 80 mL or more of blood loss during a menstrual cycle or menstrual bleeding that lasts longer than seven days [5]. By definition, this bleeding occurs at regular intervals, whether that interval is the traditional 28-day cycle or shorter or longer cycles. Realistically, the clinician and the patient are not going to be performing quantitative measurements of blood loss but relying on history and the effect on quality of life [1]. Metrorrhagia (replaced with "intermenstrual bleeding") is irregular (noncyclic) bleeding or bleeding between periods [5]. Polymenorrhea was defined as menstrual bleeding that occurs on cycles of 21 days or fewer, and menometrorrhagia referred to a combination of bleeding that is both excessive in amount and irregular in occurrence [5]. These conditions should be described accurately, and older terminology should be avoided. The term "dysfunctional uterine bleeding" should also be discarded [5].

Bleeding should be described by four characteristics: regularity (irregular, regular, absent), frequency (frequent, normal, infrequent), duration (prolonged, normal, shortened), and volume (heavy, normal, light). For regularity, periods may vary by 2 to 20 days; variation of more than 20 days is irregular. Normal frequency is 24 to 38 days, normal duration is 4.5 to 8 days, and normal volume is 5 mL to 80 mL [8]. These "normal" characteristics fall between the 5th and 95th percentile of women. Thus, what was previously termed menometrorrhagia may now be described as irregular, frequent, prolonged, heavy uterine bleeding [8]. Any additional abnormalities can be separately described, such as intermenstrual bleeding and premenstrual spotting.

As women age from adolescence onwards, their periods become shorter in duration and closer together until perimenopause, when cycle length increases and anovulation becomes more frequent [1; 2]. At the same time, volume of blood loss increases with age. Menstrual regularity improves with age until perimenopause [1].

Having discussed these definitions, it is useful to keep in mind that the National Institute for Health and Clinical Excellence (NICE) guidelines stress that improving quality of life is the goal, rather than focusing on the amount of blood loss. Effects on quality of life range from bloodstained clothes to anxiety or depression and interference with social or work life [1]. If a patient is distressed by her bleeding, whether it is technically within normal limits is not relevant.

SOURCES OF UTERINE BLEEDING: PALM-COEIN

POLYPS

Polyps are pedunculated masses within the uterine cavity or endocervix that are composed of a proliferation of epithelial tissue. They have vascular, glandular, fibromuscular, and connective tissue components. They are usually asymptomatic but can cause uterine bleeding [7]. Polyps are often benign but can co-exist with hyperplasia or carcinoma or can undergo malignant transformation (in 0.5% of cases), so removal is recommended [9].

Treatment

Cervical and endocervical polyps can be removed by grasping with an appropriate forceps and gently twisting. The endometrium should be sampled to rule out any co-existing hyperplasia or carcinoma. Endometrial polyps can be removed by hysteroscopy, which achieves better results than blind curettage [9].

ADENOMYOSIS

Adenomyosis is a condition wherein the glandular component of the endometrium invades into the myometrium. The diagnosis is usually made by histology after hysterectomy, and the reason it may cause AUB is unclear. Adenomyosis can produce a globular-appearing uterus on ultrasound, resulting from endometrial tissue invading the myometrium and the subsequent myometrial hypertrophy [7]. Treatment is similar to that of ovulatory dysfunction, which will be described in detail later in this course.

LEIOMYOMATA (FIBROIDS)

Uterine leiomyomata (or fibroids) are the most common reason for hysterectomy in the United States [10; 11]. These solid fibromuscular tumors are benign and often asymptomatic. They are diagnosed in up to 40% of women but are estimated to be present in 70% of white women and more than 80% of black, Hispanic/Latina, and Asian women by 50 years of age [7; 12; 40]. When they do produce symptoms, abnormal bleeding—usually a very heavy or prolonged period—and pelvic pressure and low back pain are the most common. Heavy bleeding can result in iron-deficiency anemia. When fibroids are large, they can lead to dyspareunia or interfere with urination or defecation by impinging on adjacent structures [10]. Fibroids usually cause ovulatory bleeding, but they may also affect fertility. The pathophysiology of their formation and growth is not well understood [11; 40].

Leiomyomata range from very tiny, subcentimeter lesions to extremely large lesions that can displace other pelvic or abdominal organs. They are classified according to their location within the uterine wall as subserosal, submucosal, or intramural. Some fibroids are also pedunculated, hanging off of the uterus or into the endometrial cavity [10].

The traditional wisdom that any rapidly enlarging fibroid should be evaluated for the possibility of leiomyosarcoma has been revised. The sarcoma rate remains 2 to 3 per 1,000; therefore, the possibility of sarcoma is no longer an indication for surgery, although symptom alleviation is a valid indication for surgery. Other risk factors for sarcoma include prior tamoxifen use or pelvic radiation, increasing age, and the rare hereditary leiomyomatosis and renal cell carcinoma syndrome. MRI is used to distinguish sarcomas from other uterine pathology [10].

Medical Treatment

Leiomyomata are often managed surgically, as medical therapies have significant risks and side effects for long-term use and can be expensive. Any treatment (medical or surgical) short of hysterectomy allows for the possibility of recurrence of fibroids, new fibroid growth, or further growth of pre-existing small fibroids. This must be weighed against the woman's childbearing desires when determining the course of treatment [10]. NICE advises that pharmaceutical treatment may be used for fibroids smaller than 3 cm in diameter. The treatment of fibroids, as with the treatment of any AUB, must be discussed in detail with the patient, including possible side effects of each treatment, alternatives, and the risks/benefits of each alternative. It is also important to clarify the patient's expectations of the treatment [1].

For initial management, most physicians turn to nonsteroidal anti-inflammatory drugs (NSAIDs) and oral contraceptives. Progesterone-only treatments are also an option. If fibroids are small, these may provide adequate relief; however, the rate of progression to surgical therapies is high [13]. Oral contraceptives are often the initial treatment for any abnormal bleeding, whether ovulatory or anovulatory, and NSAIDs are commonly used for dysmenorrhea of any etiology. However, they have not been shown to improve dysmenorrhea caused by fibroids. Data on the effectiveness of oral contraceptive treatment of fibroids are limited, and the data on progesterone-only or progesterone with gonadotropin-releasing hormone (GnRH) agonist therapy are mixed. The ACOG recommends close monitoring of fibroids when initiating treatment [10].

The levonorgestrel intrauterine system (LNG-IUS) is an intrauterine device used for treatment of heavy uterine bleeding in some cases and has also been effective for the management of bleeding resulting from leiomyomata in small-scale studies [10; 13; 14; 15; 33; 48]. The use of LNG-IUS for fibroid-related bleeding should be balanced against the risk of expulsion (due to bulky fibroids) and a higher rate of spotting [10; 14].

Hormone replacement is not contraindicated in postmenopausal women with fibroids. Transdermal estrogen use may increase the size of fibroids, but this has not been shown to increase symptoms [10].

Danazol, a synthetic steroid derivative that decreases estradiol, is no longer commonly used due to its androgenic side effects [2]. GnRH agonists such as leuprolide are used to treat symptomatic fibroids and as pre-operative therapy in women with large leiomyomata [10]. These are short-term treatments, used only for three or six months. They act by suppressing the release of luteinizing hormone (LH) and FSH from the anterior pituitary (after an initial "flare") and thus have an anti-estrogenic and anti-progesterone effect on the endometrium [1]. This produces a state of hypoestrogenism and symptoms of menopause that limit their toleration and duration of use. When used for longer than six months, low-dose hormone replacement therapy (either progesterone alone or low-dose estrogen-progesterone replacement) is recommended to protect against osteoporosis as well as to alleviate some of the menopausal side effects, such as hot flushes, that accompany this treatment [1; 10]. Add-back progesterone therapy, however, results in re-growth of leiomyomata. These agents are also limited by the fact that leiomyomata will re-grow after therapy is terminated; thus, their use is often confined to pre-operative treatment of large fibroids before myomectomy or hysterectomy. They do produce a 35% to 65% decrease in fibroid volume in the first three months of use [10]. They can also be used to temporize symptoms in women close to menopause [11].

Aromatase inhibitors are not FDA-approved for the treatment of leiomyoma; however, based on their mechanism of action, they may be effective without as many side effects as GnRH agonists. These medications inhibit production of estrogen from the ovaries within one day of treatment. At this time, more research is needed, although small studies seem promising [10].

GnRH antagonists have been studied for use in the treatment of fibroids, but they are not FDA-approved for pre-operative treatment. They have the potential to avoid the initial "flare" of side effects associated with GnRH agonists [10].

Progesterone modulators such as mifepristone block progesterone receptors, including those in the fibroid [10]. Further studies are needed, as blocking progesterone receptors in the uterus may predispose to endometrial hyperplasia without atypia and require monitoring for elevations in transaminases [10; 11]. The appropriate doses are also not currently widely available, requiring a compounding pharmacy. However, studies have shown a decrease in leiomyoma volume by 26% to 74%, possibly with a slower recurrence rate, with amenorrhea extremely common and no effect on bone mineral density [10].

Surgical Treatment

When preservation of the uterus is desired for future fertility, myomectomy is a valid option, although it will often obligate the patient to cesarean delivery of subsequent pregnancies, depending on the extent of surgery [11]. Traditionally, myomectomy has been performed via laparotomy; however, laparoscopic and robotic approaches are becoming more common. Myomectomy cannot always remove all fibroids, and the risk of recurrence and further growth of leiomyomata persists. It appears that the risk of recurrence increases with the number of leiomyomata in the uterus [10].

Abdominal myomectomy carries similar surgical morbidity rates to hysterectomy, and the risk of conversion to hysterectomy is around 1% [10]. Laparoscopic myomectomy improves recovery time and results in less blood loss, unless the fibroids are large. It is limited by the size of the leiomyomata, and because it requires advanced laparoscopic suturing techniques, it is usually only offered by advanced laparoscopic surgeons [10].

Intramural injection of vasopressin with any form of myomectomy decreases surgical blood loss [10]. Preoperative use of GnRH agonists for three to four months to shrink fibroids also results in a lower surgical blood loss [1].

As discussed, submucosal fibroids are classified according to uterine wall invasion, with type 0 leiomyomata restricted to the uterine cavity, type 1 involving less than 50% of the uterine wall, and type 2 involving more than 50% of the uterine wall [10]. Depending on the depth of invasion, these fibroids may be amenable to hysteroscopic removal. Some physicians allow a trial of labor after hysteroscopic removal of type 0 or type 1 fibroids. As with any trial of labor, a high index of suspicion for uterine rupture must be maintained [10].

NICE advises that endometrial ablation (discussed further later in this course) may be used in women with small (<3 cm) fibroids [1]. Uterine artery embolization (UAE) is a possibility for women who desire a less invasive procedure; however, the patient must understand that pregnancy following this procedure has not been studied. UAE is usually performed by an interventional radiologist and involves catheterizing the femoral artery and deploying polyvinyl alcohol particle microspheres or gelfoam and coils to embolize the uterine arteries [11]. The goal is to cut off blood supply to the uterine fibroid, leading to its "death" and involution [10].

Three-month follow-up data in one large study showed a reduction of 42% in the volume of the dominant fibroid, as well as improved quality-of-life scores including bleeding, pain, and urinary symptoms. Occasionally, patients may expel leiomyomata through the vagina after UAE. Major complication rates are similar between this procedure and hysterectomy, with UAE having less pain and shorter hospital stays but a higher readmission rate [10]. Postembolization syndrome is common, consisting of pain, cramping, nausea, and fatigue [11]. The overall complication rate is about 5% [10]. The Society of Interventional Radiology published one-year data showing a 95% rate of symptom and quality-of-life improvement, 7% amenorrhea rate, and 5.6% rate of repeat surgery (repeat embolization, myomectomy, or hysterectomy) [11]. Long-term outcomes included 10-fold higher re-operation rates compared with myomectomy. One study showed a subsequent hysterectomy rate (within five years) of 13.7% [29]. UAE also carries a small risk of subsequent ovarian failure due to compromised blood supply [10].

MRI-guided focused ultrasound surgery uses MRI to guide high-intensity ultrasound waves into a fibroid, causing protein denaturation and coagulative necrosis of the tumor [10]. Long-term studies are needed, but 12- and 24-month follow-up studies show some symptom resolution (71% at 6 months, 51% at 12 months) but only a 9.4% uterine volume reduction at 12 months. Possible complications include persistent pain, heavy bleeding (sometimes requiring blood transfusion), nausea, temporary leg and buttock pain due to sciatic nerve damage, and skin burns [10; 11]. Studies are still ongoing for this relatively new treatment modality, and there are no recommendations for fertility following treatment [11].

Hysterectomy remains the definitive treatment for women who fail medical management and/or who do not desire childbearing [49]. Fibroids are the most common indication for hysterectomy, accounting for more than 30% of hysterectomies in white women and more than 50% of those in black women [11]. Surgical risks of hysterectomy are higher in those operations done for fibroids compared with other indications, but there is no possibility of recurrence of leiomyoma [1]. Patient satisfaction rates are higher for hysterectomy than for other surgical methods [1; 10].

The route of hysterectomy (vaginal, abdominal, laparoscopic/robotic, or laparoscopic-assisted vaginal) should be determined by the patient and her surgeon after a careful consideration of risks, comorbid conditions, size of the uterus, size/location of the fibroids, mobility/descent of the uterus, prior surgeries, and any other gynecologic conditions. The FDA recommends against the use of laparoscopic power morcellators for the treatment of uterine fibroids due to the risk for mechanical spread of occult cancerous tissue and worsened clinical outcomes. As of December 2020, a boxed warning describing these risks and the need to discuss these risks with patients is required for these devices [45]. Retaining the cervix (subtotal or supra-cervical hysterectomy) can result in cyclical bleeding from the cervix (in 7% of women) and eventual cervical prolapse (in 2% of women) [1].

MALIGNANCY AND HYPERPLASIA

Endometrial (uterine) adenocarcinoma is the most common gynecologic cancer in the United States, and 90% of patients will present with vaginal bleeding [16]. The incidence peaks between 55 and 69 years of age. The primary risk factor for developing endometrial adenocarcinoma is unopposed estrogen, either pharmacologic or through obesity, nulliparity, or late menopause [9]. Hereditary nonpolyposis colorectal cancer syndrome (HNPCC) carries a lifetime risk of endometrial cancer of up to 60% [7].

Endometrial hyperplasia is described as simple or complex, according to the glandular structure of the endometrium, with both showing dilated and irregular glands, but the complex form demonstrating back-to-back glands on pathology. Hyperplasia is further characterized as with or without cytologic atypia, with nuclear enlargement among other changes. Atypical hyperplasia is much more likely to progress to carcinoma; complex atypical hyperplasia has the greatest chance of progressing to adenocarcinoma, at 29% [17]. Hyperplasia without atypia, whether simple or complex, is more reassuring but must still be addressed [17; 18]. Polyps can coexist with carcinoma, but they are not considered to be precursors of cancer and their rate of progression to carcinoma is low (3% to 4%) [9].

The ACOG recommends endometrial sampling for adult women 19 to 39 years of age with anovulatory bleeding unresponsive to medication or who have prolonged periods of unopposed estrogen stimulation and for younger women with risk factors such as obesity and longstanding, untreated anovulation [5]. All postmenopausal bleeding must be evaluated, but the traditional thinking that every postmenopausal patient must undergo an endometrial biopsy or dilation and curettage for diagnosis is obsolete. A transvaginal ultrasound showing an endometrial thickness of 4 mm or less in a postmenopausal woman has a negative predictive value approaching 100%. Because of this, an ultrasound can be the first diagnostic tool for a lower-risk (non-obese) woman. An ultrasound is also useful when a biopsy sample yields insufficient tissue for diagnosis. If the endometrial thickness is 4 mm or less, carcinoma is reliably excluded [16]. By using the ultrasound first, a woman can be spared a painful office procedure or a trip to the operating room for dilation and curettage [2].

Any woman with benign findings can go on to develop hyperplasia or neoplasia, so persistent abnormal bleeding will need to be re-evaluated [18]. Abnormal bleeding should also be evaluated with colposcopy (with cervical biopsy as indicated); endocervical curettage for abnormal cytology on Pap test;

and ultrasound, hysteroscopy, or sonohysterogram to evaluate for polyps or fibroids [18]. Any vulvar or vaginal bleeding or lesion that resists treatment should be evaluated by biopsy for dysplasia and carcinoma. Any postcoital bleeding should be evaluated for injury or dysplasia, as bleeding is a common presenting symptom of cervical carcinoma [4].

Treatment

Patients with endometrial adenocarcinoma or cervical carcinoma should be referred to a gynecologic oncologist for treatment. Many general gynecologists prefer to co-manage endometrial hyperplasia with the guidance of a gynecologic oncologist as well.

Management of endometrial hyperplasia depends on the presence or absence of atypia, which, as discussed, increases the risk of co-existing carcinoma [17; 18]. Simple hyperplasia without atypia is often not treated after dilation and curettage is performed as the rate of progression to carcinoma is extremely low, at 1% [9; 17; 19]. Complex hyperplasia without atypia is treated with continuous or periodic progesterone [17; 18]. Hysterectomy may also be performed if the patient does not desire future fertility [17]. Simple atypical hyperplasia is treated with progesterone, either continuously or for 10 to 14 days each month, or with hysterectomy, as cytologic atypia carries an almost 10% risk of co-existing carcinoma [9; 17; 18]. There are ongoing trials using the LNG-IUS as a method of delivering progesterone treatment for hyperplasia [20]. Various studies and reviews have found that the LNG-IUS achieves higher progesterone concentrations in endometrial mucosa and that this delivery may be superior to oral forms; however, only a few studies have shown, for example, a higher pooled regression rate for LNG-IUS versus oral progesterone while several studies have found no difference [41]. As such, data are currently insufficient to recommend one form over the other. High-dose oral progesterone therapy can be used in complex atypical hyperplasia, although hysterectomy is usually recommended as there is a 30% chance of progression to adenocarcinoma [17]. One small-scale study has shown the benefit of combined oral progesterone/LNG-IUS in women who opt for fertility-sparing treatment [34]. The recurrence rate was also found to be lower using combined treatment in one study [41]. Any time progesterone treatment is to be used, dilation and curettage is recommended to be sure there is no co-existing adenocarcinoma [17].

Long-term follow up and periodic endometrial sampling are required in patients treated with progesterone. Hysterectomy is recommended for those whose hyperplasia fails to regress with progesterone therapy [9]. Any patient treated for hyperplasia with progesterone requires follow-up to confirm regression of the abnormal histology [18]. Endometrial sampling should be performed every three to four months [17].

COAGULOPATHY

It is important not to overlook the possibility of bleeding disorders, such as von Willebrand disease and thrombocytopenia or hemophilia, in adolescent girls with excessive menstrual bleeding or in adult women with lifelong heavy menses [5]. Approximately 13% of women with heavy menstrual bleeding have some form of coagulopathy or disorder of hemostasis, most often von Willebrand disease [7]. Women with AUB caused by pharmacologic anticoagulation such as warfarin, although technically in the iatrogenic category, are included by FIGO in the category of coagulopathy [7].

Leukemia and idiopathic thrombocytopenic purpura can cause heavy bleeding as well [5]. A thorough work-up of heavy bleeding in an adolescent girl should include screening for coagulation disorders with a prothrombin time, partial thromboplastin time, assessment of platelet function, Factor VIII, and von Willebrand Factor antigen and activity [9]. Physical examination should include evaluation for signs of bleeding dyscrasias, such as petechiae or excessive ecchymoses [5]. In some women with bleeding disorders, however, heavy menstrual bleeding may be the only sign [9].

OVULATORY DYSFUNCTION (ANOVULATORY BLEEDING)

Anovulatory bleeding is defined by the ACOG as noncyclic menstrual blood flow that is noncyclic, unpredictable, and inconsistent in volume, resulting from continual endometrial proliferation without progesterone-withdrawal-induced shedding and bleeding, due to a lack of ovulation [5]. In a normal menstrual cycle, the endometrium will respond to hormonal stimulation by first proliferating under the influence of estrogen (the production of which is stimulated by FSH from the anterior pituitary), then entering the secretory phase with a surge in LH triggering ovulation. The secretory phase, also called the luteal phase, combines estrogen and progesterone stimulation of the endometrium, resulting in maturation of the stroma [18]. With the withdrawal of estrogen and progesterone, the thickened lining will desquamate and shed, resulting in menstrual blood flow, or the normal period [5].

When ovulation does not occur, the hormonal stimulation will be that of estrogen alone, as there is no corpus luteum to produce progesterone. This unopposed estrogen leads to unsustainable growth of the endometrium. There is no maturing effect of progesterone, so the endometrium grows to an abnormal thickness without strong stromal support [18]. The lining is fragile and unstable and undergoes spontaneous superficial breakage and bleeding. As one site heals, another site of breakdown will appear. The bleeding involves random portions of the endometrium at variable times and in asynchronous sequences [18].

There is ongoing research showing there are altered prostaglandin levels and ratios in the anovulatory endometrium that may impair vasoconstriction [5]. The result, regardless of the cause, is irregular, prolonged, and often heavy uterine bleeding. As the bleeding is caused by abnormalities in the hypothalamic-pituitary-ovarian axis, there is no distinct pathology to be seen under the microscope [1].

The most obvious result of chronic anovulation is infertility, but it carries an increased risk for the development of endometrial carcinoma as well. The hyperinsulinemia and hyperandrogenism that can be associated with anovulation increase the risk for cardiovascular disease and diabetes [18].

It is important to keep in mind that anatomic causes of bleeding must be excluded before the diagnosis of anovulatory or abnormal uterine bleeding can be made [5]. In addition, pregnancy must be excluded first in any reproductive-age woman with irregular bleeding [5]. While irregular bleeding is common in adolescents and may be considered physiologic as long as blood dyscrasias are ruled out in patients with excessive bleeding, adult women should be evaluated for the cause of any irregular bleeding.

Anovulation is common during the first few years of menstruation following menarche, as well as during the last few years before menopause [1]. In adolescents, the immature state of the hypothalamic-pituitary-gonadal axis is to blame; in perimenopausal women, diminishing ovarian function causes an irregular endometrial response [5]. Premature ovarian failure can be a cause of abnormal bleeding [11]. In perimenopausal women, attention should be paid to other health risks of menopause, including bone health [5]. Bone health is also a concern in adolescents and women with anorexia or disordered eating [2]. Bleeding disorders must be ruled out in adolescents or adult women with lifelong heavy bleeding [5].

Causes of Ovulatory Dysfunction

Polycystic Ovarian Syndrome

Polycystic ovarian syndrome (PCOS) is a common cause of secondary amenorrhea or unpredictable bleeding, occurring in 5% to 10% of women of childbearing age [35]. Along with menstrual irregularities, obesity and hirsutism are common findings in women with PCOS.

The polycystic ovary has a typical thickened appearance on inspection, resulting from chronic anovulation. FSH stimulates follicle development in the ovary, but as the FSH level in PCOS is depressed, the follicles do not reach full maturity and do not ovulate. They remain within the ovary, producing steroid hormones. The increased LH levels in PCOS stimulate ovarian theca cells to produce androstenedione and testosterone, which go on to suppress sex hormone-binding globulin (SHBG), leading to increased free estrogen and testosterone. The increased theca cells contribute to the thickened appearance of the ovary. This self-perpetuating cycle can start from any number of points, but the end result is anovulation resulting in the polycystic ovary—the appearance of the ovary is a symptom and not the disease itself [18].

Although polycystic ovaries are often seen in women with PCOS, ultrasonography is not sufficient for diagnosis of the condition, as up to 62% of the healthy (i.e., normo-ovulatory) population 25 to 30 years of age has polycystic-appearing ovaries; incidence decreases with age due to natural egg loss [47]. There are different sets of criteria for the diagnosis, but all include either clinical or biochemical hyperandrogenism and menstrual irregularities [21]. Women with PCOS have increased peripheral conversion of androgens to estrogens, decreased levels of SHBG (leading to increased free estradiol and testosterone), and increased insulin levels [18].

Other Possible Causes

Other causes of anovulation include thyroid disease, hyperprolactinemia, and hypogonadism brought about by anorexia or excessive exercise [5]. Mental stress can play a role, as can weight loss or obesity [7; 11].

A careful history should be taken to elicit other symptoms of thyroid disease, galactorrhea (which occurs in one-third of women with hyperprolactinemia), or anorexia. Certain medications—such as antipsychotics—may cause hyperprolactinemia and thus affect menstrual cycles. Anorexia or weight loss will often cause amenorrhea but can also produce irregular bleeding [18]. A low FSH level indicates that the irregular bleeding is the result of psychologic stress, anorexia, or excessive exercise [5].

Diagnosis

Laboratory Testing

PCOS and chronic anovulation patients will often have elevated testosterone, androstenedione, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEA-S), and estrone. DHEA-S is produced by the adrenal glands and is greater than normal in about 50% of anovulatory women [18; 43].

Glucose intolerance and hyperinsulinemia, or insulin resistance, is often seen in association with PCOS, and an oral glucose-tolerance test is recommended, particularly for obese women and those with a family history of type 2 diabetes [44]. Acanthosis nigricans, a velvety-appearing discoloration of the skin, commonly at the nape of the neck or in the axillae, is often seen in hyperandrogenic patients with insulin resistance. These women are often obese, with an "android" fat distribution (central body, abdominal wall, and visceral mesentery), although nonobese anovulatory women can have hyperinsulinemia and hyperandrogenism as well. Treatment of insulin resistance with metformin often has the effect of restoring ovulation, regardless of whether it leads to any weight loss [18].

Laboratory testing commonly includes FSH and LH levels to determine their ratio. LH will be elevated in anovulatory women, whereas FSH will be low or low-normal [18]. TSH testing is recommended if other symptoms of thyroid disease are present [1]. Obtaining fasting prolactin and free testosterone levels is recommended [43]. Elevated testosterone drives down SHBG, which exacerbates the problem; the increased free estradiol levels further increase LH. Some clinicians include insulin levels, particularly if diabetes or metabolic syndrome is suspected, as in women with android fat deposition [18]. The 17-hydroxyprogesterone level is an important indicator for congenital adrenal hyperplasia, although children are currently screened for this at birth in the United States [11].

If hirsutism and other virilization symptoms are rapidly progressing, an androgenic tumor should be ruled out by testing testosterone and DHEA-S [43]. If a pregnancy test is negative, FSH is normal, and there are no abnormalities of TSH or prolactin, the diagnosis of anovulation can be made [18].

In women with hyperandrogenism, a lipid panel is recommended [44]. Weight loss should be encouraged in all overweight women [18]. A 5% to 10% weight loss can restore ovulation in more than 50% of obese patients [23].

When ruling out bleeding dyscrasias, the tests to order are prothrombin time, partial thromboplastin time, Factor VIII, platelet count, and von Willebrand Factor antigen and activity [9]. Cultures for gonorrhea and chlamydia can help rule out infectious causes of bleeding [11].

Endometrial Sampling

The ACOG recommends endometrial sampling for adult women older than 45 years of age with anovulatory bleeding and sampling for women older than 19 years of age with anovulatory bleeding who do not respond to medical therapy or who have prolonged periods of unopposed estrogen stimulation [5]. The incidence of endometrial carcinoma in all women was 28.1 per 100,000 in 2014–2018, with most cases occurring in women 55 to 64 years of age [36]. The lifetime risk of endometrial carcinoma is 3.1%.

Younger adult women should be offered endometrial sampling if they have risk factors for endometrial hyperplasia/carcinoma, such as obesity or chronic anovulation with long periods of unopposed estrogen. More than two to three years of untreated anovulatory bleeding warrants an endometrial biopsy [5]. The incidence of endometrial carcinoma in girls younger than 19 years of age was less than 0.1 per 100,000 in 2018, and only 1.5% of new cases occurred in women 20 to 34 years of age, yet obesity may increase risk for hyperplasia and carcinoma due to unopposed estrogen from chronic anovulation as well as conversion of androgens to estrogens in adipose tissue [5; 36].

Obviously, pregnancy must be excluded in any age group before endometrial sampling takes place. If medical treatment does not resolve the abnormal bleeding, the patient should be re-evaluated for possible anatomic causes, coagulopathies, or hyperplasia/neoplasia. If endometrial sampling was not previously performed, it should be done at this time [5].

Treatment

The treatment choices for anovulatory bleeding will vary depending on the age of the woman, her desire for either contraception or conception, whether she desires future fertility, and the amount of bleeding and its impact on her quality of life [5].

Medical Treatment

For anovulatory AUB, as it is an endocrine pathology, medical management is the preferred first-line treatment. Besides the obvious benefit of improving quality of life for the patient with problematic bleeding, medical treatment will also reduce the risk of complications from chronic anovulation and estrogen dominance and should reduce the amount of menstrual blood flow by the third month of treatment [5]. Options for pharmacotherapy include intravenous conjugated equine estrogen, combined oral contraceptives, and oral progestin [37].

The treatment of anovulatory bleeding, as with any AUB, must be discussed in detail with the patient, including possible side effects of each treatment, alternatives, and the risks/benefits of each alternative. It is also important to clarify the patient's expectations of the treatment [1].

Adolescents. In the adolescent population, medical therapy is usually highly effective for anovulatory AUB. After leukemia and any blood dyscrasias are ruled out, high-dose estrogen therapy is indicated for acute menorrhagia, particularly if it results in anemia [5; 37]. Any underlying medical condition will of course need to be treated. High-dose estrogen will promote endometrial growth to fill in any denuded endometrial surfaces. Estrogen, in the form of conjugated equine estrogens, is usually given either intravenously at a dose of 25 mg every

4 to 6 hours for up to 24 hours or orally at a dose of 2.5 mg four times daily [23; 37]. Concomitant antinausea medication may be required. When the acute bleeding episode has resolved, the patient can be transitioned to an oral contraceptive pill or cyclic progesterone treatment to promote regular shedding of the uterine lining [5]. The ACOG recommends maintaining amenorrhea with continuous oral contraceptive pills for the first few weeks to allow for recovery from anemia, but this must be balanced against the risk for breakthrough bleeding with continuous oral contraceptives. All patients with anemia should be treated with iron [5].

For those whose severe bleeding does not respond to high-dose estrogen or who are not hemodynamically stable, dilation and curettage is indicated. As long as the patient is stable, high-dose estrogen should be given; usually one or two doses results in a significant effect [37]. High-dose estrogen therapy should be avoided in patients with a past idiopathic venous thromboembolism or a positive family history for the same [18].

Adult Women. Again, an acute bleeding episode can be treated with high-dose estrogen, as described for adolescents, in hemodynamically unstable women. Chronically anovulatory women (e.g., PCOS) can also be treated with either a combined oral contraceptive pill (35 mcg estrogen dose or lower) or cyclic progesterone [5; 18; 37]. Oral contraceptives are preferred, especially in the case of PCOS with hirsutism and hyperandrogenemia, as they suppress both ovarian and adrenal androgen production and increase levels of SHBG, which reduces free androgens in the bloodstream [5]. Progesterone administered only during the luteal phase has not been shown to decrease menstrual blood loss, but cyclic progesterone given three weeks out of each month is effective at reducing bleeding [1].

Estrogen-containing treatment methods should be avoided in women with hypertension or diabetes as well as those who smoke and are older than 35 years of age [37]. These women can be treated with cyclic progesterone or nonmedical methods, depending on their desire for future childbearing. Progesterone treatment can also be supplied in the form of injection, subcutaneous insert, or intrauterine device [1]. A progesterone-only treatment is also an option for any adolescent or adult woman who cannot tolerate oral contraceptives or who does not wish to take them. However, the risk of irregular bleeding for up to six months must be taken into account when deciding on a progesterone-only method [1; 18]. After six months, amenorrhea is a common side effect of these methods [1].

In patients with chronic disease causing problematic bleeding (e.g., uterine fibroids), the LNG-IUS is a good choice [1; 37]. Normally ovulating women with heavy periods are also good candidates for oral contraceptives or cyclic progesterone; however, LNG-IUS is the most effective medical treatment for ovulating women with very heavy periods [48; 49]. Consultation with a hematologist is recommended for women with bleeding disorders.

NSAIDs are often used to relieve dysmenorrhea, but they can have an effect of their own on reducing menstrual bleeding [1]. They inhibit cyclooxygenase, which reduces prostaglandin synthesis. Prostaglandins are involved in inflammation, pain pathways, and menstrual bleeding and cramping. Decreased prostaglandins lead to vasoconstriction, which can slow bleeding [11]. Although NSAIDs are more effective than placebo in reducing menstrual pain and uterine bleeding, they are less effective than tranexamic acid, danazol, or LNG-IUS [38]. NSAIDs should be recommended before a definitive diagnosis and treatment plan are established, and they can be used in place of other treatments (at each menses, if sufficiently effective) in women who do not want or are unable to take hormonal medications [1].

Tranexamic acid competitively inhibits plasminogen activation, which makes it an antifibrinolytic agent [37]. Although its mechanism of action involves factors necessary for blood clotting, it has no effect on normal coagulation, and thrombosis has not been seen to be more common in patients on this medication. Tranexamic acid reduces the breakdown of existing clots, and this is believed to be the mecha-

nism by which it can reduce menstrual blood flow; the clots at the spiral arterioles in the endometrium remain intact rather than breaking down and bleeding. The medication is taken three or four times daily, starting on the first day of menses, for up to four days. It should be noted that tranexamic acid is not a contraceptive and will not regulate irregular cycles [1].

NSAIDs are preferable over tranexamic acid treatment when dysmenorrhea is a main complaint, as tranexamic acid has not been shown to decrease cramping and dysmenorrhea. Neither NSAIDs nor tranexamic acid should be used for longer than three months if not effective [1].

In countries other than the United States, oral contraceptives are not the first line of treatment. The NICE guidelines in the United Kingdom list the LNG-IUS as the first-line treatment, followed by a second-line of tranexamic acid, NSAIDs, or oral contraceptives, with oral or systemic progesterone treatment as the third line [1].

If an adult woman has a lifelong history of menorrhagia and/or does not respond to treatments for AUB, the possibility of a bleeding dyscrasia should be considered and tested for [1]. Other conditions affecting ovulation should also be treated. Thyroid function should be normalized, hyperprolactinemia treated with dopamine agonists (or cessation of a medication causing this condition), and insulin resistance treated with metformin [18]. Treatment of the underlying problem may resolve the abnormal bleeding without further treatment. All women with anemia should be treated with iron [5].

Perimenopause. Women in perimenopause usually respond adequately to the treatments described for women of childbearing age. If their heavy bleeding is accompanied by hot flushes, they may have declining estrogen production and can undergo estrogen treatment with either continuous or cyclic progesterone to protect the endometrium against hyperplasia [5]. If hormone treatment is used, it should be at the smallest dose for the shortest possible duration [46].

Endometrial Ablation

As medical therapy has reduced costs and risks compared with surgical treatment of anovulatory uterine bleeding, it should be offered first unless contraindicated. In women who fail medical management and have completed childbearing, surgical treatment may be considered. It is important to counsel the patient about the failure rate of various surgical treatments so expectations may be managed.

Endometrial ablation may reduce heavy bleeding and help to avoid anemia, but amenorrhea cannot be guaranteed and should not be the patient's expectation. Endometrial ablation aims to destroy all or most of the endometrium (including the basal glands from which the endometrium develops), which in turn will reduce or eliminate menstrual bleeding [39]. The goal is to decrease the amount of bleeding to a manageable level.

The American College of Obstetricians and Gynecologists advises that patients who choose endometrial ablation should be willing to accept normalization of menstrual flow, not necessarily amenorrhea, as an outcome.

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Level of Evidence: C (Based primarily on consensus and expert opinion)

Endometrial ablation may be performed with or without a hysteroscope. The trend is toward nonhysteroscopic methods, which avoid the risk of fluid overload. These are termed second-generation ablation methods and include microwave, hydrothermablation, and cryotherapy [39]. Two more common nonhysteroscopic methods used in the United States are the thermal balloon, which heats to 85°C when applied to the inner uterine wall, and bipolar radiofrequency ablation.

Hysteroscopic methods of ablation traditionally included the use of the resectoscope to remove the uterine lining with an electrocautery loop or rollerball. An yttrium aluminum garnet laser can also be used. These hysteroscopic methods carry a risk of fluid overload in addition to the risk of uterine perforation and require preoperative treatment to thin the endometrium [5; 9]. NICE recommendations advise the use of second-generation ablation techniques when there are no structural or histologic abnormalities in the uterine cavity. If a myomectomy is to be performed hysteroscopically, a first-generation ablation technique is appropriate [1].

Amenorrhea rates with hysteroscopic ablation are about 40% to 50%, and the 12-month satisfaction rate among women with this type of ablation is about 90% [5; 39]. The high degree of satisfaction indicates that reduction of flow is adequate symptom control for most women, and achievement of amenorrhea is not as important. With nonhysteroscopic, second-generation ablations, the thermal balloon gives an amenorrhea rate of 15% and a 12-month satisfaction rate of 90% [39]. Although the amenorrhea rate is lower, the same proportion of women report being satisfied with their results. Results from the radioablation procedure show 36% to 41% amenorrhea at one year and 90% reported satisfaction with the technique (i.e., normal bleeding or less) [24; 39].

There is evidence to support either danazol treatment or a GnRH agonist such as leuprolide to prepare the endometrium for rollerball ablation [39]. However, these agents can have significant side effects and with newer ablation methods may not be necessary. NICE does not recommend endometrial thinning before thermal balloon ablations and microwave ablations [1]. Instead, it simply recommends scheduling microwave ablation just after menstruation.

NICE advises that ablation may be used in women with small (<3 cm) fibroids [1]. The radiofrequency ablation technique has an amenorrhea rate of 69% at one year and a satisfaction rate of 95% when used for fibroids of this size [25].

Hysterectomy

For women who fail both medical management and the less invasive ablation or who decline those options or have anatomic causes of bleeding that preclude ablation, hysterectomy is the definitive surgical treatment. By definition, women who have their uterus and cervix removed will have no further periods. They will not require progesterone supplementation should they undergo estrogen replacement therapy in the future, whereas women treated only with ablation will require this protection for the residual endometrium [5]. The morbidity rate for women undergoing hysterectomy is between 5.2% and 9.4% and the mortality rate is approximately 1 per 1,000 hysterectomies for all indications [26].

Comparing satisfaction rates between hysterectomy and ablation does show higher satisfaction with hysterectomy. It is also worth noting that a retrospective cohort study showed that 10% to 30% of women who underwent endometrial ablation later went on to have a hysterectomy; progression to hysterectomy was highest with rollerball ablation and lowest with cryotherapy [27]. The ACOG has evaluated several studies comparing costs and outcomes between ablation and hysterectomy. They state that endometrial ablation is more cost effective, with less morbidity and a shorter recovery time. However, if up to one-third of women go on to have hysterectomies in the following five years, this could have a significant impact on the cost analysis [5].

Before scheduling a hysterectomy, there should be a documented discussion about the alternatives to surgical removal of the uterus and clear consent from the patient [1]. The route of hysterectomy (e.g., vaginal, abdominal, laparoscopic/robotic, or laparoscopic-assisted vaginal) should be determined by the patient and her surgeon after a careful consideration of risks, adverse effects, comorbid conditions, size of the uterus, presence of fibroids, mobility/descent of the uterus, prior surgeries, and any other gynecologic conditions. The discussion of whether or not to retain ovaries at the time of hysterectomy should also occur at this point.

Dilation and Curettage

Dilation and curettage is not recommended as a treatment for heavy menstrual bleeding, as any reduction in bleeding is temporary [1]. It can be used in emergent or urgent situations in which bleeding is not controlled by pharmacologic methods. It also provides a tissue sample to rule out hyperplasia or malignancy, but this can be more easily and cost effectively done by office endometrial biopsy [9].

ENDOMETRIAL BLEEDING

Endometrial bleeding can have many causes relating to deficiencies in vasoconstrictors, accelerated clot dissolution, increased prostaglandins, inflammation, or infection. There are no clinically available tests for the former causes, and the relationship between the latter causes and bleeding is unclear (with the exception of chlamydial infection of the endometrium, which is known to cause bleeding). Therefore, FIGO considers this a category of exclusion [7]. Treatment is the same as that described for bleeding from ovulatory dysfunction.

IATROGENIC BLEEDING

Iatrogenic causes of uterine bleeding include breakthrough bleeding from steroid administration (e.g., oral contraceptives, progesterone delivery systems). This could be a normal side effect or could be due to poor compliance with patient-dependent delivery methods. Cigarette smoking can enhance hepatic metabolism of steroids and contribute to breakthrough bleeding [7]. Some medications (e.g., rifampin, griseofulvin, certain antibiotics, anticonvulsants) can decrease circulating estrogens and progesterones and produce AUB. As discussed, women on anticoagulants who are experiencing AUB are classified within the category of coagulopathies [7].

Any agent that inhibits serotonin will impact dopamine and prolactin, which can affect ovulation. This is most commonly seen in tricyclic antidepressants and phenothiazines, and in fact, use of these medications places the bleeding in the category of ovulatory dysfunction [7]. Radiation and chemotherapy also can lead to ovulatory dysfunction and abnormal bleeding [11]. Finally, use of specific herbal supplements (e.g., ginseng) can result in abnormal bleeding [18].

NOT YET CLASSIFIED

The relationship between conditions or lesions such as endometriosis, arteriovenous malformations, and/or myometrial hypertrophy and uterine bleeding has been poorly defined, inadequately examined, or both [7]. These are considered to be rare etiologies of AUB. This category also includes any other disorder that has yet to be identified [7].

UTERINE BLEEDING IN SPECIAL POPULATIONS

PEDIATRIC

As noted, a small amount of withdrawal bleeding is normal in newborn girls as maternal estrogen levels dissipate. Any other uterine bleeding in children should be evaluated. On physical exam, other indicators of precocious puberty (pubertal development before 8 years of age), such as breast bud development and height/weight acceleration, should be evaluated [2]. In an unestrogenized, prepubertal girl, the mucosa of the vagina will be red and thin, rather than the pink, thicker tissue associated with puberty and estrogenization [3]. If a diagnosis of precocious puberty, whether central (GnRH dependent, as in central nervous system tumor or injury), peripheral (GnRH independent, as in adrenal or ovarian tumors, among other causes), or idiopathic, referral to a reproductive endocrinology and infertility specialist or endocrine specialist is warranted. Sexual abuse should also be considered in pediatric patients with unexplained bleeding.

PREGNANCY

Any woman of reproductive age experiencing uterine bleeding must be confirmed not to be pregnant before any further work-up or treatment is undertaken. The topic of bleeding in pregnancy is beyond the scope of this course; however, it is important to evaluate a woman with a positive pregnancy test and vaginal bleeding for ectopic pregnancy, threatened or inevitable abortion, or gestational trophoblastic disease [5].

Women who recently delivered a pregnancy can have uterine bleeding over and above normal lochia. These women should be evaluated for retained products of conception, gestational trophoblastic disease, and uterine atony or subinvolution of the uterus [5]. It is normal to experience a temporary increase in lochia and bleeding approximately one week after delivery (ranging from 7 to 14 days), lasting for one to two hours, and usually reassurance is all that is needed [6]. If bleeding is extremely heavy or persistent, it should be evaluated.

POSTMENOPAUSAL BLEEDING

The first concern with postmenopausal bleeding is to rule out uterine cancer. Hyperplasia and neoplasia have been discussed in the PALM-COEIN rubric. As noted, another common cause of bleeding in a postmenopausal woman is simply atrophy of the vulvovaginal tissues. Menopausal atrophy of the endometrium can cause intermittent spotting or bleeding. It is important to rule out any other cause, such as hyperplasia, polyps, or leiomyoma, before attributing bleeding to atrophy [2].

Menopause is a retroactive diagnosis, occurring after 12 months have passed from the last menstrual period. In the perimenopausal years, an irregular bleeding pattern is common. However, 12 months after a woman's last period, any bleeding at all should be evaluated [2].

Treatment of endometrial hyperplasia should follow the guidelines discussed previously in this course. Atrophic endometrium can be treated hormonally to resolve bleeding, although higher-than-usual doses of estrogen may be needed to stop the bleeding. If the bleeding does not respond to hormone treatment, re-evaluation is necessary [28].

As discussed in the section on vaginal bleeding, local estrogen replacement is the most effective treatment for bleeding resulting from vulvovaginal atrophy. Estrogen may be applied topically as a cream or inserted vaginally as a suppository or ring. Soothing ointments may also be used on the atrophic tissues if the woman does not desire hormonal treatment, even locally. Certain dermatoses, such as lichen sclerosus or lichen planus, may require treatment with a high-potency topical steroid ointment [2].

COMMUNICATION WITH NON-ENGLISH-PROFICIENT PATIENTS

Because evaluating and diagnosing AUB is linked so closely to an appropriate patient history and treatment often relies on patient involvement and compliance with recommended plans, communication is a vital aspect of the management of abnormal bleeding. The patient population in the United States is diverse and becoming more so. Therefore, consideration should be given to those patients who are not proficient in spoken and/or written English. When there is an obvious disconnect in the communication process between the practitioner and patient, an interpreter is required.

In this multicultural landscape, interpreters are a valuable resource to help bridge the communication and cultural gap between patients and practitioners. Interpreters are more than passive agents who translate and transmit information back and forth from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, interpreters serve as cultural brokers who ultimately enhance the clinical encounter. When providing care for patients for whom English is a second language, consideration of the use of an interpreter and/or patient education materials in their native language may improve patient understanding and outcomes.

CONCLUSION

Vaginal and uterine bleeding are common complaints seen by primary care providers and urgent/emergent care providers. Although there are many possible etiologies of bleeding, a systematic approach to determining the cause of bleeding will help elucidate the proper treatment options. The aim of the PALM-COEIN mnemonic developed by FIGO is to provide a consistent method of description across various disciplines. Standardization of language also serves this purpose. It is also important to keep in mind that etiologies of bleeding may vary by the age group of the presenting patient.

GLOSSARY OF TERMS

Acanthosis nigricans: a disorder in which there are skin changes characterized by darkened areas, typically over the nape of the neck and axillae, seen with insulin resistance.

Adenocarcinoma: cancer derived from glandular tissue or that forms glandular structures.

Adenomyosis: invasion of endometrial glands and stroma into the myometrium, usually causing hypertrophy of the myometrium.

Anovulatory/anovulation: the absence of ovulation.

Antifibrinolytic: inhibiting the breakdown of fibrin and therefore the breakdown of clots.

Atony: lacking tone.

Atrophy: thinning of tissues or cells.

Coagulopathy: a disorder of blood coagulation.

Colposcopy: examination of the cervix through a magnifying scope.

Condyloma: warts caused by the human papillomavirus.

Congenital adrenal hyperplasia: a group of inherited disorders characterized by enzyme deficiencies and hyperplasia of the adrenal glands and hyperandrogenemia.

Dilation and curettage: a procedure wherein the cervical os is dilated and a blunt suction curette or sharp metal curette is used to remove uterine contents and denude the lining of the endometrium.

Dysmenorrhea: painful menstruation.

Ecchymosis: bruising.

Ectopic pregnancy: a pregnancy implanted outside of the uterine cavity.

Embolization: using a substance to occlude a blood vessel.

Embryonal rhabdomyosarcoma (sarcoma botryoides): a vaginal tumor appearing as a polypoid, grape-like structure.

Endocervical curettage: scraping the endocervix to gather cells for diagnosis, usually at the time of colposcopy.

Endometrial ablation: destruction of the lining of the uterus by mechanical means.

FSH: follicle-stimulating hormone.

Gestational trophoblastic disease: a group of pregnancy-related tumors (benign or malignant) formed of placental and/or fetal tissue.

GnRH: gonadotropin-releasing hormone.

Hemangioma/cavernous hemangioma: a benign tumor made up of blood vessels.

Hyperplasia: abnormally elevated number of cells in a tissue.

Hypogonadism: decreased gonadal function.

Hysterectomy: surgical removal of the uterus that may or may not involve removing the cervix, fallopian tubes, and ovaries.

Hysteroscopy: using a camera to view the inside of the uterus.

Iatrogenic: caused by medical intervention.

Idiopathic thrombocytopenic purpura (ITP): abnormally low platelets, thought to be of immune origin.

Inevitable abortion: spontaneous abortion in progress, with an open cervical os.

Intracavitary: within the uterine cavity.

Intramural fibroids: benign tumors contained within the muscular wall of the uterus.

Leukemia: cancer of the blood or bone marrow, leading to abnormally high levels of white blood cells.

LH: luteinizing hormone.

Lichen planus: inflammatory disorder of the vulva or oral mucosa.

Lichen sclerosus: atrophic skin disease of the vulva that destroys vulvar architecture and causes scarring. Rarely precedes squamous cell carcinoma.

Lochia: vaginal discharge after delivery, mainly consisting of blood, mucus, and white blood cells.

Menopause: a retrospective diagnosis made after menses have ceased for 12 months or longer.

Myomectomy: surgical removal of one or more fibroids from the uterus.

Myometrium: the muscular wall of the uterus lined on the inside by the endometrium and the outside by the serosa.

Nulliparity: the state of never having been pregnant.

Pedunculated: hanging on a stalk.

Perimenopause: the period of several years before actual menopause when symptoms such as hot flushes and irregular menses are common.

Petechiae: tiny hemorrhages.

Precocious puberty: puberty occurring at an abnormally early age.

Prolapse: displacement of an organ from its usual position.

Pruritus: itching.

Psoriasis: dermatitis characterized by scaling patches.

Resectoscope: a hysteroscope (or cystoscope) fitted with an electric-wire loop to biopsy or remove lesions.

Sarcoma: malignant tumor derived from connective tissue.

Seborrheic dermatitis: dermatitis characterized by excessive secretion of sebum.

Serosa: a serous membrane, usually lining organs or body cavities.

Submucosal fibroids: benign tumors protruding into the uterine cavity.

Subserosal fibroids: benign tumors on the external surface of the uterus.

Threatened abortion: vaginal bleeding in pregnancy with a viable fetus and a closed cervical os.

TSH: thyroid-stimulating hormone.

Vasopressin: a hormone that stimulates contraction of the muscular layers of capillaries and arterioles. Used in gynecologic surgery to decrease blood flow to fibroids before their removal.

von Willebrand disease: inherited bleeding disorder with a deficiency of coagulation Factor VIII.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

Works Cited

1. National Collaborating Center for Women's and Children's Health. *National Institute for Health and Care Excellence Clinical Guidelines: Heavy Menstrual Bleeding*. Available at https://www.nice.org.uk/guidance/qs47. Last accessed August 20, 2021.
2. Curtis MG, Linares ST, Antoniewicz L. *Glass' Office Gynecology*. 7th ed. Philadelphia, PA: Lipincott Williams & Wilkins; 2014.
3. Emans SJ, Laufer MR. *Emans, Laufer, Goldstein's Pediatric and Adolescent Gynecology*. 6th ed. Philadelphia, PA: Lipincott Williams & Wilkins; 2012.
4. Tewari D. Invasive Cervical Cancer. Lecture presented at: 32nd Annual Review Course in Clinical Obstetrics and Gynecology; October 20, 2009; Costa Mesa, CA.
5. American College of Obstetricians and Gynecologists Committee on Practice Bulletins. Practice bulletin no. 136: management of abnormal uterine bleeding associated with ovulatory dysfunction. *Obstet Gynecol*. 2013;122(1):176-185. [Reaffirmed 2018].
6. Gabbe SG, Niebyl FR, Simpson FL, et al. *Obstetrics, Normal and Problem Pregnancies*. 7th ed. Philadelphia, PA: Elsevier; 2016.
7. Munro MG, Critchley HO, Fraser IS. The FIGO classification of causes of abnormal uterine bleeding. *Int J Gynaecol Obstet*. 2011;113:3-13.
8. Fraser IS, Critchley HO, Munro MG, Broder M. Can we achieve international agreement on terminologies and definitions used to describe abnormalities of menstrual bleeding? *Hum Reprod*. 2007;22(3):635-643.
9. Lobo RA, Gershenson DM, Lentz GM, Valea FA. *Comprehensive Gynecology*. 7th ed. Philadelphia, PA: Elsevier Mosby; 2016.
10. American College of Obstetricians and Gynecologists. Alternatives to hysterectomy in the management of leiomyomas. *Obstet Gynecol*. 2008;112(2 pt 1):387-400.
11. Vuchinich KM. Abnormal Uterine Bleeding/Fibroids. Lecture presented at: 32nd Annual Review Course in Clinical Obstetrics and Gynecology; October 17, 2009; Costa Mesa, CA.
12. Day Baird D, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. *Am J Obstet Gynecol*. 2003;188(1):100-107.
13. Marjoribanks J, Lethaby A, Farquhar C. Surgery versus medical therapy for heavy menstrual bleeding. *Cochrane Database Syst Rev*. 2016;1:CD003855.
14. Marshall LM, Spiegelman D, Goldman MB, et al. A prospective study of reproductive factors and oral contraceptive use in relation to the risk of uterine leiomyomata. *Fertil Steril*. 1998;70(3):432-439.
15. Mercorio F, De Simone R, Di Spiezio Sardo A, et al. The effect of a levonorgestrel-releasing intrauterine device in the treatment of myoma-related menorrhagia. *Contraception*. 2003;67(4):277-280.
16. American College of Obstetricians and Gynecologists. The role of transvaginal ultrasonography in the evaluation of postmenopausal bleeding. *Obstet Gynecol*. 2009;113(2 pt 1):462-464.
17. Chi DS, Berchuck A, Dizon DS, Yashar CM (eds). *Principles and Practice of Gynecologic Oncology*. 7th ed. Philadelphia, PA: Lipincott Williams & Wilkins; 2017.
18. Fritz MA, Speroff L. *Clinical Gynecologic Endocrinology and Infertility*. 8th ed. Baltimore, MD: Lipincott Williams & Wilkins; 2012.
19. Randall L. Endometrial Cancer. Lecture presented at: 32nd Annual Review Course in Clinical Obstetrics and Gynecology; October 20, 2009; Costa Mesa, CA.
20. Baker J, Obermair A, Gebski V, Janda M. Efficacy of oral or intrauterine device-delivered progestin in patients with complex endometrial hyperplasia with atypia or early endometrial adenocarcinoma: a meta-analysis and systematic review of the literature. *Gynecol Oncol*. 2012;125(1):263-270.
21. Moayeri SE. Polycystic Ovary Syndrome. Lecture presented at: 32nd Annual Review Course in Clinical Obstetrics and Gynecology; October 16, 2009; Costa Mesa, CA.
22. National Cancer Institute. SEER Cancer Statistics Review, 1975–2018. Available at https://seer.cancer.gov/csr/1975_2018. Last accessed August 20, 2021.
23. DeVore GR, Owens O, Kase N. Use of intravenous Premarin in the treatment of dysfunctional uterine bleeding: a double-blind randomized controlled study. *Obstet Gynecol*. 1982;59(3):285-291.
24. Cooper J, Gimpelson R, Laberge P. A randomized, multicenter trial of safety and efficacy of the NovaSure system in the treatment of menorrhagia. *J Am Assoc Gynecol Laprosc*. 2002;9(4):418-428.
25. Sabbah R, Desaulniers G. Use of the NovaSure Impedance Controlled Endometrial Ablation System in patients with intracavitary disease: 12-month follow-up results of a prospective, single-arm clinical study. *J Minim Invasive Gynecol*. 2006;13(5):467-471.
26. Kafy S, Huang JY, Al-Sunaidi M, Wiener D, Tulandi T. Audit of morbidity and mortality rates of 1792 hysterectomies. *J Minim Invasive Gynecol*. 2006;13(1):55-59.
27. Shavell VI, Diamond MP, Senter JP, Kruger ML, Johns DA. Hysterectomy subsequent to endometrial ablation. *J Minim Invasive Gynecol*. 2012;19(4):459-464.
28. Oriel KA, Schrager S. Abnormal uterine bleeding. *American Family Physician*. 1999;60(5):1371-1382.

29. Spies JB, Bruno J, Czeyda-Pommershein F, et al. Long-term outcome of artery embolization of leiomyomata. *Obstet Gynecol*. 2005;106(5 pt 1):933-939.
30. National Cancer Institute. Cervical Cancer Screening (PDQ). Available at https://www.cancer.gov/types/cervical/hp/cervical-screening-pdq. Last accessed August 20, 2021.
31. Workowski KA, Bolan GA. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep*. 2015;64(RR-03):1-137.
32. American College of Obstetricians and Gynecologists Committee on Adolescent Health Care, Committee on Gynecologic Practice. Committee Opinion No. 580: von Willebrand disease in women. *Obstet Gynecol*. 2013;122(6):1368-1373.
33. Senol T, Kahramanoglu I, Dogan Y, Baktiroglu M, Karateke A, Suer N. Levonorgestrel-releasing intrauterine device use as an alternative to surgical therapy for uterine leiomyoma. *Clin Exp Obstet Gynecol*. 2015;42(2):224-227.
34. Kudesia R, Singer T, Caputo TA, et al. Reproductive and oncologic outcomes after progestin therapy for endometrial complex atypical hyperplasia or carcinoma. *Am J Obstet Gynecol*. 2014;210(3):255.e1-e4.
35. Office on Women's Health. Polycystic Ovary Syndrome. Available at https://www.womenshealth.gov/a-z-topics/polycystic-ovary-syndrome. Last accessed August 20, 2021.
36. National Cancer Institute. SEER Stat Fact Sheets: Endometrial Cancer. Available at https://seer.cancer.gov/statfacts/html/corp.html. Last accessed August 20, 2021.
37. American College of Obstetricians and Gynecologists Committee on Adolescent Health Care, Committee on Gynecologic Practice. Committee opinion no. 557: management of acute abnormal uterine bleeding in nonpregnant reproductive-aged women. *Obstet Gynecol*. 2013;121(4):891-896.
38. Lethaby A, Duckitt K, Farquhar C. Non-steroidal anti-inflammatory drugs for heavy menstrual bleeding. *Cochrane Database Syst Rev*. 2013:31;1:CD000400.
39. Lipscomb GH. Endometrial Ablation. Available at https://www.glowm.com/section-view/heading/Endometrial%20Ablation/item/24. Last accessed August 20, 2021.
40. Sparic R, Mirkovic L, Malvasi A, Tinelli A. Epidemiology of uterine myomas: a review. *Int J Fertil Steril*. 2016;9(4):424-435.
41. Zhang Q, Qi G, Kanis MJ, Dong R, Cui B, Yang X, Kong B. Comparison among fertility-sparing therapies for well differentiated early-stage endometrial carcinoma and complex atypical hyperplasia. *Oncotarget*. 2017;8(34):57642-57653.
42. Williams T, Mortada R, Porter S. Diagnosis and treatment of polycystic ovary syndrome. *Am Fam Physician*. 2016;94(2):106-113.
43. Goodman NF, Cobin RH, Futterweit W, et al. American Association of Clinical Endocrinologists, American College of Endocrinology, and Androgen Excess and PCOS Society disease state clinical review: guide to the best practices in the evaluation and treatment of polycystic ovary syndrome—part 1. *Endocr Pract*. 2015;21(11):1291-1300.
44. Goodman NF, Cobin RH, Futterweit W, et al. American Association of Clinical Endocrinologists, American College of Endocrinology, and Androgen Excess and PCOS Society disease state clinical review: guide to the best practices in the evaluation and treatment of polycystic ovary syndrome—part 2. *Endocr Pract*. 2015;21(12):1415-1426.
45. U.S. Food and Drug Administration. Product Labeling for Laparoscopic Power Morcellators. Available at https://www.fda.gov/media/90012/download. Last accessed August 20, 2021.
46. American College of Obstetricians and Gynecologists. Committee Opinion 532: Compounded Bioidentical Menopausal Hormone Therapy. Available at https://www.acog.org/Clinical-Guidance-and-Publications/Committee-Opinions/Committee-on-Gynecologic-Practice/Compounded-Bioidentical-Menopausal-Hormone-Therapy. Last accessed August 20, 2021.
47. Johnstone EB, Rosen MP, Neril R, et al. The polycystic ovary post-Rotterdam: a common, age-dependent finding in ovulatory women without metabolic significance. *J Clin Endocrinol Metab*. 2010;95:4965-4972.
48. Lethaby A, Hussain M, Rishworth JR, Rees MC. Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding. *Cochrane Database Syst Rev*. 2015;(4):CD002126.
49. Wouk N, Helton M. Abnormal uterine bleeding in premenopausal women. *Am Fam Physician*. 2019;99(7):435-443.

Evidence-Based Practice Recommendations Citations

American College of Radiology. *ACR Appropriateness Criteria: Abnormal Vaginal Bleeding*. Reston, VA: American College of Radiology; 2020. Available at https://acsearch.acr.org/docs/69458/Narrative. Last accessed August 20, 2021.

North American Menopause Society. The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society. *Menopause*. 2020;27(9):976-992. Available at https://www.menopause.org/docs/default-source/default-document-library/2020-gsm-ps.pdf. Last accessed August 20, 2021.

American College of Obstetricians and Gynecologists. *Endometrial Ablation*. Washington, DC: American College of Obstetricians and Gynecologists; 2007, 2018. Available at https://journals.lww.com/greenjournal/Citation/2007/05000/ACOG_Practice_Bulletin_No__81__Endometrial.43.aspx. Last accessed August 20, 2021.