Abnormal Uterine Bleeding

Sonia Elguero, Bansari Patel, Anna V. Jones, and William W. Hurd

Contents

T. Falcone, W. W. Hurd (eds.), *Clinical Reproductive Medicine and Surgery*,
https://doi.org/10.1007/978-3-030-99596-6_8

Key Points

- Abnormal vaginal bleeding is one of the most common gynecologic problems of reproductive-aged women.
- Abnormal uterine bleeding (AUB) is an important subset of abnormal vaginal bleeding defined as bleeding that occurs in nonpregnant, reproductive-aged women originating from the uterine fundus or cervix.
- The **PALM-COEIN** classification system advocated by ACOG includes many of the most common causes of AUB.
- The **SPIN** (**S**ystemic, **P**regnancy, **I**nfection, **N**eoplasms) classification system offers a comprehensive system for managing women with abnormal vaginal bleeding.
- Pregnancy should be excluded in all reproductive-aged women presenting with presumed AUB.
- The most common cause of AUB is anovulatory bleeding, often related to polycystic ovary syndrome, but also commonly occurring in the healthy peri-menarcheal and perimenopausal women.
- AUB related to structural abnormalities is most commonly treated surgically; AUB in women with normal pelvic anatomy can usually be managed medically with hormones, antibiotics, antifibrinolytics, nonsteroidal anti-inflammatory drugs, or a combination of these.

8.1 Introduction

Vaginal bleeding that occurs outside the parameters of normal menstruation is one of the most common clinical problems confronting women and their gynecologists. The possible etiologies of abnormal vaginal bleeding range from a temporary interruption of the normal menstrual cycle to the earliest symptom of a potentially life-threatening condition. Chronic abnormal vaginal bleeding impairs quality of life as a result of significant physical, emotional, sexual, social, and financial burdens [1].

Abnormal uterine bleeding (AUB) is a subset of abnormal vaginal bleeding where vaginal bleeding originates from either the uterine fundus or cervix and does not include bleeding related to pregnancy or that originating in the lower genital tract [2]. AUB can be described according to bleeding pattern using terms such as heavy menstrual bleeding; nonmenstrual bleeding that is irregular, intermenstrual, or prolonged; or any combination of these bleeding patterns.

Experienced clinicians are well aware that what *appears to be* AUB has a broad spectrum of possible causes and can be related to pregnancy or originate from non-uterine sources, including the vagina, bladder, or rectum. With this in mind, every gynecologist must develop a thorough and cost-effective approach to the diagnosis and management of abnormal vaginal bleeding. The ability to expediently evaluate and treat women with abnormal vaginal bleeding depends on a broad understanding of its various causes and their diverse presentations.

Case Vignette

A 37-year-old G0 P0 presents to her gynecologist's office with profuse vaginal bleeding that began the prior evening. Her gynecologic history is significant for a diagnosis of polycystic ovary syndrome (PCOS) and only 3–4 menses per year. She is not using any contraceptive method but has not been able to get pregnant for 3 years. Her vital signs are stable, and she has no symptoms other than bleeding. Her pelvic exam reveals clots in the vagina and blood actively coming from a normal-appearing cervix. Bimanual pelvic examination, made difficult by her obesity, does not reveal uterine or adnexal masses or tenderness. Pelvic ultrasound shows a normal-sized anteverted uterus with a 16 mm endometrial stripe and what appear to be clots in the uterine cavity. Laboratory evaluation includes a negative urine pregnancy test, white blood cell count of 9500 per mcL, hemoglobin of 8.8 g/dL, and platelet count of 250,000 per mcL. Other laboratory results are pending.

8.1.1 Prevalence

Abnormal vaginal bleeding is one of the most common chief complaints for which women see obstetrician-gynecologists. AUB accounts for approximately 30% of all gynecology visits [3]. Despite its frequency, AUB remains a difficult diagnostic and therapeutic challenge and still accounts for 10–20%of all hysterectomies performed in the USA [4]. In years past, approximately 20% of hysterectomy specimens removed for AUB have no discernible pathology [5]. More recently, the use of hysterectomy to treat AUB has decreased as more of these patients are treated using effective medical or minimally invasive surgical modalities.

8.1.2 Terminology

The narrowly defined term AUB refers only to vaginal bleeding that occurs outside the parameters of normal menstruation and (a) originates from the uterine fundus or cervix, (b) occurs during the reproductive years, and is (c) unrelated to pregnancy [2]. AUB is characterized in terms of volume, duration, frequency, regularity, and chronicity. The arcane terms "menorrhagia" and "metrorrhagia" have been recommended for replacement with the simplified terms "heavy menstrual bleeding" and "intermenstrual bleeding," although both sets of terms remain in common usage. When AUB has persisted for 6 months or more, it is termed "chronic."

The single most common cause of AUB is anovulatory bleeding resulting from exposure of the endometrium to estrogen, unopposed by progesterone. Anovulatory bleeding has been classified by the International Federation of Gynaecology and Obstetrics (FIGO) as "Abnormal uterine bleeding associated with ovulatory dysfunction (AUB-O)". A similar, outdated term is "dysfunctional uterine bleeding" (DUB) defined as excessive uterine bleeding when no uterine pathology can be identified [6]. Use of the term DUB is discouraged because it encompasses a wide array of unrelated nonanatomical causes of bleeding that can almost always be identified using the more sophisticated diagnostic techniques available today [7]. The ability of clinicians to identify a specific etiology for the vast majority of AUB has resulted in an increased likelihood of effective treatment for AUB without having to resort to hysterectomy.

8.2 Normal Menstrual Cycle and Menstruation

A solid understanding of the normal menstrual cycle is essential to effectively evaluate and treat women with abnormal vaginal bleeding. Complex interactions between the hypothalamus, pituitary, and ovary (see ► Chap. 1) result in monthly ovulation, which leads to either pregnancy or menstruation within approximately 2 weeks. Each month, the endometrium of normally ovulating women is exposed to physiologic levels of estradiol (50–250 pg/mL), accompanied in the last 12–14 days of each cycle by progesterone (mid-luteal phase progesterone >12 nmol/L). The result is a structurally stable endometrium 5–16 mm thick as measured by transvaginal ultrasound.

Menstruation is the universal breakdown and uniform shedding of the endometrial functional layer. Unless pregnancy occurs, involution of the corpus luteum results in rapid decreases in both progesterone and estrogen. This hormonal withdrawal activates matrix metalloproteinases, which enzymatically dissolve the endometrium [8]. Hemostasis is achieved by a combination of vasoconstriction of the spiral arterioles and normal coagulation mechanisms. Normal menstruation occurs every 28 ± 7 days with duration of flow of 4 ± 2 days and a blood loss of 40 ± 40 mL [9].

Normal menstruation should not cause severe pain or include passage of large clots. However, what constitutes "normal" menstruation is subjective and varies between individual women and between cultures. In most women, 90% of blood loss per cycle occurs within the first 3 days of menstruation [10]. The amount of blood lost during a normal menstrual period should be <80 mL. However,

menstrual blood loss is extremely difficult to estimate clinically as much of the menstrual effluent is dissolved endometrium rather than blood. Clinically, heavy menstrual bleeding (i.e., menorrhagia or AUB-H) is diagnosed when a woman is changing pads or tampons more than once per hour.

8.3 Diagnostic Classifications

Classification systems have been developed to organize the multiple possible etiologies of abnormal vaginal bleeding. The most widely used is the PALM-COEIN classification for AUB, developed by the FIGO and endorsed by the American College of Obstetricians and Gynecologists (ACOG) [2] [11]. This system classifies the majority of AUB etiologies as either structural or nonstructural using the PALM-COEIN acronym as a memory aid (▶ Box 8.1).

Box 8.1 PALM-COEIN Classification for Abnormal Uterine Bleeding (AUB)

- PALM (structural)
  - Polyp
  - Adenomyosis
  - Leiomyoma
  - Malignancy and hyperplasia
- COEIN (nonstructural)
  - Coagulopathy
  - Ovulatory dysfunction
  - Endometrial
  - Iatrogenic
  - Not yet classified

The PALM-COEIN classification system, although simple, has its limitations. In order to form a memorable mnemonic, this classification uses several imprecise terms (e.g., endometrial, iatrogenic, not yet classified). Another limitation is that it does not include a number of relatively common causes of AUB, including endometritis, cervicitis, cervical dysplasia, hypothyroidism, and hyperprolactinemia. A third limitation of this classification is that it classifies only vaginal bleeding originating from the nonpregnant uterus, thus excluding both pregnancy-related bleeding and bleeding originating from elsewhere within the reproductive tract (e.g., vagina). In clinical practice, all sources and possible causes must be considered in every patient presenting with abnormal vaginal bleeding.

With this in mind, we have constructed a comprehensive classification of abnormal vaginal bleeding based on the acronym **SPIN** (**S**ystemic, **P**regnancy, **I**nfection, **N**eoplasms) and subcategorized according to anatomic locations where appropriate (Table 8.1). The remainder of this chapter will examine the various causes of abnormal vaginal bleeding using this **SPIN** classification.

8.4 Systemic Causes of AUB

Monthly menstruation depends on a systemic orchestration of a number of hormones originating in the brain and ovaries. Anything that disrupts this coordinated process will manifest as anovulation and AUB. Thus, anovulatory dysfunction can be either a primary process or secondary to other systemic diseases that interfere with hormone production or metabolism. AUB also includes the disruptive effects of exogenous hormones taken for contraception.

8.4.1 Ovulatory Dysfunction

Ovulatory dysfunction is the final common pathway connecting systemic disorder to AUB. Anovulation is the result of disruption of the complex hormonal process involved in ovulation on either a temporary or chronic basis and is one of the most common causes of AUB. It can be a primary problem or secondary to an identifiable disease process (▶ Box 8.2). Occasional anovulation is common in the early and late reproductive years. Chronic ovulatory dysfunction is a central characteristic of the most common endocrine abnormality of reproductive-aged women, polycystic ovary syndrome (PCOS). Anovulation can also be the most obvious manifestation of a number of other systemic conditions.

Table 8.1 SPIN classification

	Uterine fundus	Cervix	Adnexa	Vagina	Other
Systemic	–	–	–	–	Anovulatory bleeding Systemic conditions Hormone therapy Coagulopathy
Pregnancy	Viable pregnancy Spontaneous abortion Molar pregnancy	Ectopic pregnancy	Ectopic pregnancy	–	–
Infection	Endometritis	Cervicitis	Pelvic inflammatory disease	Vaginitis	–
Neoplasms	Fibroids Polyps Adenomyosis Hyperplasia Cancer	Polyp Dysplasia Cancer	Cancer	Cancer	–

8

Box 8.2 Causes of Ovulation Dysfunction

- Physiologic oligo-ovulation:
  - Perimenarchal
  - Perimenopasual
  - Papanicolaou smear
  - Polycystic ovary syndrome
  - Hyperandrogenic states
  - Congenital adrenal hyperplasia, adultonset
  - Cushing's syndrome
  - Ovarian and adrenal tumors
  - Systemic diseases that interfere with ovulation
  - Hypothyroidism
  - Hyperprolactinemia
  - Renal failure
  - Liver disease

8.4.2 Mechanisms of Bleeding in Anovulatory Patients

The mechanism of bleeding in anovulatory patients depends on whether the estrogen levels are normal or low, which in turn depends on etiology. In the absence of postovulatory progesterone, prolonged endometrial exposure to unopposed estrogen results in breakthrough bleeding which can manifest clinically in dramatically different ways ranging from spotting to massive hemorrhage. Chronically low estrogen levels result in endometrial atrophy which can also result in AUB.

8.4.2.1 Estrogen Breakthrough Bleeding

Endometrial stimulation by estrogen results in endometrial growth, manifested as increased endometrial stroma and glands, and increased size and depth of the spiral arteries supplying the endometrium [12]. In contrast, endometrial stimulation by progesterone results in decreased endometrial proliferation and thickness, increased structural support, and development of more complex, glycogen-filled glands. In the absence of cyclic progesterone exposure, prolonged endometrial exposure to normal estrogen levels results in increased thickness and structurally incompetent. Rather than the universal endometrial

shedding that occurs in menstruation, asynchronous shedding of portions of the endometrium results in bleeding unaccompanied by vasoconstriction, termed estrogen breakthrough bleeding.

Estrogen breakthrough bleeding can manifest in a variety of different ways, including occasional spotting, prolonged periods of moderate bleeding, and/or infrequent and potentially life-threateningly heavy AUB. Since the blood resulting from breakthrough bleeding is not lysed by endometrial enzymes, blood clots are often passed, usually resulting in increased menstrual cramping. Prolonged periods of bleeding without universal endometrial shedding can result in subclinical endometritis, which can further exacerbate bleeding by interfering with normal clotting mechanisms, thus making the endometrium unresponsive to hormonal therapy [13].

In addition to breakthrough bleeding, prolonged endometrial exposure to unopposed estrogen can result in the development of endometrial polyps, endometrial hyperplasia, and endometrial cancer. In turn, these conditions can result in persistent AUB unresponsive to hormonal therapy.

8.4.2.2 Endometrial Atrophy

Endometrial atrophy can result from prolonged periods of exposure to low estrogen levels, exogenous progestins, or elevated androgens. Prolonged low estrogen levels result in atrophy of both endometrial glands and stroma. Histologically, scanty, small glands are observed in dense stroma. Secretory changes are minimal, but stromal decidualization is present, resulting in discordance between small inactive glands and decidualized stroma. Numerous granular lymphocytes are often present. Transvaginal ultrasonography will reveal an endometrial thickness of <4 mm.

AUB resulting from endometrial atrophy is the result of inflammation and is usually described as spotting [12]. Atrophic endometrium lacks the fluid present in healthy endometrium that prevents intracavitary friction between apposing endometrial surfaces. This friction results in surface epithelium micro-erosions and a chronic inflammatory reaction that results in a cascade of events similar to chronic endometritis as discussed in ▶ Sect. 8.6.2.

8.4.3 Causes of Ovulatory Dysfunction

The complex interactions of the hypothalamic-pituitary-ovarian (HPO) axis can be easily perturbed, resulting in anovulation. Typically, women ovulate monthly throughout their reproductive years. However, occasional anovulation is not uncommon among reproductive-aged women not using hormonal contraception. Chronic anovulation occurs in >10% of all reproductive-aged women.

8.4.3.1 Extremes of the Reproductive Years

Adolescents often have anovulatory cycles during the peri-menarchal years as part of the maturation process of the hypothalamic-pituitary-ovarian axis [14]. In the peri-menopausal years (40–50 years of age), anovulatory cycles again become more common as the remaining antral follicles become less sensitive to LH and FSH, resulting in a higher prevalence of anovulatory cycles [15]. In both groups, occasional anovulation results in increased and variable menstrual cycle length and can result in clinically significant AUB.

8.4.3.2 Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is the single most common cause of ovulatory dysfunction, affecting 6–10% of reproductive-aged women [16]. PCOS is a heterogeneous endocrine and metabolic disorder that is diagnosed when a woman without an underlying medical condition is found to have two out of the following three criteria: (1) oligo- or anovulation, (2) clinical and/or biochemical evidence of hyperandrogenemia, and (3) polycystic ovaries [17]. These women have circulating estrogen levels in the normal range, but anovulatory progesterone levels.

Insulin resistance is believed to be the underlying cause of PCOS in many women, particularly those who are obese. However, as many as 50% of women with PCOS are not obese [18]. Insulin resistance will be found in approximately 95% of women with PCOS who are obese, but <25% of those who are not obese [19].

In women with insulin resistance, elevated insulin levels appear to stimulate increased androgen production by the ovaries, primarily androstenedione and testosterone [20]. Insulin increases androgen secretion by both theca cells and ovarian stroma cells. These increased androgens can contribute to hirsutism and may contribute to the increased body mass often seen in PCOS patients. These androgens can be aromatized peripherally in both fat and muscle to estrogen (primarily estrone), which acts on the pituitary to increase secretion of LH, stimulating the ovaries to secrete more androgens in concert with insulin. The positive feedback loop that results is believed to be the cause of PCOS in insulin-resistant women. The accuracy of this interpretation is supported by the observation that in many overweight patients, either weight loss or the use of an insulin-sensitizing agent (e.g., metformin) will simultaneously improve insulin resistance and restore regular ovulatory cycles.

8.4.3.3 Systemic Conditions Mimicking PCOS

Some patients with oligo- or anovulatory that appear to have PCOS actually have an underlying systemic disease. Systemic medical conditions that can result in signs and symptoms identical to PCOS can be divided into two groups: conditions that cause hyperandrogenemia and systemic illnesses.

Any condition that causes hyperandrogenemia can interfere with ovulation and result in a clinical syndrome often indistinguishable from PCOS [21]. Most common among these are nonclassic ("adult-onset") congenital adrenal hyperplasia (CAH), Cushing's syndrome or disease, and androgen-secreting neoplasms of the ovaries or adrenal glands. Nonclassic CAH should be suspected whenever PCOS symptoms occur simultaneously with menarche. Cushing's and androgen-secreting tumors should be suspected when hyperandrogenism and ovulation dysfunction present rapidly in a woman with previously normal menstrual cycles.

The primary purpose of measuring androgen levels in women with PCOS is to detect pathologic conditions associated with hyperandrogenemia that can mimic PCOS. Women with PCOS often have mildly elevated dehydroepiandrosterone sulfate (DHEAS), or free and/or total testosterone, and these elevations fulfill the PCOS diagnostic criteria for hyperandrogenemia. Marked elevation of DHEAS is an indication of adrenal dysfunction or tumor. Substantial elevation of total testosterone most likely indicates the presence of an ovarian or adrenal tumor. Marked elevation of either DHEAS or testosterone requires careful imaging of the ovaries with transvaginal ultrasound and the adrenal glands with computerized tomography. Any elevation of 17-hydroxyprogesterone suggests the presence of nonclassic CAH.

Serious systemic illness can mimic PCOS by chronically interrupting ovulation. Both hypothyroidism and hyperprolactinemia are relatively common conditions that can present with ovulatory dysfunction as the initial manifestation. Accordingly, all women presenting with what appears to be PCOS should be screened with a TSH and prolactin.

Serious systemic disease, such as chronic liver or kidney disease, often results in chronic ovulatory dysfunction and infertility [22, 23]. Liver dysfunction appears to interfere with ovulation by hindering steroid hormone metabolism, whereas the mechanisms by which chronic kidney disease results in anovulation are uncertain. In general, patients with liver or kidney disease significant enough to impair ovulation will have other recognizable symptoms of their disease process [24]. Women with AUB and symptoms of serious liver or kidney disease should undergo targeted evaluation for their condition.

8.4.3.4 Hypogonadism

Cessation of ovarian function, either primary (e.g., menopause, premature ovarian insufficiency) or central (i.e., secondary to hypothalamic-pituitary dysfunction), manifests as anovulation and hypoestrogenemia, and consequent endometrial atrophy. Although amenorrhea is more common in this situation, AUB can result, usually in the form of spotting.

The most common cause of hypoestrogenemia is cessation of ovarian function. Menopause, the physiologic loss of ovarian function, occurs at an average age of approximately 51 years, but occurrence any time after the age of 40 is considered to be within the normal range [25]. Premature menopause before the age of 40 years of age, i.e., primary ovarian insufficiency (POI), occurs in approximately 1% of women. Women diagnosed with POI should be further evaluated for a number of possible causes (see ► Chap. 6).

With normally functioning ovaries, hypogonadism results from lack of gonadal hormonal stimulation secondary to hypothalamic or pituitary dysfunction, collectively referred to as hypogonadotropic hypogonadism. Hypothalamic amenorrhea can be secondary to congenital or acquired hypothalamic pathology (e.g., Kallmann syndrome or hypothalamic tumors), the result of chronic physiologic stress (e.g., excessive exercise, eating disorders), or idiopathic. Pituitary tumors, most commonly prolactinomas, can result in hypogonadism related to hyperprolactinemia. When hypogonadism is suspected, screening tests should include prolactin, FSH, LH, and estradiol. Further investigation will depend on the age of the patient, as discussed in ► Chap. 6.

8.4.4 Hormonal Therapy and AUB

Irregular uterine bleeding is one of the most common complaints of women receiving exogenous hormone therapy, e.g., hormone contraceptives or hormone replacement therapy (see ► Chaps. 9 and 25). AUB is the most common reason for discontinuation of these hormone therapies.

8.4.4.1 Hormone Contraceptives

At least ten million women in the USA are using some type of hormonal contraception, including combination oral contraceptives, progestin-only pills, depot medroxyprogesterone acetate injections, progestin-containing intrauterine devices, subdermal levonorgestrel implants, transdermal combination hormone patches, or intravaginal rings. For these women, AUB is a frequent reason to visit primary care physicians and gynecologists, and a common reason for discontinuing a number of different types of contraception [26].

During the first 3 months of combination oral contraceptive use, as many as one-third of women will experience AUB. For the vast majority of women, the most effective treatment approach is reassurance and watchful waiting. As the uterus adapts to the new regimen of hormonal exposure, the monthly withdrawal bleeding becomes regular, lighter, and less painful than natural menstruation in most women.

If abnormal bleeding persists beyond the first 3 months of hormonal contraceptive use, other common causes should be excluded. Subclinical uterine infections remain a problem for some subgroups of sexually active women, and sexually transmitted diseases should be excluded. One study of women with intermenstrual spotting while on oral contraceptives found that one-third had otherwise asymptomatic *Chlamydia trachomatis* infections [27].

Once infectious causes have been excluded, an often effective treatment of AUB for women on combined oral contraceptives is changing to a different oral contraceptive formulation. Women on low estrogen dose formulations often benefit from changing to a higher estrogen dose. Those on monophasic formulations might have better success with multiphasic contraceptives and vice versa.

Women using continuous combined formulations or progestin-only contraceptives (oral or implant) can have AUB related to endometrial atrophy resulting from prolonged progesterone exposure (see ► Sect. 8.4.2.2). For those using continuous combined formulations, taking a week off the pills will often allow endome-

trial regeneration and AUB resolution. Those using progestin-only oral contraceptives might have to switch to combined oral contraceptives. Women using progestin implants can be treated with the addition of supplemental oral estrogen or low-dose combination oral contraceptives for 2–3 months. Persistent irregular bleeding is a common reason for discontinuation of these contraception methods.

8.4.5 Coagulopathies

Persistent menorrhagia can be the result of any condition that interferes with the body's normal hemostatic mechanisms (► Box 8.3).

Box 8.3 Most Common Coagulopathies

- Hereditary bleeding disorders
  - von Willebrand disease
  - Disorders of platelet function and fibrinolysis
- Acquired bleeding abnormalities
  - Idiopathic thrombocytopenic purpura
  - Leukemia
  - Aplastic anemia
- Anticoagulation therapy

8.4.5.1 Hereditary Bleeding Disorders

von Willebrand disease and less common disorders of platelet function and fibrinolysis are characterized by excessive menstrual bleeding that begins at menarche and is usually regular [28]. Of adolescents who present with menorrhagia significant enough to cause anemia or hospitalization, as many as 20% will be found to have a bleeding disorder. However, it is important to remember that most AUB in this age group is due to anovulation.

The most common hereditary bleeding disorder is von Willebrand disease, which affects 1–2% of the population [29]. This hereditary deficiency (or abnormality) of the von Willebrand factor results in decreased platelet adherence, with von Willebrand factor interacting with platelets to form a platelet plug. A fibrin clot will then form on this plug. There are three main types of von Willebrand disease. The mild form (type 1) is responsible for over 70% of cases and is characterized by an absolute decrease in the protein. The mechanism by which an abnormal factor leads to bleeding at the level of the endometrium is unclear. The vast majority of women with this disease report AUB, specifically menorrhagia. The prevalence of this disorder in adults can range from 7% to 20%. Other inherited conditions include thrombocytopenia and rare clotting factor deficiencies (e.g., factors I, II, V, VII, X, XI, XIII).

8.4.5.2 Acquired Bleeding Disorders

Women with the new onset of extremely heavy menses not amenable to hormonal therapy will sometimes be found to have an acquired bleeding abnormality, usually apparent on a CBC. Such abnormalities include idiopathic thrombocytopenic purpura (ITP) and hematologic diseases affecting platelet production, such as leukemia. Women with grave systemic diseases, such as sepsis and liver disorders, can develop hemostatic disorder resulting in AUB.

8.4.5.3 Anticoagulant Therapy

Excessive bleeding can be a significant problem for women on anticoagulant therapy, including both conventional anticoagulants (i.e., warfarin, heparin) and the new generation of direct oral anticoagulants (e.g., apixaban, rivaroxaban, edoxaban, dabigatran). Although the overall risk of severe uterine bleeding during anticoagulation is <0.2%, this risk in women treated with rivaroxaban might be as high as 1% [30]. In rare cases, emergency hysterectomy can be necessary to effectively treat life-threatening uterine bleeding in women taking anticoagulants [31].

8.5 Pregnancy

Vaginal bleeding is common during both normal and abnormal pregnancies. Pregnancy must be excluded in every reproductive-aged woman presenting with apparent AUB, even in

women with other apparent etiologies such as PCOS and prolonged amenorrhea. Fortunately, the availability of inexpensive, quick, and accurate pregnancy tests has made the historically difficult task of diagnosing early pregnancy exceedingly easy.

8.5.1 Viable Intrauterine Pregnancy

As many as 50% of pregnant women will experience uterine spotting or bleeding during the first trimester. At least half of these pregnancies will progress normally beyond the first trimester, while the remainder will prove to be nonviable pregnancies [32]. The majority of nonviable pregnancies are spontaneous abortions, while<2% are ectopic or molar pregnancies.

8.5.2 Early Pregnancy Loss

Early pregnancy loss, defined as spontaneous abortions occurring prior to 13 weeks of gestation, complicates at least 20% of intrauterine pregnancies [32]. In the past, the majority of nonviable intrauterine pregnancies ended with spontaneous uterine bleeding culminating in spontaneous abortion. However, with the widespread utilization of transvaginal ultrasound in early pregnancy, an ever-increasing percentage of spontaneous abortions are diagnosed and treated prior to the onset of bleeding [32].

8.5.3 Ectopic Pregnancy

Ectopic pregnancies implanted outside the endometrial cavity make up <2% of all pregnancies [33]. Pregnancies implanted within a fallopian tube account for >90%ectopic pregnancies, with the remainder implanting within a cesarean scar, ovary, cervix, or abdomen [34]. Ectopic pregnancies often present with uterine bleeding. Almost 20% of women presenting to the emergency department with first-trimester vaginal bleeding, or abdominal pain, or both, will be found to have an ectopic pregnancy. Diagnosis and management details are presented in Chap. 23.

8.5.4 Molar Pregnancy

A molar pregnancy, also known as a hydatidiform mole, refers to any one of a group of genetically abnormal pregnancies characterized by cystic degeneration of chorionic villi. These gestational trophoblastic diseases represent <0.5% of pregnancies in North America and Europe. In the past, uterine bleeding in early pregnancy was the initial presentation in 84% of cases [35]. However, this percentage is likely to have decreased with the widespread application of transvaginal ultrasound in early pregnancy prior to the occurrence of vaginal bleeding. Risks of molar pregnancy include life-threatening hemorrhage and malignancy. Although rare, molar pregnancies can coexist with a twin viable pregnancy.

8.6 Infection

Infections of the reproductive tract are probably one of the most unrecognized and thus undiagnosed and treated causes of AUB. Although the original publication of the PALM-COEIN classification had no mention of this important, and often subtle, cause of AUB, subsequent publications include infection causes under "Not yet classified" [2, 11].

8.6.1 Pelvic Inflammatory Disease

Pelvic inflammatory disease (PID) is an inflammatory disorder of the upper female genital tract that includes any combination of endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis, commonly in association with cervicitis [36]. The clinical presentation of PID can range in severity from subclinical to life-threatening. In obvious cases of PID, vaginal bleeding will be one of their presenting symptoms for approximately 40% of patients [37, 38]. This can be the result of hormonal disturbances secondary to ovarian inflammation, cervicitis, or the universally presence of endometritis [39].

8.6.2 Endometritis

Endometritis is an important and often unrecognized cause of AUB. Endometritis is often present in women with other causes of AUB, including infectious causes such as PID and cervicitis, and structural abnormalities, including endometrial polyps and leiomyomas [40].

Endometritis can manifest as AUB unresponsive to hormonal therapy even in the absence of infectious or structural uterine abnormalities [41]. Normal endometrial hemostasis depends on thrombus formation via platelet aggregation and fibrin deposition [42]. Infection and inflammation of the endometrium interferes with these normal hemostatic mechanisms by consuming platelets and clotting proteins necessary for clotting [13]. Menstrual blood is an excellent bacterial culture media [43], theoretically explaining why prolonged AUB is often unresponsive to hormonal therapy.

8.6.2.1 Diagnosis and Treatment

For research purposes, the diagnosis of endometritis is made by endometrial biopsy. Classically, endometritis has been defined histologically by the presence of plasma cells on biopsy. However, in the presence of AUB, endometritis can manifest as reactive changes in the surface endometrium in the absence of identifiable inflammatory cells [39].

In women with AUB, a presumptive diagnosis of endometritis should be made in the presence of pelvic pain or tenderness. These patients should be treated for PID, even in the absence of more overt signs of pelvic infection, such as the presence of chlamydia or gonorrhea by nucleic acid amplification test, purulent cervicitis, WBC elevation, and fever [36]. Subclinical endometritis should be suspected in women with AUB unresponsive to hormonal therapy, particularly the presence of cervicitis or vaginitis, or structural abnormalities such as submucosal leiomyomas.

Women with AUB presumed to have endometriosis should be treated empirically while awaiting the results of nucleic acid amplification tests for chlamydia or gonorrhea. A diagnosis of PID should be given to women with AUB associated with tenderness of the cervix, uterine fundus, or adnexa, and they should be treated following CDC guidelines [36]. Women who do not meet the criteria for hospitalization should be treated with a combination of intramuscular and oral antibiotics, such as ceftriaxone plus doxycycline with or without metronidazole [36]. In the absence of tenderness, women with AUB and a presumptive diagnosis of endometritis can be treated effectively with either doxycycline or azithromycin [44].

8.6.3 Cervicitis

Cervicitis is a common cause of intermenstrual AUB, often described as postcoital spotting. Acute cervicitis is usually infectious, while chronic cervicitis is more likely to be idiopathic. Infectious agents that commonly cause cervicitis include sexually transmitted diseases (e.g., chlamydia, gonorrhea) and common infectious causes of vaginitis, including trichomonas [45]. Treatment of cervicitis is important to avoid ascending infections and bothersome symptoms.

The diagnosis of cervicitis is made when cervical examination reveals purulent discharge originating from the cervical ectropion and external os, accompanied by a friable endocervix that bleeds upon contact with a cotton-tipped swab. Nucleic acid amplification testing is performed to detect chlamydia and gonorrhea. When cervicitis is accompanied by vaginitis, standard evaluation should be carried out to identify bacterial vaginosis or trichomonas. Verification of a recent negative Papanicolaou smear is also important since cervical cancer and dysplasia can manifest as cervical bleeding [46].

Cervicitis is treated with targeted antibiotics when specific organisms have been identified, e.g., chlamydia, gonorrhea, and trichomonas. When no specific organism is identified, initial treatment is empiric using broad-spectrum antibiotics that are known to treat the most common vaginal pathogens, such as doxycycline and azithromycin.

Chronic cervicitis that does not respond to antibiotic therapy is presumed noninfectious. Nonresponsive chronic cervicitis will often respond to treatments such as cryotherapy, silver nitrate, and electrosurgery that induce squamous metaplasia of the columnar cells of the ectropion and endocervix.

8.6.4 Vaginitis

Vaginitis during the reproductive years can cause vaginal spotting, although the symptoms of vaginitis usually overshadow complaints of vaginal spotting. As discussed above, women with vaginitis often have subclinical endometritis which can result in AUB. After menopause, vaginal bleeding can be the primary manifestation of atrophic vaginitis related to estrogen deficiency. Appropriate diagnosis and treatment of vaginitis will often resolve associated AUB.

8.7 Neoplasms

Reproductive tract neoplasms, including benign, premalignant, and malignant processes, are one of the leading causes of vaginal bleeding. Focal intracavitary lesions, e.g., leiomyoma and polyps, account for up to 40% of cases of AUB [47]. Malignant and premalignant lesions of the cervix and uterine fundus, while not the most common causes of AUB, are certainly the most important to identify and treat. Neoplasms of the ovary can indirectly cause irregular bleeding by interfering with ovulation, as discussed below.

8.7.1 Benign Uterine Neoplasms

8.7.1.1 Leiomyomas

These remarkably common benign tumors of the myometrium can be found in almost 70% of white women and >80% of black women upon ultrasonographic examination by age 50 [48]. While the majority of these leiomyomas are subclinical, 20–40% will be symptomatic.

Leiomyomas most likely to result in menorrhagia are located either submucosal and intracavitary and are presumed to have a direct effect on the adjacent endometrium. In addition, intramural leiomyomas that are large and/or multiple can also result in menorrhagia, although the mechanism is uncertain. Small intramural or subserosal leiomyomas and those that are pedunculated on the uterine exterior are less likely to be related to AUB.

8.7.1.2 Endometrial Polyps

Endometrial polyps are localized overgrowths of the endometrium that project into the uterine cavity. These polyps may be broad-based (sessile) or pedunculated. Endometrial polyps are common in both pre- and postmenopausal women and are found in at least 20% of women undergoing hysteroscopy or hysterectomy [49]. The incidence of these polyps rises steadily with increasing age, peaks in the fifth decade of life, and gradually declines after menopause.

In premenopausal women complaining of AUB, studies have shown that from 5% to 33% will be found to have endometrial polyps [50]. Endometrial polyps are commonly found in patients with a long history of anovulatory bleeding, suggesting that polyps may be the result of chronic anovulation in some women. Polyps can also be found in women complaining of postmenstrual spotting or bleeding in ovulatory cycles or during cyclic hormonal therapy.

Endometrial polyps in premenopausal women are almost always benign [49]. However, the risk of endometrial malignancy increases with age, and one study reported the risk of malignancy in polyps in women >65 years old was >50%.

8.7.1.3 Adenomyosis

This benign condition involves the penetration of the endometrium into the myometrium. Microscopic examination of the uterus reveals endometrial glands and stroma deep within the endometrium surrounded by hypertrophic and hyperplastic myometrium. This histopathologic diagnosis is found in over 60% of hysterectomy specimens [51]. Clinically, two-

thirds of patients with adenomyosis will complain of menorrhagia and dysmenorrhea, and pelvic examination usually reveals a diffusely enlarged and tender uterus.

Diagnostic tests that help suggest the diagnosis of adenomyosis include both transvaginal ultrasonography and magnetic resonance imaging. The sensitivity for ultrasonography approaches 50%, and the sensitivity of MRI ranges from 80% to 100% [51]. Research continues to focus on more effective adenomyosis diagnostic testing and treatments short of hysterectomy.

8.7.2 Malignant and Premalignant Uterine Neoplasms

8.7.2.1 Endometrial Hyperplasia and Cancer

Endometrial hyperplasia is commonly found in women with AUB caused by prolonged anovulation [52]. Rather than a primary etiology of AUB, it is the result of prolonged unopposed estrogen exposure of the endometrium that occurs in women with chronic anovulation. Endometrial hyperplasia is a precursor to endometrial cancer and, in the presence of atypia, can be a marker for concurrent endometrial cancer elsewhere in the uterus.

Endometrial cancer is the most important disease to identify early in woman with AUB, particularly those who are peri- or postmenopausal. Approximately 20% of endometrial cancer is diagnosed in women before menopause and 5% before the age of 40 years [53]. After the menopause, approximately 10% of women with AUB not taking exogenous hormones will be found to have endometrial cancer, and the incidence rises with each decade of life thereafter.

8.7.2.2 Endocervical Polyps

These soft, fleshy growths originate from the mucosal surface of the endocervical canal. They usually arise from a stalk and protrude through the cervical os, although some may be broad-based. They commonly range in size from 3 to 20 mm but can be larger. Endocervical polyps are known to be more frequent in women on oral contraceptives and with chronic cervicitis; however, the etiology remains unclear. Endocervical polyps are relatively common among sexually active women. Many endocervical polyps are asymptomatic and are discovered incidentally on visual examination of the cervix. In other instances, these polyps can manifest as intermenstrual and/or postcoital spotting.

Microscopically, endocervical polyps consist of a vascular core surrounded by a glandular mucous membrane and may be covered completely or partially with stratified squamous epithelium. In some polyps, the connective tissue core may be relatively fibrous. Endocervical polyps removed from women taking oral contraceptives can show a pattern of microglandular hyperplasia [54].

8.7.2.3 Cervical Dysplasia and Cancer

Cervical dysplasia and cancer can both present as postcoital bleeding. In one study of women presenting with postcoital spotting, 17% were found to have cervical dysplasia and 4% had invasive cervical cancer [46]. In the absence of a visible lesion, Papanicolaou smears, human papillomavirus (HPV) testing, and colposcopy (if indicated) are important diagnostic tools. In the presence of a visible cervical lesion, it is critical to biopsy the lesion to determine the diagnosis.

8.7.3 Ovarian Malignancies

Ovarian malignancies are uncommon in reproductive-aged women, and mainly occur in postmenopausal women. The presence of an ovarian tumor can interfere with the function of the HPO axis, and as a result, AUB can be an early symptom for some women with an ovarian malignancy. However, the most common early symptoms of an ovarian malignancy are gastrointestinal complaints [55]. However, the majority of ovarian malignancies present at an advanced stage of disease with symptoms including for pain and abdominal distension related to ascites.

Granulosa cell tumors are a notable exception and differ from other ovarian malignan-

cies in terms of both age distribution and presentation [56]. Although granulosa cell tumors represent <5% of all ovarian malignancies, approximately half of these estrogen-secreting tumors occur in reproductive-aged women, and AUB is the most common presenting symptoms. In reproductive-aged women, AUB usually manifests as irregular menses, menorrhagia, and intermenstrual bleeding, although amenorrhea might also result. In older women, postmenopausal bleeding is one of the most common presenting symptoms. Unopposed estrogen secreted by granulosa cell tumors results in an association between these tumors and both endometrial hyperplasia in up to 50% of these women and endometrial carcinoma in up to >10%.

8.7.4 Vaginal Malignancies

Vaginal malignancies are uncommon, making up <2% of gynecologic cancers [57] that arise in the female genital system. Over 80% are squamous cell carcinoma, usually related to HPV infections. Most other vaginal cancers are adenocarcinomas. They occur most commonly in older women, with the median age at diagnosis of 68 years [58]. One of the most common presenting symptoms is intermenstrual spotting [57], and the diagnosis is made by directed biopsies.

8.8 Clinical Evaluation of Abnormal Vaginal Bleeding

The evaluation of abnormal vaginal bleeding should be tailored to the clinical presentation, and importantly, the age of the patient should be taken into consideration (Fig. 8.1). The clinician should be aware of common causes of AUB that might not be clinically obvious but still must be excluded.

An important point to keep in mind is that AUB can often have more than one etiology. Sometimes subtle comorbid conditions, such as endometritis, can make single-factor therapy surprisingly ineffective [41]. In other women, obvious causes of chronic anovulation can be associated with endometrial hyperplasia and/or cancer. Careful evaluation of the patient for multiple simultaneous causes of AUB is important.

8.8.1 Exclude Pregnancy

In reproductive-aged women, the presence of signs and symptoms of pregnancy is important to determine. Pregnancy should be one of the first causes of abnormal bleeding that is ruled out. Current contraceptive methods and past pregnancy history are also important.

8.8.2 Characterize Bleeding

Once pregnancy is excluded, the amount and character of the bleeding is important to ascertain. Careful, stepwise retrospective questioning will usually give a clear picture of the bleeding pattern over the previous days, months, and even years. In nonemergency cases of bleeding, the use of a prospective menstrual calendar is an excellent way to document the problem as well as the response to therapy. It is important to determine when the bleeding problems were first noticed, since menorrhagia starting at menarche should alert the clinician to the possibility of an underlying bleeding disorder.

The amount of bleeding is probably the most difficult to elicit from the patient, since normal or heavy menstrual bleeding can be very subjective. For research purposes, menorrhagia can be defined as a monthly blood loss of >80 mL on three consecutive menses as measured by the alkaline hematin method [59]. Unfortunately, this type of accurate evaluation is neither cost-effective nor readily available.

In adolescents with menorrhagia, it is important to determine any past history of excess bleeding during surgical, dental, or obstetric procedures since this has been found to be predictive of von Willebrand disease [60]. Interestingly, in this same study, epistaxis and easy bruising were not clear discriminatory symptoms.

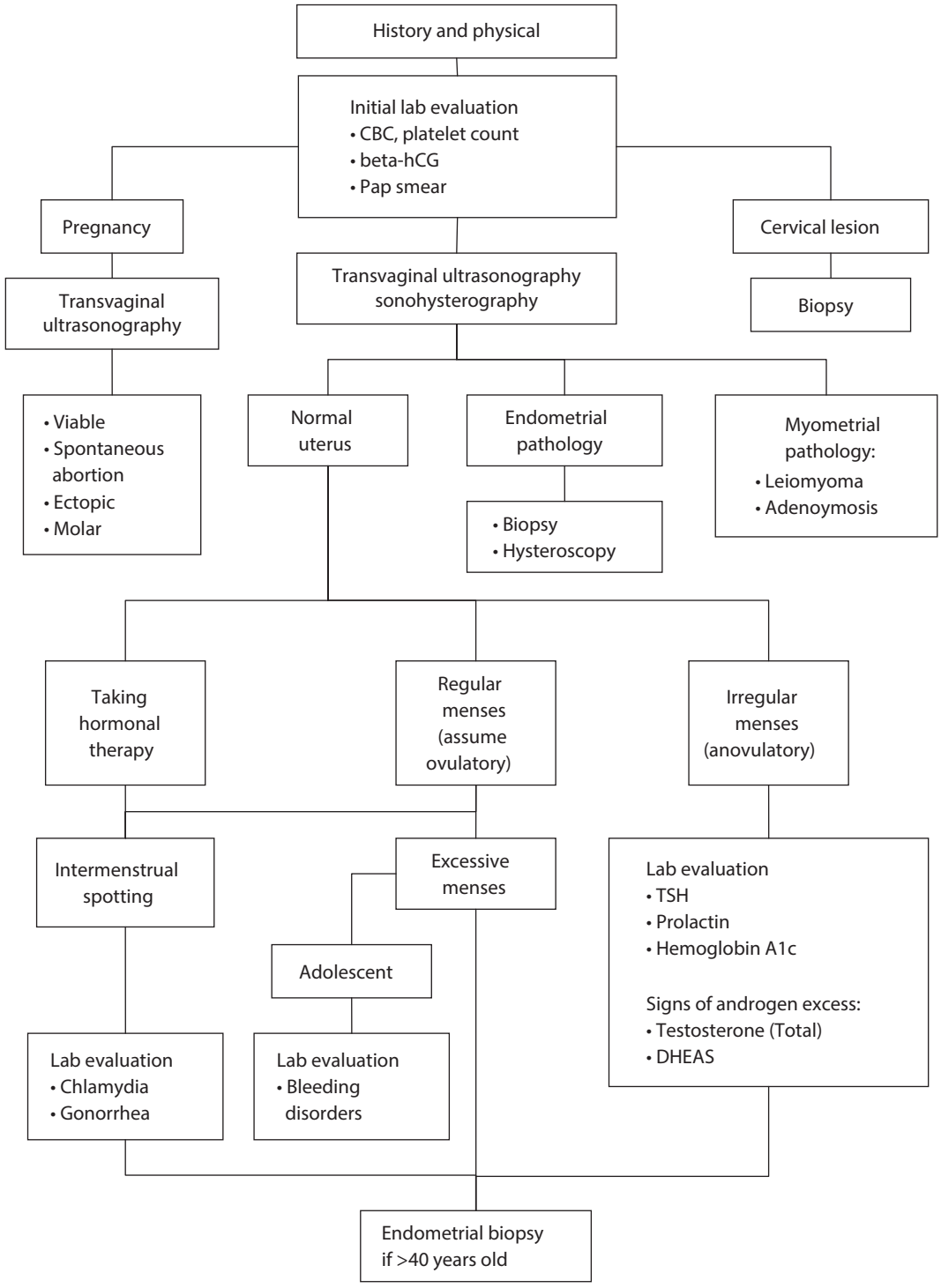


Fig. 8.1 Algorithm for evaluating women with abnormal uterine bleeding (AUB)

8.8.3 Medical History

A careful history is the most important factor in determining the appropriate diagnostic approach. This should include the patient's menstrual patterns and history, the extent of recent bleeding, sexual activity, and contraception. Important questions include symptoms of pregnancy, infection, changes in body hair, excessive bleeding, and systemic disease. Current medication and information about prior Papanicolaou smears are also important. The review of systems should include symptoms of systemic disease, such as weight gain or loss, abdominal swelling, somnolence, and nipple discharge.

8.8.4 Physical Examination

The physical examination is intended to detect both gynecologic and systemic diseases. Special care should be taken to document the presence of hirsutism, acne, or other signs of excess androgens, as well as galactorrhea.

The pelvic examination begins with a speculum examination to inspect the cervix for polyps, signs of infection, or inflammation. A bimanual examination is important to determine uterine size and the presence and location of any tenderness. In the presence of bleeding in early pregnancy, great care should be taken to avoid adnexal compression during the bimanual examination since this can lead to rupture of an ectopic pregnancy. The role of bimanual examination for detecting and characterizing adnexal masses has been replaced for the most part by more accurate and precise transvaginal ultrasound, particularly in overweight women.

8.8.5 Laboratory Testing

Laboratory evaluation is an important part of the initial evaluation of all patients with AUB (▶ Box 8.4). However, rather than ordering every test at the first visit, laboratory tests should be obtained in a stepwise fashion based on presentation (◘ Fig. 8.1).

Box 8.4 Laboratory Testing for AUB

- All patients
  - Pregnancy test
  - Complete blood count (including platelets)
  - Papanicolaou smear
  - Cervical tests for gonorrhea and chlamydia
- Anovulatory bleeding
  - Thyroid-stimulating hormone
  - Prolactin
  - Hemoglobin A1c
  - Testosterone (total and free)
  - Dehydroepiandrosterone sulfate (DHEAS)
- >40 years of age
  - Endometrial biopsy
- New-onset heavy menstrual bleeding
  - Prothrombin time
  - Activated partial thromboplastin time
  - Bleeding time
- Heavy menstrual bleeding since menarche
  - Above plus
  - Iron profile, serum creatinine
  - Factor VII level
  - von Willebrand factor (vWF) antigen
  - Ristocetin cofactor
  - Platelet aggregation studies
- If the above are negative, consider
  - Factor XI level
  - Euglobulin clot lysis time

8.8.5.1 Urine Tests

The most important test for all reproductive-aged women complaining of AUB is an hCG test for pregnancy. This can be readily obtained through urine testing as a preliminary qualitative test. If positive, quantitative serum HCG testing can be completed.

8.8.5.2 Blood Tests

For all cases, except the most insignificant bleeding, a CBC (including platelets) is important to detect significant anemia and disorders of platelet production or survival. Unless precluded by extremely heavy bleeding, a Papanicolaou smear should be performed on any woman who has not had recent screening as per the current screening guidelines. For patients with apparent oligo- or anovulation, thyroid-stimulating hormone (TSH) and prolactin testing will detect subtle pituitary function disorders that might present with AUB as the earliest symptom. Since cervical and uterine infections are common, nucleic acid amplification tests for gonorrhea and chlamydia are helpful in women with intermenstrual spotting, as well as any woman at risk for these infections.

Several patient groups may require additional ancillary tests. Obese patients with apparent AUB are at increased risk for type 2 diabetes. Several authors recommend measurement of hemoglobin A1c (HbA1c) as a good diabetes screen that does not require fasting or a return visit for provocative testing. Patients with hirsutism or other evidence of androgen excess should be screened for ovarian and adrenal malignancies with total testosterone and DHEAS. All women >45 years old should have an endometrial biopsy to rule out endometrial hyperplasia or cancer. Similarly, women younger than 45 with persistent abnormal bleeding or chronic unopposed estrogen exposure should have an endometrial biopsy after pregnancy has been excluded.

PCOS and nonclassic CAH may sometimes be indistinguishable by clinical presentation, since both disorders are often characterized by hirsutism, acne, menstrual abnormalities, and infertility [61]. Unfortunately, no discriminatory screening test exists for this heterologous condition, which is most commonly caused by 21-hydroxylase or 11-beta-hydroxylase deficiency. Measuring baseline serum 17-hydroxyprogesterone will detect nonclassic CAH in the majority of women with this condition. However, as many as 10% of women with nonclassic CAH will have normal baseline levels of 17-hydroxyprogesterone and demonstrate elevated levels only after stimulation with an ACTH analogue. If ovulation dysfunction and signs of androgen excess begin at the time of puberty, such women should be investigated appropriately (see ► Chap. 7).

8.8.5.3 Evaluation for Hemostatic Disorders

Patients with new onset of significant menorrhagia should be evaluated for bleeding disorders with a CBC, prothrombin time, activated partial thromboplastin time, and bleeding time [62]. Any patient with a history of menorrhagia since menarche, especially with a history of surgical or dental-related bleeding or postpartum hemorrhage, should be evaluated for heritable bleeding disorders. These tests include specific tests for von Willebrand disease, such as von Willebrand factor antigen, von Willebrand factor functional activity (ristocetin cofactor activity), and factor VIII level. These levels can fluctuate; therefore, these tests should be repeated if clinical suspicion is high. Normal ranges should be adjusted for the observation that von Willebrand factor levels are 25% lower in women with blood type O compared with other blood groups. Further studies, such as platelet aggregation studies, may also be required [62]. If these studies are negative, factor XI level and euglobulin clot lysis time can be evaluated.

8.8.6 Papanicolaou Smear

In the setting of mild vaginal bleeding, a Pap smear should be performed to rule out bleeding from cervical carcinoma. It is important to not delay this sampling due to the bleeding, and a large cotton-tipped swab can be used to carefully clear the bleeding before obtaining sampling. Importantly, other forms of cervical bleeding such as cervical polyps and ectropion can be ruled out through physical examination.

8.8.7 Endometrial Biopsy

For premenopausal women over the age of 40 years old, AUB is often the result of anovulatory bleeding, which is a normal physiological response to declining ovarian function. However, the risk of endometrial hyperplasia and carcinoma also increases with age. For this reason, once pregnancy has been excluded, an endometrial biopsy should be obtained in all women older than 45 years of age who present with AUB. Endometrial biopsy should also be performed in all women who are younger than 45 years of age who have a history of persistent AUB, unopposed estrogen exposure, or failed medical management [11].

8.8.8 Imaging

Over the last two decades, our ability to visualize the uterine cavity and adnexa has dramatically increased. In addition to the bimanual pelvic examination, the only other available methods were hysterosalpingogram (HSG) and dilation and curettage. Although the radiation exposure and discomfort associated with HSG are both considered acceptable, this technique effectively identifies only marked abnormalities of the uterine cavity. Lesions <1 cm in size are often missed. Likewise, the previously blind procedure of dilation and curettage gave the operator only the roughest idea of the depth and contour of the uterine cavity. Intrauterine findings at the time of hysterectomy were often a surprise. In obese patients in whom bimanual examinations are difficult, unexpected ovarian masses at laparotomy were commonplace.

8.8.8.1 Transvaginal Ultrasound

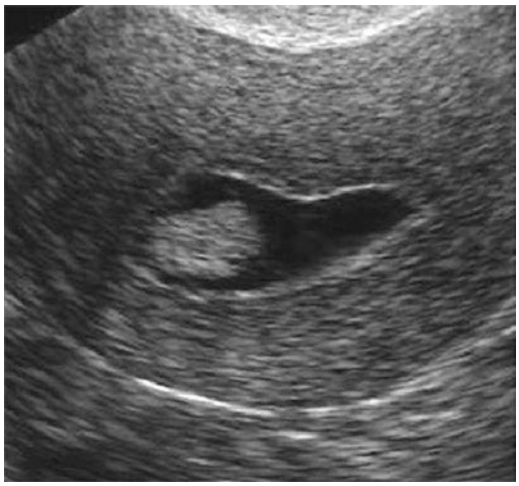
Today, transvaginal ultrasonography and sonohysterography have made unexpected findings at surgery much less common (See ▶ Chaps. 5 and 6). Ultrasonography and sonohysterography have become important steps in the evaluation of AUB. Transvaginal ultrasonography can accurately determine uterine size and configuration, and reveal the nature of both palpable and nonpalpable adnexal masses. Knowledge about the size and location of leiomyoma and the potential that an ovarian mass might be malignant is invaluable prior to surgery.

8.8.8.2 Sonohysterogram

Sonohysterography can be used to accurately visualize most intrauterine abnormalities once pregnancy has been excluded. Accurate evaluation of the uterine cavity is of the utmost importance for the evaluation and treatment of AUB. This procedure involves injection of sterile saline into the uterus while a transvaginal sonogram is performed. It may cause a small amount of discomfort to the patient. When the uterine cavity is distended with saline, intracavitary lesions (e.g., polyps, fibroids, cancer) as small as 3 mm can be clearly seen (◘ Fig. 8.2).

8.8.8.3 Hysterosalpingogram

A hysterosalpingogram can be used to evaluate the uterine cavity and fallopian tubes. It involves injection of contrast dye through the cervical canal. This can be used to evaluate for intracavitary lesions such as fibroids. Additional imaging such as sonohysterography or hysteroscopy can provide more specificity and accuracy on the type of lesion including characterization of the lesion.



◘ **Fig. 8.2** Endometrial polyps diagnosed by sonohysterography (SIS)

8.8.9 Hysteroscopy

Hysteroscopy (See ▶ Chaps. 5 and 16) is another excellent outpatient method for visualizing the uterine cavity, and in experienced hands can be performed safely in the office. The discomfort and risk can be greater than sonohysterography, and the procedure can be difficult in the presence of cervical stenosis or when the cervix is difficult to visualize. However, the color photographs depicting the lesion can be very informative for patients.

Hysteroscopy done in the OR can be both diagnostic and therapeutic. Diagnostic hysteroscopy can provide information on uterine contour, presence of inflammation (visually and via endometrial biopsy), and the depth and size of intracavitary lesions, such as fibroids and polyps. These lesions can then be removed, and importantly a tissue diagnosis ruling out malignancy can be obtained. Endometrial sampling can be wider, effectively ruling out hyperplasia and carcinoma. Performing hysteroscopy in the OR setting allows for patient comfort and definitive management. It is a safe and effective minimally invasive treatment approach when performed appropriately [63].

8.9 Acute Management of AUB

Targeted, expedient, and effective management of AUB is a cornerstone of gynecologic practice. Once pregnancy has been excluded, various systemic, infectious, and neoplastic causes of AUB must be effectively treated. Most patients presenting with AUB will be hemodynamically stable, allowing outpatient treatment. On occasion, these patients will present with vaginal hemorrhage requiring emergency intervention and possibly hospital admission for stabilization and definitive treatment.

8.9.1 Emergency AUB Treatment for Hemodynamically Unstable Patients

Women can present with AUB-related acute hemorrhage significant enough to result in hemodynamic compromise. This degree of hemorrhage can be the result of a number of causes, most notably gynecologic malignancies and anovulatory bleeding after prolonged amenorrhea. Evaluation of all patients with AUB should include assessment for signs of anemia, and potential hemodynamic instability related to hypovolemia [64]. This is particularly important for older women with additional risk factors for cardiovascular disease for whom extreme anemia and/or hypotension could provoke a cardiac event [65].

For women with AUB who are hemodynamically unstable, the first step is establishing intravenous access in an acute care environment followed by replacement of fluids and blood products. Once stabilized, careful assessment to determine the AUB etiology can be carried out.

Definitive treatment will depend on AUB etiology as described elsewhere in this chapter. Urgent treatment of two of the most common causes of acute hemorrhage, anovulatory bleeding and malignancy, deserves special attention.

8.9.1.1 Hemorrhage Related to Anovulation

The approach for women who present with acute hemorrhage with presumed anovulatory bleeding and normal pelvic anatomy should be done in a stepwise manner. Bleeding in this circumstance is related to asynchronous endometrial shedding and originates from innumerable spiral arterioles in the endometrium. After the patient is stabilized with intravascular resuscitation, the initial approach can be intravenous conjugated equine estrogen for patients not at increased risk for thromboembolism [64]. Intravenous estrogens, the only FDA-approved hormonal treatment for AUB, has been reported to stop bleeding in >60% of these patients.

Anovulatory patients who continue to hemorrhage despite treatment with intravenous estrogens will usually respond to uterine dilation and curettage. Concomitant hysteroscopy, when possible, is an important adjuvant to diagnose and treat intrauterine pathology such as polyps or leiomyomas.

8.9.1.2 Arterial Embolization for Pelvic Malignancies

Women with AUB related to cervical or endometrial malignancies can present with massive arterial hemorrhage. When pelvic examination reveals a tumor mass as the bleeding source, the initial approach is vaginal packing and intravenous resuscitation with fluid and blood products. When pressure and clotting factors do not control hemorrhage, intravascular arterial embolization by an interventional radiologist can be lifesaving. Embolization has been reported to result in complete or partial hemorrhage control in up to 90% of these patients [66]. Once these patients are stabilized, irradiation or surgical intervention can be utilized as indicated.

8.9.2 Acute Outpatient Treatment of AUB

8.9.2.1 Progestin Endometrial Synchronization

Progestin therapy is the first-line approach to stop bleeding in hemodynamically stable patients. Progestins are also used for women with chronic irregular bleeding to synchronize the endometrium prior to the initiation of cyclic hormones. Synchronization can reduce breakthrough bleeding encountered with subsequent therapy.

Approaches to synchronization use either an oral contraceptive taper or a potent progestin (Table 8.2). For women with heavy vaginal bleeding, oral contraceptives starting at three tablets per day will often decrease or stop bleeding quickly, although many women experience nausea with this high-dose regimen [67]. Alternatively, medroxyprogesterone acetate, at a dose of 10 mg per day for 10–14 days, usually improves bleeding within 2–3 days and serves to stabilize the endometrial lining prior to withdrawal bleeding.

Patients treated with either of these methods should be counseled that they may experience moderately heavy bleeding within 1–2 days of stopping their medication and should start oral contraceptives on the Sunday following the withdrawal bleeding. A combination of oral and intramuscular medroxyprogesterone will result in a longer period of amenorrhea [68]. However, this intramuscular medroxyprogesterone should be avoided in women wishing to conceive in the near future because the median delay in conception after the last injection has been reported as approximately 9 months.

8.10 Long-Term Management of Ovulatory Dysfunction

The most appropriate long-term management of chronic anovulation requires accurate diagnosis of any underlying pathology. For anovulatory women desiring conception, ovulation induction is usually the most appropriate treatment. For women not immediately desiring conception, this is followed by a combination of hormonal management and management of associated comorbidi-

Table 8.2 Effective acute outpatient therapies for anovulatory bleeding

Medication	Routine	Dosage	Frequency and duration
Ethinyl estradiol plus Norethindrone (OCPs)	PO	35 μg 1 mg	TID × 1 week, then QD × 3 week
Medroxyprogesterone	PO	20 mg	TID × 1 week, then QD × 3 week
Medroxyprogesterone	IM Plus PO	150 mg 20 mg	Once TID × 3 days

Abbreviations: *IM* intramuscular injection, *PO* oral, *QD* once daily, *TID* three times daily, *OCPs* oral contraceptive pills

ties including obesity, type 2 diabetes mellitus, and endometrial hyperplasia and cancer.

8.10.1 Ovulation Induction

Restoration of ovulation for women desiring conception is of paramount importance. Restoration of regular ovulatory cycles may necessitate treatment of any underlying condition responsible for anovulation. For example, in patients with hyperprolactinemia, using a dopamine agonist to normalize prolactin levels will often result in ovulation and subsequent pregnancy. In cases of PCOS, recent studies have demonstrated that insulin-sensitizing agents, such as metformin, can promote ovulation (See ► Chaps. 5 and 8). It is important to note, however, that utilization of these agents alone may not be sufficient for ovulation induction and conception. A recent randomized clinical trial did not demonstrate an improvement with live birth rates when adding metformin to clomiphene citrate [69].

While waiting for systemic therapies to result in resumption of ovulation and normal menses, monthly induction of withdrawal bleeding with an oral progestin should be considered to avoid ongoing AUB. In women not using combined oral contraception, the use of micronized progesterone (200–300 mg daily for 14 days) will result in reasonable withdrawal bleeding and will be safe should pregnancy occur. For patients who do not resume ovulation with systemic therapy, induction of ovulation using clomiphene citrate, aromatase inhibitors, or injectable gonadotropins should be considered (See ► Chaps. 5 and 7).

8.10.2 Hormonal Treatment of Anovulatory Bleeding

Women who do not desire pregnancy may initiate combined oral contraception or other hormonal therapies, such as cyclic progestins and a progestin-containing intrauterine device.

8.10.2.1 Oral Contraceptives

For decades, combined oral contraceptive pills have been the first-line therapy for managing AUB, and studies have repeatedly demonstrated their utility in decreasing the duration and amount of menstrual flow as well as dysmenorrhea [70]. In addition, extending the number of consecutive days of active pills and decreasing the annual number of menses may further minimize menstrual-related symptoms [70]. Extended cycle regimens increase the risk of spotting and breakthrough bleeding when compared with standard monthly cycle regimens, but the risk generally decreases over time [71].

8.10.2.2 Progestins

Progestin therapy, cyclic or continuous, represents another option for long-term management of AUB. The administration of progestins, such as 10 mg medroxyprogesterone or 300 mg micronized progesterone, daily, from day 15 to 26 of each cycle, will regulate menses in anovulatory patients. Cyclic progestin therapy represents a safe and effective approach to managing AUB and does not have the side effects or risks associated with oral estrogen. Additionally, cyclic progestin therapy provides endometrial protection against endometrial hyperplasia and cancer. Notable side effects of progestin therapy include mood changes or depression, nausea, breast tenderness, and bloating. Both progestin and continuous oral contraceptive therapy are equally efficacious in the treatment of AUB; however, progestin-only therapy has demonstrated superior patient satisfaction rates in direct comparison with combined oral contraceptives [67].

8.10.2.3 Levonorgestrel-Releasing Intrauterine Devices

Levonorgestrel-releasing intrauterine devices (LNG-IUDs), originally developed for contraception, have been shown to be an effective treatment for dysmenorrhea, AUB-H, and endometrial hyperplasia. These IUDs release the potent progestin levonorgestrel (LNG) directly into the uterine cavity, suppressing endometrial proliferation and decreasing menstrual blood loss by as much as 97% [72].

While many women will experience irregular or intermenstrual bleeding in the first 6 months of their use, at least 50% will have amenorrhea by 24 months [73].

LNG-IUDs have very few systemic side effects compared to oral and parenteral contraceptives containing progestins. However, extremely low amounts of LNG can be detected in the systemic circulation among LNG-containing IUD users [74]. As a result, some users will experience hirsutism, acne, weight change, nausea, headache, mood changes, and/or breast tenderness.

The first LNG-IUDs contained 52 mg of LNG and released 20 μg every 24 hours from this polymer cylinder. LNG-IUDs are now available that contain and release less LNG: 13.5 mg/device and 19.5 mg/device. Initial LNG release rates are reduced by 50% after 5 years. Although the initial cost of an LNG-IUD is higher than other medical treatment options, long term they provide cost-effective therapy of AUB-H.

8.11 Treatment of AUB in Ovulatory Patients

In ovulatory women, AUB can be either between menses, often postcoital, or excessive bleeding (HMB) that occurs at normal, regular intervals. Intermenstrual bleeding can be related to cervical or endometrial infections or neoplasms, as discussed above. Chronic HMB is most often related to an anatomical cause, e.g., leiomyoma or adenomyosis, but can also be related to congenital or acquired bleeding disorders.

Unfortunately, despite a thorough evaluation, approximately one-half of women with HMB have no discernible cause. These women must be treated with empiric hormonal or surgical therapies until a treatable cause can be identified or menopause occurs.

8.11.1 Medical Treatment

The majority of patients who present with AUB will be medically stable and thus good candidates for outpatient management.

8.11.1.1 Combination Oral Contraceptives

Estrogen-progestin oral contraceptives (OCPs) are often used for first-line management for AUB/HMB. Significant advantages include reduction of menstrual flow, amelioration of dysmenorrhea, and providing contraception. Randomized trials have demonstrated the ability of OCPs to decrease menstrual blood loss in women with AUB from 35% to 69% [75]. Alternative routes of administration of estrogen-progestin include the transdermal contraceptive patch and vaginal contraceptive ring. The efficacy of these in treating AUB is likely similar to that of OCPs, and compliance may be improved. Furthermore, underscoring the impact of formulation on HMB, shorter duration of hormone free-intervals may be associated with less withdrawal bleeding than formulations with 7 hormone-free days per 28-day pill pack. Indeed, the only OC approved by the US Food and Drug Administration for treatment of AUB has a short hormone-free interval [76]. In a randomized trial, this OCP formulation significantly reduced menstrual blood loss compared with placebo (reduced by 64% versus 8%) [77].

Similarly to patients with anovulatory AUB, OCPs may be prescribed in a myriad of dosing regimens: a cyclic (with a monthly withdrawal bleed), extended (withdrawal bleeding every 3 months), or continuous (no withdrawal bleed) regimen. Although extended or continuous OCP use may be more efficacious in suppression of menstrual blood loss, breakthrough bleeding is a concern with this approach, limiting the utility of this strategy for some patients.

8.11.1.2 Progestins

Progestin-containing hormonal preparations are also effective in the treatment of HMB. High-dose oral progestin formulations are generally reserved for patients who have contraindications, prefer to avoid estrogen, or who are trying to conceive a pregnancy. Examples of treatment regimens include norethindrone 5 mg one to three times a day or medroxyprogesterone 5–30 mg daily. Norethindrone is substantially more potent than medroxyprogesterone in the attenu-

ation of menstrual flow [75]. Norethindrone is the most-studied progestin-only regimen for the treatment of AUB; however, other regimens including megestrol may be equally efficacious. Blood loss with progestin therapy use has demonstrated reductions by approximately 30% in some studies. High-dose progestin formulations, unfortunately, may instigate progestin-related side effects, including mood lability, bloating, and an increased appetite.

Levonorgestrel-containing IUDs may be offered as a first-line treatment for patients with HMB wishing to defer conception in the near future. The 52 mg-containing IUD system (LNG 52) has been approved by the FDA for treatment of HMB due to its efficacy and compliance. Studies demonstrate superiority of LNG-containing IUDs in improving quality of life in patients with HMB by significant menstrual suppression, with the majority of patients experiencing amenorrhea or infrequent bleeding [73]. After 6 months, LNG 52 IUD treatment of women with HMB has been shown to increase their hemoglobin and ferritin levels by 7.5% and 68.8%, respectively. Further study is required to determine the efficacy of IUDs containing lower LNG dosages (e.g., 19.5 mg and 13.5 mg) for treatment of HMB.

8.11.1.3 Nonsteroidal Anti-inflammatory Drugs

Prostaglandins significantly impact endometrial hemostasis, and by inhibiting prostaglandin synthesis, NSAIDs serve to decrease menstrual blood loss. NSAIDs may reduce menstrual blood loss by 30–40% [78]. While naproxen has been the most extensively studied NSAID, no member of the drug class offers distinct advantages for AUB [79]. Additionally, NSAIDs provide an effective treatment for dysmenorrhea, which is often present in those with AUB.

8.11.1.4 Tranexamic Acid

Tranexamic acid, an antifibrinolytic agent, is a nonhormonal modality utilized in the treatment of AUB. A Cochrane analysis has confirmed efficacy and patient tolerance of tranexamic acid in the treatment of HMB, and in Europe this medication has become the preferred treatment for women with heavy menstrual bleeding [80]. The FDA has approved tranexamic acid for use in the treatment of HMB. This therapy is administered orally at a dose of 1300 mg three times daily for 5 days, initiated with onset of menses. Studies have demonstrated the superiority of this class of drugs in comparison with NSAIDs. Conversely, tranexamic acid is inferior to LNG 52 in the treatment of AUB [81]

To date, studies have not demonstrated an increased risk of venous or arterial thromboembolism [82]. However, tranexamic acid should not be concomitantly administered with combined oral contraception or in women with an increased risk of thromboembolism.

8.11.2 Surgical Treatment of AUB

In the past, surgery was one of the most common treatments of AUB related to either structural or nonstructural abnormalities, primarily in the form of hysterectomy [5]. This was likely related to both an incomplete understanding of AUB and a paucity of effective medical treatments. Surgical treatments are now reserved for women with coexisting surgical indications in addition to AUB (e.g., pelvic organ prolapse, infertility, possible malignancy) or those who have completed childbearing and find medical treatment ineffective or unacceptable because of risks or side effects.

Surgical approaches can be either conservative (e.g., myomectomy, polypectomy) or definitive (e.g., endometrial ablation, hysterectomy). The choice of surgical approach depends on the patient's diagnosis, therapeutic goals, and desire for future fertility. For younger women whose fertility desires might change in the future, it should be kept in mind that hormonal management with a progestin-releasing IUD can often be as effective as a definitive surgery for controlling AUB [83]. The details of surgical approaches are provided in ▶ Chaps. 20, 21, and 22.

8.11.2.1 Medical Pretreatment of Uterine Leiomyomas with GnRH Analogues

Medical pretreatment with GnRH agonists has been shown to be useful in some cases to decrease the size of leiomyoma by up to 47% prior to surgical intervention [84]. This approach has been shown to facilitate removal using minimally invasive approaches, decrease blood loss during open myomectomy, and facilitate specimen removal during hysterectomy. GnRH agonist injections result in an initial increase in pituitary and ovarian hormones (i.e., "flair") followed by pituitary downregulation, hypoestrogenemia, and cessation of menses. The side effects of estrogen deprivation include hot flashes, mood alterations, and bone loss, which can be diminished by "add-back" therapy with oral norethindrone. More recently, oral GnRH antagonists have become available to avoid the hormonal flare. However, their clinical utility remains to be determined for presurgical treatment of leiomyoma.

8.11.2.2 Myomectomy

Surgical removal of leiomyomas in symptomatic women is an effective treatment, although subsequent growth of addition leiomyomas often necessitates the need for additional surgery (see ▶ Chap. 22). The best approach depends on the size and location of the fibroids in addition to the level of surgical expertise of the provider. Hysteroscopic resection is the ideal approach for all but the largest intracavitary and submucosal leiomyomas (FIGO stage 0, I, or II) because of the decreased morbidity and faster recovery. Myomectomy for larger fibroids (FIGO stage III or higher) can be performed laparoscopically, with or without robotic assistance, or using an abdominal approach. For patients desiring future childbearing, caution must be undertaken during repair of the endometrium to prevent intracavitary scarring in cases where the uterine cavity is entered.

8.11.2.3 Endometrial Ablation

Endometrial ablation is a minimally invasive surgical procedure that, compared to hysterectomy, has less morbidity, shorter recovery, and greater cost-effectiveness (see ▶ Chap. 20). Ablation is not indicated for women who desire to maintain fertility, since pregnancies after ablation are at markedly increased risks of adverse pregnancy outcomes, including preterm premature rupture of membranes (PPROM) and abnormal placentation. Women undergoing this procedure should consider permanent sterilization since endometrial ablation does not provide reliable contraception [85].

8.11.2.4 Hysterectomy

Hysterectomy remains the best option for some women with AUB who fail medical or surgical management or who have additional indications for hysterectomy. As many as 20% of women who initially undergo endometrial ablation will require hysterectomy within 5 years. Some studies have demonstrated a higher satisfaction rate in women who initially underwent hysterectomy rather than endometrial ablation [86].

8.12 Review Questions

1. A 36-year-old woman is having frequent and heavy menses. After pregnancy was excluded, sonohysterogram revealed an intracavitary lesion consistent with a 3 cm intra cavitary (type 0) fibroid. What is the next best step?
   A. Do nothing.
   B. Place her on oral contraceptive pills.
   C. Order a hysterosalpingogram.
   D. Proceed with hysteroscopic myomectomy.

2. At 27-year-old woman presents with abnormal uterine bleeding. A careful history reveals new-onset acne, hirsutism, and deepening of the voice. Which test(s) would be most helpful at this point?
   A. Hysterosalpingogram
   B. CBC
   C. Serum testosterone and dehydroepiandrosterone
   D. Endometrial biopsy

3. A 33-year-old woman with a normal-appearing uterus on transvaginal ultrasound has continued to bleed for 3 weeks despite treatment with high-dose oral contraceptives. What is the first adjuvant therapy would you consider?
   A. Sonohysterogram
   B. Oral antibiotics
   C. Endometrial biopsy
   D. Vaginal Hysterectomy

4. A 23-year-old woman taking oral contraceptives presents with several months of postcoital spotting. Which test would be least helpful at this point?
   A. Pelvic examination with visualization of the cervix
   B. Papanicolaou smear
   C. Nucleic acid amplification tests for chlamydia and gonorrhea
   D. Endometrial biopsy

8.13 Answers

1. D
2. C
3. B
4. D

References

1. Matteson KA, Baker CA, Clark MA, Frick KD. Abnormal uterine bleeding, health status, and usual source of medical care: analyses using the Medical Expenditures Panel Survey. J Women's Health (Larchmt). 2013;22:959–65.
2. Munro MG, Critchley HO, Broder MS, Fraser IS, FIGO Working Group on Menstrual Disorders. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int J Gynaecol Obstet. 2011;113(1):3–13.
3. Coulter A, Bradlow J, Agass M, Martin-Bates C, Tulloch A. Outcomes of referrals to gynaecology outpatient clinics for menstrual problems: an audit of general practice records. Br J Obstet Gynaecol. 1991;98:789–96.
4. Morgan DM, Kamdar NS, Swenson CW, Kobernik EK, Sammarco AG, Nallamothu B. Nationwide trends in the utilization of and payments for hysterectomy in the United States among commercially insured women. Am J Obstet Gynecol. 2018;218(4):425.e1–425.e18.
5. Carlson KJ, Nichols DH, Schiff I. Indications for hysterectomy. N Engl J Med. 1993;328:856–60.
6. Bayer SR, DeCherney AH. Clinical manifestations and treatment of dysfunctional uterine bleeding. JAMA. 1993;269(14):1823–8.
7. Fraser IS, Critchley HO, Munro MG, Broder M, Writing Group for this Menstrual Agreement Process. A process designed to lead to international agreement on terminologies and definitions used to describe abnormalities of menstrual bleeding. Fertil Steril. 2007;87(3):466–76.
8. Zhang J, Salamonsen LA. In vivo evidence for active matrix metalloproteinases in human endometrium supports their role in tissue breakdown at menstruation. J Clin Endocrinol Metab. 2002;87(5):2346–51.
9. Brenner PF. Differential diagnosis of abnormal uterine bleeding. Am J Obstet Gynecol. 1996;175(3 Pt 2):766–9.
10. Haynes PJ, Hodgson H, Anderson AB, Turnbull AC. Measurement of menstrual blood loss in patients complaining of menorrhagia. Br J Obstet Gynaecol. 1977;84(10):763–8. https://doi.org/10.1111/j.1471-0528.1977.tb12490.x.
11. ACOG Committee on Practice Bulletins—Gynecology. Practice bulletin no. 128: diagnosis of abnormal uterine bleeding in reproductive-aged women. Obstet Gynecol. 2012;120(1):197–206. https://doi.org/10.1097/AOG.0b013e318262e320.
12. Ferenczy A. Pathophysiology of endometrial bleeding. Maturitas. 2003;45(1):1–14.
13. van Gorp EC, Suharti C, ten Cate H, Dolmans WM, van der Meer JW, ten Cate JW, Brandjes DP. Review: infectious diseases and coagulation disorders. J Infect Dis. 1999;180(1):176–86. https://doi.org/10.1086/314829.
14. American Academy of Pediatrics Committee on Adolescence, American College of Obstetricians and Gynecologists Committee on Adolescent Health Care, Diaz A, Laufer MR, Breech LL. Menstruation in girls and adolescents: using the menstrual cycle as a vital sign. Pediatrics. 2006;118(5):2245–50.
15. O'Connor KA, Holman DJ, Wood JW. Menstrual cycle variability and the perimenopause. Am J Hum Biol. 2001;13(4):465–78.
16. Tsilchorozidou T, Overton C, Conway GS. The pathophysiology of polycystic ovary syndrome. Clin Endocrinol. 2004;60(1):1–17.
17. Zawadski JK, Dunaif A. Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. Polycystic ovary syndrome. Boston: Blackwell Scientific; 1992. p. 377–84.

18. Hoeger KM. Obesity and lifestyle management in polycystic ovary syndrome. Clin Obstet Gynecol. 2007;50(1):277–94.
19. Hurd WW, Abdel-Rahman MY, Ismail SA, Abdellah MA, Schmotzer CL, Sood A. Comparison of diabetes mellitus and insulin resistance screening methods for women with polycystic ovary syndrome. Fertil Steril. 2011;96(4):1043–7.
20. Brennan K, Huang A, Azziz R. Dehydroepiandrosterone sulfate and insulin resistance in patients with polycystic ovary syndrome. Fertil Steril. 2009;91(5):1848–52. https://doi.org/10.1016/j.fertnstert.2008.02.101. Epub 2008 Apr 25. PMID: 18439591; PMCID: PMC2691796.
21. Chang RJ. A practical approach to the diagnosis of polycystic ovary syndrome. Am J Obstet Gynecol. 2004;191(3):713–7.
22. Dumanski SM, Ahmed SB. Fertility and reproductive care in chronic kidney disease. J Nephrol. 2019;32(1):39–50. https://doi.org/10.1007/s40620-018-00569-9. Epub 2019 Jan 2
23. Shaaban MM, Ghaneimah SA, Hammad WA, El-Sharkawy MM, Elwan SI, Ahmed YA. Sex steroids in women with liver cirrhosis. Int J Gynaecol Obstet. 1980;18(3):181–4. https://doi.org/10.1002/j.1879-3479.1980.tb00276.x.
24. Holley JL. The hypothalamic-pituitary axis in men and women with chronic kidney disease. Adv Chronic Kidney Dis. 2004;11(4):337–41.
25. Okeke T, Anyaehie U, Ezenyeaku C. Premature menopause. Ann Med Health Sci Res. 2013;3(1):90–5. https://doi.org/10.4103/2141-9248.109458. PMID: 23634337; PMCID: PMC3634232.
26. Britton LE, Alspaugh A, Greene MZ, McLemore MR. CE: an evidence-based update on contraception. Am J Nurs. 2020;120(2):22–33.
27. Krettek JE, Arkin SI, Chaisilwattana P, Monif GR. Chlamydia trachomatis in patients who used oral contraceptives and had intermenstrual spotting. Obstet Gynecol. 1993;81(5):728–31.
28. Falcone T, Desjardins C, Bourque J, Granger L, Hemmings R, Quiros E. Dysfunctional uterine bleeding in adolescents. J Reprod Med. 1994;39:761–4.
29. ACOG Committee on Practice Bulletins—Gynecology. Committee ACOG. Opinion no. 451: Von Willebrand disease in women. Obstet Gynecol. 2009;114:1439–43.
30. Weaver J, Shoaibi A, Truong HQ, Larbi L, Wu S, Wildgoose P, Rao G, Freedman A, Wang L, Yuan Z, Barnathan E. Comparative risk assessment of severe uterine bleeding following exposure to direct oral anticoagulants: a network study across four observational databases in the USA. Drug Saf. 2021;44(4):479–97.
31. Minakuchi K, Hirai K, Kawamura N, Ishiko O, Kanaoka Y, Ogita S. Case of hemorrhagic shock due to hypermenorrhea during anticoagulant therapy. Arch Gynecol Obstet. 2000;264(2):99–100.
32. Knez J, Day A, Jurkovic D. Ultrasound imaging in the management of bleeding and pain in early pregnancy. Best Pract Res Clin Obstet Gynaecol. 2014;28(5):621–36. https://doi.org/10.1016/j.bpobgyn.2014.04.003. Epub 2014 Apr 24. PMID: 24841987.
33. Hendriks E, Rosenberg R, Prine L. Ectopic pregnancy: diagnosis and management. Am Fam Physician. 2020;101(10):599–606. PMID: 32412215.
34. ACOG Committee on Practice Bulletins—Gynecology. ACOG practice bulletin no. 191: tubal ectopic pregnancy. Obstet Gynecol. 2018;131(2):e65–77.
35. Stevens FT, Katzorke N, Tempfer C, Kreimer U, Bizjak GI, Fleisch MC, Fehm TN. Gestational trophoblastic disorders: an update in 2015. Geburtshilfe Frauenheilkd. 2015;75(10):1043–50. https://doi.org/10.1055/s-0035-1558054. PMID: 26556906; PMCID: PMC4629994.
36. Workowski KA, Bolan GA, Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015;64(RR-03):1–137. Erratum in: MMWR Recomm Rep. 2015;64(33):924.
37. Eschenbach DA. Acute pelvic inflammatory disease: etiology, risk factors and pathogenesis. Clin Obstet Gynecol. 1976;19(1):147–69.
38. Bjartling C, Osser S, Johnsson A, Persson K. Clinical manifestations and epidemiology of the new genetic variant of Chlamydia trachomatis. Sex Transm Dis. 2009;36(9):529–35. https://doi.org/10.1097/OLQ.0b013e3181a8cef1.
39. Heatley MK. The association between clinical and pathological features in histologically identified chronic endometritis. J Obstet Gynaecol. 2004;24(7):801–3.
40. Gilmore H, Fleischhacker D, Hecht JL. Diagnosis of chronic endometritis in biopsies with stromal breakdown. Hum Pathol. 2007;38(4):581–4.
41. Eckert LO, Thwin SS, Hillier SL, Kiviat NB, Eschenbach DA. The antimicrobial treatment of subacute endometritis: a proof of concept study. Am J Obstet Gynecol. 2004;190(2):305–13.
42. Davies J, Kadir RA. Endometrial haemostasis and menstruation. Rev Endocr Metab Disord. 2012;13(4):289–99. https://doi.org/10.1007/s11154-012-9226-4.
43. Khan KN, Kitajima M, Hiraki K, Yamaguchi N, Katamine S, Matsuyama T, Nakashima M, Fujishita A, Ishimaru T, Masuzaki H. Escherichia coli contamination of menstrual blood and effect of bacterial endotoxin on endometriosis. Fertil Steril. 2010;94(7):2860-3.e1-3.
44. Savaris RF, Teixeira LM, Torres TG, Edelweiss MI, Moncada J, Schachter J. Comparing ceftriaxone plus azithromycin or doxycycline for pelvic inflammatory disease: a randomized controlled trial. Obstet Gynecol. 2007;110(1):53–60.
45. Marrazzo JM, Handsfield HH, Whittington WL. Predicting chlamydial and gonococcal cervical infection: implications for management of cervicitis. Obstet Gynecol. 2002;100(3):579–84.
46. Rosenthal AN, Panoskaltsis T, Smith T, Soutter WP. The frequency of significant pathology in

women attending a general gynaecological service for postcoital bleeding. BJOG. 2001;108(1):103–6.
47. Telner DE, Jakubovicz D. Approach to diagnosis and management of abnormal uterine bleeding. Can Fam Physician. 2007;53(1):58–64.
48. 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;188:100–7.
49. Nathani F, Clark TJ. Uterine polypectomy in the management of abnormal uterine bleeding: a systematic review. J Minim Invasive Gynecol. 2006;13(4):260–8.
50. Clevenger-Hoeft M, Syrop CH, Stovall DW, Van Voorhis BJ. Sonohysterography in premenopausal women with and without abnormal bleeding. Obstet Gynecol. 1999;94:516.
51. Bazot M, Cortez A, Darai E, Rouger J, Chopier J, Antoine JM, et al. Ultrasonography compared with magnetic resonance imaging for the diagnosis of adenomyosis: correlation with histopathology. Hum Reprod. 2001;16:2427–33.
52. Armstrong AJ, Hurd WW, Shaker ME, Elguero SB, Barker NG, Zanotti KM. Diagnosis and management of endometrial hyperplasia. J Minim Invasive Gynecol. 2012;19(5):562–71.
53. Sorosky J. Endometrial cancer. Obstet Gynecol. 2008;112(1):186–7.
54. Young RH, Clement PB. Pseudoneoplastic glandular lesions of the uterine cervix. Semin Diagn Pathol. 1991;8(4):234–49.
55. Chapman GW Jr. Management of early carcinoma of the ovary. J Natl Med Assoc. 1988;80(9):1033–7.
56. Koukourakis GV, Kouloulias VE, Koukourakis MJ, Zacharias GA, Papadimitriou C, Mystakidou K, Pistevou-Gompaki K, Kouvaris J, Gouliamos A. Granulosa cell tumor of the ovary: tumor review. Integr Cancer Ther. 2008;7(3):204–15.
57. PDQ Adult Treatment Editorial Board. Vaginal cancer treatment (PDQ®): health professional version. 2021 Feb 22. In: PDQ cancer information summaries [Internet]. Bethesda: National Cancer Institute (US); 2002.
58. Centers for Disease Control and Prevention. Gynecologic Cancer Incidence, United States—2012–2016, USCS Data Brief, no 11. Atlanta: Centers for Disease Control and Prevention, US Department of Health and Human Services; 2019.
59. Kouides PA. Evaluation of abnormal bleeding in women. Curr Hematol Rep. 2002;1(1):11–8.
60. Woo YL, White B, Corbally R, Byrne M, O'Connell N, O'Shea E, et al. Von Willebrand's disease: an important cause of dysfunctional uterine bleeding. Blood Coagul Fibrinolysis. 2002;13(2):89–93.
61. Sahin Y, Kelestimur F. The frequency of late-onset 21-hydroxylase and 11 beta-hydroxylase deficiency in women with polycystic ovary syndrome. Eur J Endocrinol. 1997;137(6):670–4.
62. Kouides PA. Menorrhagia from a haematologist's point of view. Part I: initial evaluation. Haemophilia. 2002;8(3):330–8.
63. Valentine L. Hysteroscopy for abnormal uterine bleeding and fibroids. Clin Obstet Gynecol. 2017;60(2):231–44.
64. ACOG Committee on Practice Bulletins—Gynecology. Committee opinion number 557: management of acute abnormal uterine bleeding in non pregnant reproductive-aged women. Obstet Gynecol. 2013;120(1):891–6. Reaffirmed in 2020.
65. Schapiro L, Thorp JM. Management of leiomyoma causing myocardial infarction. Eur J Obstet Gynecol Reprod Biol. 1996;65(2):235–6.
66. Wu CC, Lee MH. Transcatheter arterial embolotherapy: a therapeutic alternative in obstetrics and gynecologic emergencies. Semin Intervent Radiol. 2006;23(3):240–8.
67. Munro MG, Mainor N, Basu R, Brisinger M, Barreda L. Oral medroxyprogesterone acetate and combination oral contraceptives for acute uterine bleeding: a randomized controlled trial. Obstet Gynecol. 2006;108(4):924–9.
68. Ammerman SR, Nelson AL. A new progestogen-only medical therapy for outpatient management of acute, abnormal uterine bleeding: a pilot study. Am J Obstet Gynecol. 2013;208(6):499.e1–5.
69. Legro RS, Barnhart HX, Schlaff WD, Carr BR, Diamond MP, Carson SA, et al. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. N Engl J Med. 2007;356(6):551–66.
70. Sulak PJ. The career woman and oral contraceptive use. Int J Fertil. 1991;36(Suppl 2):90–7.
71. Anderson FD, Hait H. A multicenter, randomized study of an extended cycle oral contraceptive. Contraception. 2003;68:89–96.
72. Hurskainen R, Teperi J, Rissanen P, Aalto AM, Grenman S, Kivelä A, et al. Clinical outcomes and costs with the levonorgestrel-releasing intrauterine system or hysterectomy for treatment of menorrhagia; randomized trial 5 year follow up. JAMA. 2004;291:1456–63.
73. Hidalgo M, Bahamondes L, Perrotti M, Diaz J, DantasMonteiro C, Petta C. Bleeding patterns and clinical performance of the levonorgestrel-releasing intrauterine system (Mirena) up to two years. Contraception. 2002;65(2):129–32.
74. Nilsson CG, Lahteenmaki PL, Luukkainen T, Robertson DN. Sustained intrauterine release of levonorgestrel over five years. Fertil Steril. 1986;45(6):805–7.
75. Hillard TC, Siddle NC, Whitehead MI, Fraser DI, Pryse-Davies J. Continuous combined conjugated equine estrogen-progestogen therapy: effects of medroxyprogesterone acetate and norethindrone acetate on bleeding patterns and endometrial histologic diagnosis. Am J Obstet Gynecol. 1992;167(1):1–7.
76. Rafie S, Borgelt L, Koepf ER, Temple-Cooper ME, Lehman KJ. Novel oral contraceptive for heavy

menstrual bleeding: estradiol valerate and dienogest. Int J Women's Health. 2013;5:313–21.
77. Wright KP, Johnson JV. Evaluation of extended and continuous use oral contraceptives. Ther Clin Risk Manag. 2008;4(5):905–11.
78. Livshits A, Seidman DS. Role of non-steroidal anti-inflammatory drugs in gynecology. Pharmaceuticals (Basel). 2010;3(7):2082–9.
79. Lethaby A, Puscasiu L, Vollenhoven B. Pre-operative medical therapy before surgery for uterine fibroids. Cochrane Database Syst Rev. 2017;11(11):CD000547.
80. Cooke I, Lethaby A, Farquhar C. Antifibrinolytics for heavy menstrual bleeding. Cochrane Database Syst Rev. 2000;2:CD000249.
81. Matteson KA, Rahn DD, Wheeler TL 2nd, Casiano E, Siddiqui NY, Harvie HS, Mamik MM, Balk EM, Sung VW, Society of Gynecologic Surgeons Systematic Review Group. Nonsurgical management of heavy menstrual bleeding: a systematic review. Obstet Gynecol. 2013;121(3):632–43.
82. Fraser IS, Porte RJ, Kouides PA, Lukes AS. A benefit-risk review of systemic haemostatic agents: part 2: in excessive or heavy menstrual bleeding. Drug Saf. 2008;31(4):275–82.
83. Kaunitz AM, Meredith S, Inki P, Kubba A, Sanchez-Ramos L. Levonorgestrel-releasing intrauterine system and endometrial ablation in heavy menstrual bleeding: a systematic review and meta-analysis. Obstet Gynecol. 2009;113(5):1104–16.
84. Lethaby A, Augood C, Duckitt K, Farquhar C. Nonsteroidal anti-inflammatory drugs for heavy menstrual bleeding. Cochrane Database Syst Rev. 2007;4:CD000400.
85. ACOG Committee on Practice Bulletins—Gynecology. ACOG practice bulletin no. 81: endometrial ablation. Obstet Gynecol. 2007;109:1233–48.
86. Lethaby A, Shepperd S, Cooke I, Farquhar C. Endometrial resection and ablation versus hysterectomy for heavy menstrual bleeding. Cochrane Database Syst Rev. 2000;2:CD000329.