Abnormal Uterine Bleeding

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8.1 Introduction

Abnormal uterine bleeding (AUB) is a common clinical problem, and is a cause of significant public health concern as it impairs quality of life by creating significant physical, emotional, sexual, social, and financial burdens [1–3].

A broad definition of AUB includes any uterine bleeding that occurs outside the parameters of normal menstruation during the reproductive years. Specifically, AUB is a term utilized to describe a spectrum of symptoms, including heavy menstrual bleeding (HMB), intermenstrual bleeding, and a combination of both heavy and prolonged menstrual bleeding. This terminology was established by the International Federation of Gynecology and Obstetrics (FIGO) Menstrual Disorders Working Group in 2011 and has since been adopted worldwide [4]. It includes bleeding originating from either the uterine fundus or cervix and does not include bleeding that originates in the lower genital tract.

It is important for gynecologists to develop a safe and cost-effective approach to the diagnosis and management of AUB. The most expedient methods for evaluation and treatment are dependent on understanding the various causes of AUB and the corresponding presenting symptoms.

Clinical Case

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 a contraceptive method but has been unable to get pregnant for 3 years and is not currently pregnant. 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. Her bimanual examination is difficult because of her obesity, but does not reveal uterine or adnexal masses or tenderness. Pelvic ultrasound shows a normal size anteverted uterus with a 16 mm endometrial stripe and what appear to be clots in the uterine cavity. Laboratory evaluation includes a negative blood hCG, 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.

8.2 Diagnostic Criteria

AUB is broadly defined as any uterine bleeding that occurs outside the parameters of normal menstruation during the reproductive years. It includes bleeding originating from either the uterine fundus or cervix and does not include bleeding that originates in the lower genital tract (i.e., the vagina or vulva). However, these causes can be difficult to distinguish clinically. Therefore, both of these origins should be considered in all patients presenting with bleeding from the uterus. It can be further characterized in terms of volume, duration, frequency, and regularity. AUB can be classified as acute or chronic. Chronic abnormal uterine bleeding is bleeding that has occurred for at least 6 months.

The terms "menorrhagia" and "metrorrhagia" have now been replaced by more descriptive terms, including "heavy menstrual bleeding" and "intermenstrual bleeding." A new classification system is also being used to classify AUB according to the etiology [4]. The acronym PALM COEIN classifies the causes of AUB into structural abnormalities and nonstructural abnormalities (Table 8.1).

Table 8.1 PALM COEIN classification for abnormal uterine bleeding (AUB)

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

Abnormal bleeding can occur during childhood, the reproductive years, and after menopause. Since the differential diagnoses and corresponding diagnostic approaches are markedly different during these time periods, AUB in women before and after the reproductive years is considered separately in ▶ Chaps. 4 and 10.

8.3 Prevalence

AUB accounts for approximately 30% of all gynecology visits [5]. Despite its frequency, AUB is a difficult diagnostic and therapeutic challenge and accounts for more than half of all hysterectomies performed in the USA. Approximately 20% of hysterectomy specimens removed for AUB have no visible pathology [6]. This suggests that many cases of AUB are potentially treatable using hormonal therapy or other systemic or local treatment modalities.

8.4 Normal Menstruation

A solid understanding of the normal menstrual cycle is essential to effectively evaluate and treat women with irregularities. The concept of normal menstruation is somewhat subjective and often varies between individual women and certainly between cultures. The normal menstrual cycle occurs over a span of 4.5–8 days every 24–38 days, with cycle-to-cycle variation over 12 months of ±2 to 20 days [4]. Normal menstruation should not cause severe pain or include passage of large clots.

Peri-menarchal (age <20) and peri-menopausal (age >40) stages have tremendous cycle length variation as these age ranges have the highest prevalence of anovulatory cycles [7].

The total amount of blood lost during a normal menstrual period has been estimated to average 30 mL and should be <80 mL. In most women, 90% of all blood loss per cycle occurs within the first 3 days of menstruation [8]. However, menstrual blood loss is difficult to estimate clinically, because much of the menstrual effluent is dissolved endometrium [9]. If the patient is changing pads or tampons more than once per hour, this is considered to be outside the parameters of normal menstruation.

The different bleeding patterns of AUB often give hints to the etiology and can be used to guide the appropriate diagnostic work-up. Due to the marked variation in presentation and the possible existence of multiple causes of bleeding, presentation alone cannot be used to clinically exclude common conditions.

8.5 Dysfunctional Uterine Bleeding

Dysfunctional uterine bleeding (DUB) is a term that refers to excessive uterine bleeding in cases in which no uterine pathology can be identified and is therefore a diagnosis of exclusion [10]. Due to the development of a greater understanding of AUB and the availability of more sophisticated diagnostic techniques, this term is less frequently used today.

In many cases that would have been referred to as DUB in the past, modern diagnostic techniques identify either uterine or systemic pathologies that (1) result in anovulation (e.g., hypothyroidism), (2) result from anovulation (e.g., endometrial hyperplasia or carcinoma), or (3) coexists with anovulatory bleeding but may or may not be causal (e.g., leiomyomata). Bleeding unrelated to uterine pathology can usually be determined to be a result of chronic anovulation (polycystic ovary syndrome [PCOS] and related conditions), exogenous steroid hormones (contraceptives or hormone replacement therapy), or hemostatic disorders (e.g., von Willebrand disease).

Treatment is most likely to be effective when specific causes of AUB can be identified. Since the term "DUB" is used to refer to widely divergent causes of AUB, a national consensus group recently concluded that this term is unlikely to improve diagnosis or treatment and thus no longer has any usefulness in clinical medicine [11].

8.6 Abnormal Uterine Bleeding Caused by Uterine Conditions

AUB can be grouped according to the basic pathophysiology of the various etiologies. The clinician must keep in mind that any individual patient can simultaneously have more than one

Table 8.2 Common uterine conditions associated with AUB

Pregnancy
Early normal pregnancy
Spontaneous abortion
Ectopic pregnancy
Gestational trophoblastic disease
Infection
Pelvic inflammatory disease
Endometritis
Cervicitis
Neoplasms
Benign
Leiomyoma
Endometrial polyps
Endocervical polyps
Malignant
Endometrial carcinoma
Cervical carcinoma
Adenomyosis

cause of uterine bleeding (Table 8.2). Therefore, the work-up should include an appropriate evaluation encompassing both likely and serious anatomic and systemic etiologies.

8.7 Pregnancy

It is important to exclude pregnancy in every case of AUB in a reproductive-aged woman, no matter how obvious any alternative diagnosis may be. Pregnancies are the most common cause of AUB in the reproductive age group, including normal pregnancies, spontaneous abortions, ectopic pregnancies, and gestational trophoblastic disease.

First-trimester bleeding occurs in up to 25% of all pregnancies and is associated with an increased risk of many common complications [12]. In approximately half of these cases, bleeding will be an early symptom of impending spontaneous abortion, whereas the remaining half will ultimately prove to have a viable pregnancy. Ectopic pregnancies currently make up 2% of all pregnancies and commonly present with AUB as one of the presenting symptoms [13]. Gestational trophoblastic disease is another pregnancy-related problem that presents as AUB in >80% of cases [14].

8.8 Uterine Pathology

It is a priority for gynecologists to precisely identify uterine pathology that might contribute to uterine bleeding. Most of these diagnoses can be determined to be related to infection and neoplasm. Additionally, a common uterine pathology related to AUB is adenomyosis.

8.9 Infection

Infection, in the form of endometritis, is an under-recognized cause of AUB and is often the basis of what appears to be AUB. In obvious cases of pelvic inflammatory disease, approximately 40% of patients will present with vaginal bleeding [15]. However, subclinical endometritis can also result in AUB.

Chronic endometritis was diagnosed in the past only when plasma cells were found on endometrial biopsy. More recent studies have shown an association between AUB and endometritis that manifests only as reactive changes in the surface endometrium and not in association with the presence of a particular type of inflammatory cell [16]. Other studies have verified that subclinical endometritis is a common finding in patients diagnosed with AUB and can be related to any of a number of different pathogens [17].

Cervicitis is another commonly recognized cause of AUB and is characterized by postcoital spotting. Postcoital bleeding is the most common presenting symptom in women found to have *Chlamydia* infections [18]. In addition to common sexually transmitted diseases (i.e., chlamydia and gonorrhea), other vaginal flora and pathogens can also cause cervicitis [19].

8.10 Neoplasms

AUB can be a presenting symptom for gynecologic neoplasms involving the cervix, uterine fundus, or ovaries. These neoplasms can be benign

(e.g., endometrial or endocervical polyps, leiomyoma) or malignant (e.g., endometrial or cervical carcinoma). Focal intracavitary lesions account for up to 40% of cases of AUB [20]. Neoplasms of the ovary can indirectly cause irregular bleeding by interfering with ovulation, as discussed below. Some of the most common neoplasms known to cause AUB are reviewed below.

8.11 Leiomyomas

These benign tumors of the myometrium are remarkably common and by age 50 can be found in almost 70% of white women and >80% of black women upon ultrasonographic examination [21]. Many of these leiomyomas are subclinical, and estimates of symptomatic leiomyomas range from 20–40%.

Submucosal and intracavitary leiomyomas that distort the uterine cavity are most likely to result in menorrhagia, presumably because of a direct effect on the adjacent endometrium. Large intramural leiomyomas can sometimes result in menorrhagia. However, the majority of leiomyomas that are intramural, subserosal, or pedunculated on the external uterine surface are not associated with AUB.

8.12 Adenomyosis

This benign condition involves the invasion of 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 [22]. 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% [22]. Perhaps in the future, there will be more effective diagnostic testing for adenomyosis and treatments other than hysterectomy.

8.13 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 [23]. 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 [24]. 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 [23]. 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%.

8.14 Endometrial Hyperplasia

It is unlikely that endometrial hyperplasia causes AUB. However, this condition is most often found in premenopausal women with AUB with prolonged anovulation [25]. Although endometrial hyperplasia is not in itself a health risk, it is both a precursor to and marker for concurrent endometrial cancer, particularly in the presence of atypia.

8.15 Endometrial Cancer

The single most important disease to identify early in the evaluation of a peri- or postmenopausal woman with AUB is endometrial cancer. Approximately 20% of endometrial cancer is diagnosed in women before menopause and 5% before the age of 40 years [26]. After the menopause, approximately 10% of women with AUB will be found to have endometrial cancer, and the incidence rises with each decade of life thereafter.

8.16 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 usually range in size from 3 to 20 mm, but occasionally 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. 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 often show a pattern of microglandular hyperplasia [27].

Endocervical polyps are relatively common in sexually active women, but are rare before menarche. 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.

8.17 Cervical Cancer

Cervical dysplasia can be found in up to 17% of women presenting with postcoital spotting, and 4% will have invasive cancer [28]. In the absence of a visible lesion, Papanicolaou smears and colposcopy (if indicated) are important diagnostic tools. In the presence of a visible cervical lesion, it is critical to biopsy the lesion to confirm the clinical diagnosis.

8.18 Abnormal Uterine Bleeding Unrelated to Uterine Pathology

Many women experience heavy or irregular menstrual bleeding that is not caused by an underlying condition of the uterus. Anovulatory bleeding is one of the most common underlying causes; however, a number of other unrelated causes, such as exogenous hormones and bleeding disorders, must also be considered (Table 8.3).

Table 8.3 Causes of AUB unrelated to pregnancy or uterine pathology

Exogenous hormones
Hormone contraceptives
Hormone replacement therapy
Ovulation defects
Physiologic oligo-ovulation
Perimenarchal
Perimenopasual
Polycystic ovary syndrome
Hyperandrogenic states
Congenital adrenal hyperplasia, adult-onset
Cushing's syndrome
Ovarian and adrenal tumors
Systemic diseases that interfere with ovulation
Hypothyroidism
Hyperprolactinemia
Renal failure
Liver disease
Endometrial atrophy
Menopause
Premature ovarian failure
Hypogonadotropic hypogonadism
Exogenous progestins
Hyperandrogenemia
Coagulopathy
Hereditary bleeding disorders
Von Willebrand disease
Disorders of platelet function and fibrinolysis
Acquired bleeding abnormalities
Idiopathic thrombocytopenic purpura
Leukemia
Aplastic anemia
Anticoagulation therapy

8.19 Exogenous Hormones

Hormonal therapy is one of the most common causes of AUB. Specifically, irregular bleeding is the most common symptom of women receiving contraceptive therapy and hormone replacement therapy (see ▶ Chap. 10) and the most common reason for discontinuation of these therapies.

8.20 Hormone Contraceptives

Approximately ten million women in the USA use some type of hormone contraception, including combination oral contraceptives, progestin-only pills, depot medroxyprogesterone acetate injections, progestin-containing intrauterine devices, subdermal levonorgestrel implants, transdermal combination hormone patches, and intravaginal rings. In addition to being a common reason to visit primary care physicians and gynecologists, AUB is the major reason for contraception discontinuation and subsequent unplanned pregnancy.

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 patient 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 3 months while a patient is on hormonal contraceptives, other common causes should be excluded. In young, sexually active women, sexually transmitted diseases should be excluded, because in one study, almost one-third of women on oral contraceptives who experienced abnormal bleeding were found to have otherwise asymptomatic *Chlamydia trachomatis* infections [29]. If no cause for AUB other than hormonal therapy is found, treatment options include the use of supplemental estrogen or changing to an oral contraceptive with a different formulation that has a different progestin or higher estrogen content.

Women using progestin-only contraceptives have a greater risk of continued AUB than those using combined oral contraceptives. Prolonged exposure to progestins results in a microscopic condition sometimes called "pseudoatrophy" (see the section on Endometrial Atrophy). When reassurance is not sufficient, administration of supplemental estrogen during these bleeding episodes is sometimes useful.

8.21 Ovulation Defects

Abnormal or absent ovulation is a common cause of AUB during the reproductive years. A brief description of normal menstrual physiology (which is covered in depth in Chap. 1) is useful in understanding anovulation as an underlying cause of AUB.

8.22 Normal Menstruation

Each month, the endometrium of normally ovulating women is exposed to physiologic levels of estradiol (50–250 pg/mL), accompanied in the last 14 days of each cycle by progesterone (midluteal phase >12 nmol/L). The result is a structurally stable endometrium 5–20-mm thick as measured by transvaginal ultrasound.

Withdrawal of progesterone and estrogen results in menstruation, which involves the breakdown and uniform shedding of much of the functional layer of the endometrium, which is enzymatically dissolved by matrix metalloproteinases [30]. Normal menses occur every 28 ± 7 days, with duration of flow of 4 ± 2 days, and a blood loss of 40 ± 40 mL [31]. Hemostasis is achieved by a combination of vasoconstriction of the spiral arterioles and normal coagulation mechanisms.

8.23 Oligo- and Anovulation

Irregularity or absence of ovulation is common among reproductive-aged women not using hormonal contraception. In the perimenarchal years,

adolescents often have anovulatory cycles as part of the maturation process, but only occasionally do they complain of clinically significant AUB. In the perimenopausal years, anovulatory cycles again become more common for many women. These episodes of endometrial exposure to unopposed estrogen increase the risk of not only AUB but also endometrial hyperplasia and endometrial cancer. During the intervening years, both chronic and intermittent intervals of anovulation can occur, usually as a result of a treatable underlying condition.

8.24 Mechanism of Anovulatory Bleeding

Anovulation results in AUB as a result of chronic exposure of the endometrium to estrogen, without the effect of cyclic exposure to postovulatory progesterone. Endometrium that is exposed to unopposed estrogen becomes abnormally thickened and structurally incompetent. The result is asynchronous shedding of portions of the endometrium unaccompanied by vasoconstriction.

The bleeding associated with unopposed estrogen exposure is usually heavy. Since the blood has not been lysed by endometrial enzymes, blood clots are often passed, resulting in increased menstrual cramping in many women. Prolonged periods of bleeding also appear to predispose to subclinical endometritis, which can further exacerbate bleeding, and is often unresponsive to hormonal therapy.

8.25 Polycystic Ovary Syndrome

The most common cause of chronic anovulation is a disorder that can present with a constellation of symptoms and is referred to as PCOS (see ▸ Chap. 8). PCOS is a heterogeneous endocrine and metabolic disorder that affects 6–10% of reproductive age women [32]. This syndrome is diagnosed when a woman without an underlying 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 [33]. These women have circulating estrogen levels in the normal range, but anovulatory progesterone levels.

PCOS is believed to result from insulin resistance in many women [32]. In today's culture, insulin resistance is often the result of obesity. However, only 70% of women with PCOS are obese [33]. Insulin resistance will be found in approximately 75% of women with PCOS who are obese, but <40% of those who are not obese [34].

The mechanism whereby insulin resistance results in PCOS is intriguing [35]. Insulin increases production of androgens by both the ovaries (primarily androstenedione and testosterone) and adrenal gland (primarily dehydroepiandrosterone). In the ovary, insulin increases androgen secretion by both theca cells, which are LH-dependent, and ovarian stroma cells. These increased androgens 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, which in turn stimulates the ovaries to secrete more androgens in concert with insulin. The positive-feedback loop that results is believed to be the cause of many cases of PCOS. 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 [35].

8.26 Systemic Diseases that can Mimic PCOS

Some patients that are oligo- or anovulatory can have an underlying systemic disease, which makes these patients clinically indistinguishable from PCOS. Although some diseases can be detected with appropriate testing, not all of these systemic conditions can be treated such that the symptoms completely resolve.

Conditions that result in signs and symptoms identical to PCOS can be divided into two groups. The first group includes conditions that cause hyperandrogenemia, which in turn can interfere with ovulation and result in a clinical picture identical to PCOS [36]. These include adult-onset congenital adrenal hyperplasia, Cushing's syndrome and disease, and androgen-secreting neoplasms of the ovary or adrenal gland. Adult-onset congenital

adrenal hyperplasia 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 second group consists of any systemic condition that can interrupt ovulation. Both hypothyroidism and hyperprolactinemia are relatively common conditions that can have no other symptoms other than interfering with ovulation. Simple blood tests can screen for these conditions in the initial evaluation of PCOS. In addition, any serious systemic disease can interfere with ovulation—most notably, renal failure and chronic liver disease. These systemic disorders can also affect hemostasis. Patients with serious systemic diseases, however, usually manifest significant symptoms in addition to ovulatory dysfunction and AUB [37].

8.27 Endometrial Atrophy

Endometrial atrophy from any cause can result in AUB and is usually described as spotting. The significance of this type of AUB is that it is indistinguishable from the earliest symptoms of endometrial cancer and thus must be carefully evaluated in the peri- and postmenopausal woman.

Hypoestrogenemia is most commonly the result of surgical or natural menopause. Although natural menopause occurs at an average age of approximately 51 years, 2% of women undergo premature menopause before the age of 40 years. Hypoestrogenemia also occurs in women with normal ovaries who lack gonadal hormonal stimulation due to pituitary or hypothalamic pathology, descriptively grouped together as having hypogonadotropic hypogonadism. Causes of this condition include hypothalamic amenorrhea, usually secondary to conditions such as anorexia nervosa, repetitive or prolonged strenuous exercise, or starvation, and the relatively uncommon pituitary failure. Hypoestrogenemia can also occur secondary to hyperprolactinemia.

Histologically, hypoestrogenemia leads to atrophy of both endometrial glands and stroma. Scanty, small glands can be seen in dense stroma. The result is thinning of the endometrium, which can be <5-mm thick by transvaginal ultrasonography.

Prolonged exposure to exogenous progestins, with or without estrogen, can also result in endometrial atrophy. Long-term use of combined oral contraceptives results in poorly developed glands lined by a single layer of low columnar to cuboidal cells. 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. Progestin-only contraception results in endometrial atrophy with sparse, narrow glands lined by flattened epithelium in a spindle-cell stroma without decidual reaction. Women with hyperandrogenemia can develop a similar clinical and histological picture.

8.28 Coagulopathy

A surprisingly common cause of menorrhagia is one of the several inborn or acquired conditions that can interfere with the body's normal hemostatic mechanisms.

8.29 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. As many as 20% of adolescents who present with menorrhagia significant enough to cause anemia or hospitalization have a bleeding disorder, and should therefore undergo an evaluation for coagulopathy. However, it is important to remember that most AUB in this age group is probably due to anovulation [38].

The most common bleeding disorder is von Willebrand disease, which affects 1–2% of the population [39]. 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 thrombocytopenias and rare clotting factor deficiencies (e.g., factor I, II, V, VII, X, XI, XIII).

8.30 Acquired Bleeding Disorders

New onset of extremely heavy menses not amenable to hormonal therapy can sometimes be related to acquired bleeding abnormalities. Such abnormalities include idiopathic thrombocytopenia purpura (ITP) or hematologic diseases affecting platelet production, such as leukemia. Other systemic disorders, such as sepsis and liver disorders, can also cause an acquired hemostatic disorder resulting in bleeding.

8.31 Anticoagulant Therapy

Excessive bleeding can rarely be a significant problem for women taking anticoagulant therapy, such as warfarin or heparin. Fortunately, most women taking anticoagulants do not have problems with AUB, which is considered to be an adverse reaction to anticoagulant therapy. Life-threatening genital bleeding in women taking anticoagulants is rare, but may lead to emergency hysterectomy [40].

8.32 Clinical Evaluation of AUB

The work-up for AUB should be tailored to the clinical presentation of the patient and, importantly, the age should be taken into consideration. At the same time, the clinician must 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 cause. Sometimes subtle comorbid conditions, such as endometritis, can make single-factor therapy surprisingly ineffective [17]. 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.

8.33 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.

8.34 Pregnancy

In reproductive-aged women, the presence of signs and symptoms of pregnancy is important to ascertain. Current contraceptive methods and past pregnancy history are also important.

8.35 Characterization of 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 on history, 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 [41]. 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 [42]. Interestingly, in this same study, epistaxis and easy bruising were not clear discriminatory symptoms.

8.36 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, adnexal masses, and the presence and character of any tenderness.

8.37 Laboratory Testing

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

The most important test for all reproductive-aged women complaining of AUB is a beta-HCG test for pregnancy. 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, cervical 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 II 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 >40 years old should have an endometrial biopsy after pregnancy is excluded to detect endometrial hyperplasia or cancer.

Table 8.4 Laboratory testing for AUB

All patients
Pregnancy test
Complete blood count (including platelets)
Papanicolaou smear
Cervical tests for gonorrhea and chlamydia
Anovulation
Thyroid-stimulating hormone
Prolactin
Obesity
Type II diabetes screen: HgA1c
Hirsutism
Testosterone
DHEA-S
>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
VWf antigen
Ristocetin cofactor
Platelet aggregation studies
If the above are negative, consider
Factor XI level
Euglobulin clot lysis time

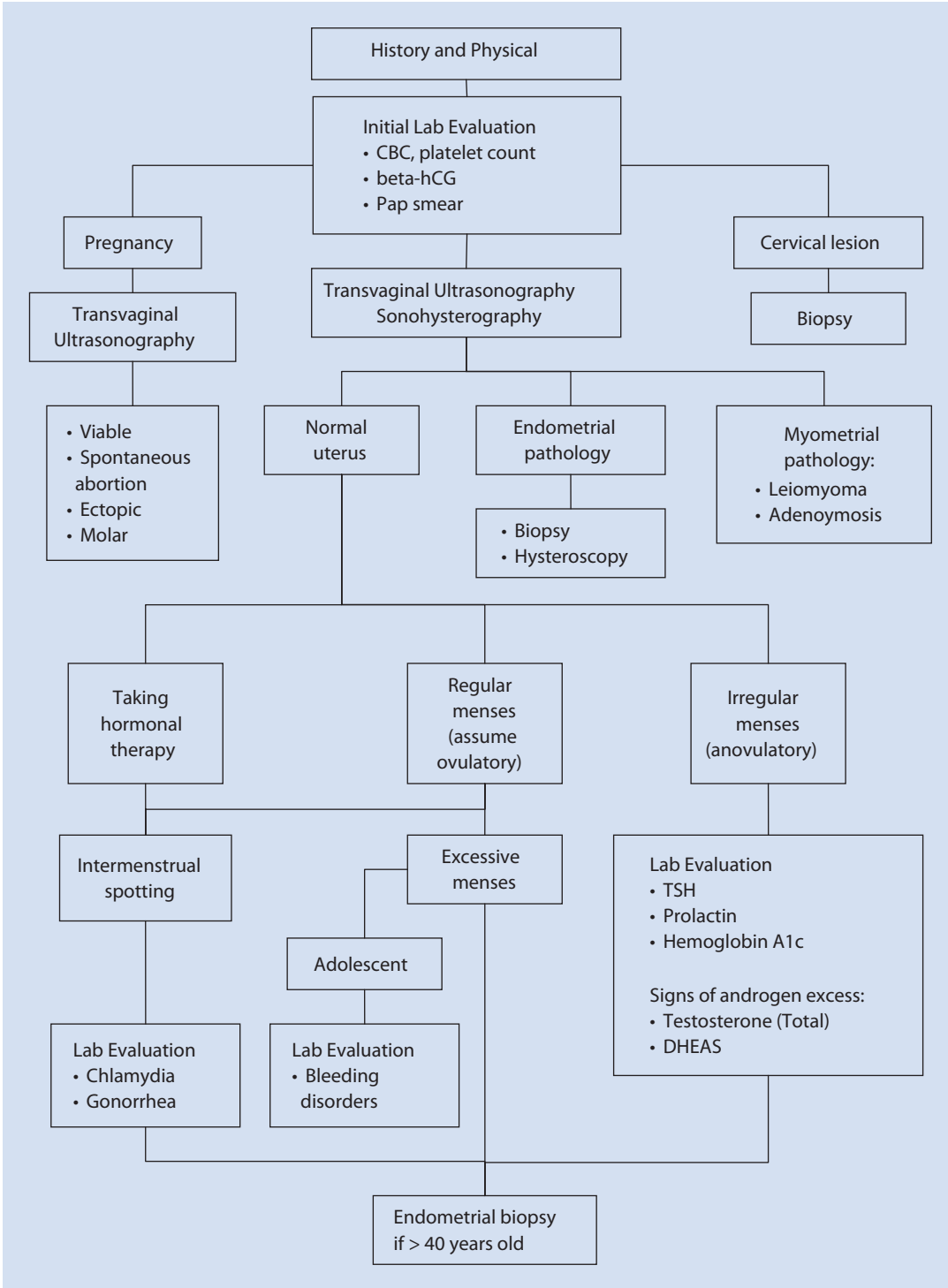

Fig. 8.1 Algorithm for evaluating women with AUB

PCOS and adult-onset congenital adrenal hyperplasia may sometimes be indistinguishable by clinical presentation, since both disorders are often characterized by hirsutism, acne, menstrual abnormalities, and infertility [43]. Unfortunately, no discriminatory screening test exists for this heterologous condition, which is most commonly caused by 21-hydroxylase or 11 beta-hydroxylase deficiency. If ovulation dysfunction and signs of androgen excess begin at the time of puberty, such women should be investigated appropriately (see ▶ Chap. 4).

8.38 Hemostatic Disorders

Patients with new onset of significant menorrhagia should be evaluated for bleeding disorders with prothrombin time, activated partial thromboplastin time, and bleeding time [44]. 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 hereditable 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 [44]. If these studies are negative, factor XI level and euglobulin clot lysis time can be evaluated.

8.39 Malignancies and Premalignancies

8.39.1 Endometrial Biopsy

AUB in women 40 years of age to menopause can often be attributed to anovulatory bleeding, which is a normal physiological response to declining ovarian function. However, the risk of endometrial hyperplasia and carcinoma 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 [45].

8.39.2 Imaging and Hysteroscopy

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.

8.39.3 Transvaginal Ultrasonography

Today, transvaginal ultrasonography and sonohysterography have made unexpected findings at surgery a rare occurrence (see ▶ Chap. 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. Sonohysterography can be used to accurately visualize most intrauterine abnormities 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

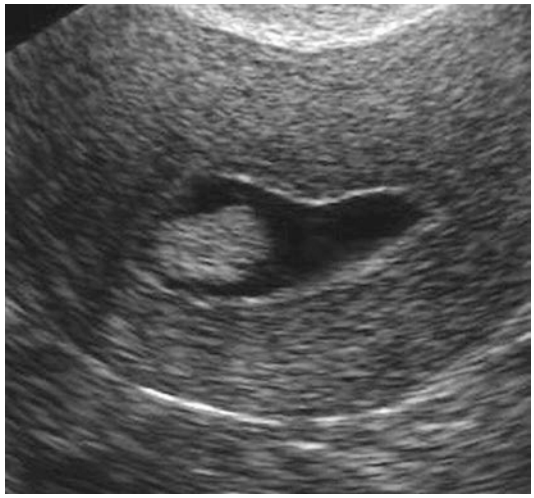

Fig. 8.2 Endometrial polyps diagnosed by sonohysterography

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).

8.39.4 Office Hysteroscopy

Office hysteroscopy (see ▸ Chap. 16) is another excellent outpatient method for visualizing the uterine cavity. The discomfort and risk is somewhat more 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.

8.40 Management of AUB Unrelated to Pregnancy or Uterine Pathology

In more than half of patients presenting with AUB, the etiology will be determined to be unrelated to pregnancy or underlying uterine pathology. Treatment of these cases consists of managing underlying systemic medical conditions or comorbidities and normalizing the endometrium with exogenous hormone therapy, when necessary. In patients with hypothyroidism, for example, restoration of a euthyroid state with thyroid hormone replacement will restore normal ovulatory function in most cases. Likewise, treatment of underlying conditions, such as hyperprolactinemia, PCOS, or other endocrine dysfunction, such as an adrenal enzyme deficiency, may restore normal menstrual function.

8.41 Anovulatory Bleeding

For heavy, acute anovulatory bleeding, the primary focus of initial management is the expedient bleeding cessation by achieving rapid structural stability of the endometrium. After stabilization of the endometrium, long-term therapeutic goals for women who do not desire pregnancy include promoting synchronous endometrial shedding at regular intervals or achieving amenorrhea with exogenous hormone administration. This approach should prevent subsequent episodes of heavy bleeding that require emergent evaluation and management.

8.42 Hemodynamic Stabilization and Initial Evaluation

While hemorrhagic shock secondary to AUB is rare, many patients will present with critically low hemoglobin levels and symptomatic anemia. Healthy women of reproductive age can often compensate physiologically for severe anemia and thus have minimal symptoms. In contrast, older women, particularly those with underlying cardiovascular disease, may present with significant symptoms from heavy uterine bleeding. Initial management of hemodynamically unstable patients includes intravenous fluid resuscitation and blood product replacement, as indicated.

With stabilization, an expedient evaluation should be performed to detect pregnancy or anatomic pathology. Pertinent laboratory tests should be obtained, including CBC and quantitative beta-HCG. Transvaginal ultrasonography is an important initial diagnostic tool to evaluate for the presence of underlying anatomic pathology. However, differentiating intrauterine lesions such as leiomyomata or polyps from clots may be difficult in the setting of acute bleeding. Hormonal therapy, as discussed below, should be initiated to decrease uterine bleeding. Endometrial evaluation is an important part of the evaluation for many women, depending on age and risk factors

for endometrial hyperplasia or malignancy, but can safely be deferred until the bleeding decreases with medical management. Therefore, hormonal therapy does not have to be delayed until histologic sampling can be performed.

8.43 Dilation and Curettage

In cases in which massive, life-threatening, anovulatory uterine bleeding is present, dilation and curettage provides a rapid means to decrease bleeding and evaluate for endometrial pathology. As a surgical approach to the management of AUB, disadvantages include the risks of anesthesia, which depend on an individual patient's underlying medical conditions, and the small surgical risks of the procedure. Dilation and curettage has no long-term therapeutic effect; therefore, long-term treatment must be initiated postoperatively. In most cases of AUB, medical management can be safely used as the first-line treatment.

8.44 Intravenous Estrogen Therapy

In the absence of life-threatening bleeding requiring surgical intervention, AUB should be initially managed with hormonal therapy. Historically, first-line therapy consists of the administration of intravenous conjugated estrogens, 25 mg every 4 h, until the cessation of bleeding or for 24 h [46]. Given that this therapy is often associated with nausea, concomitant intravenous or oral antiemetics should be administered. Patients who do not respond to estrogen therapy may require dilation and curettage, as described above.

Given the pathophysiology of anovulatory bleeding, namely, prolonged exposure to unopposed estrogen, treatment with estrogen may seem paradoxical. By simulating clotting at the capillary level and promoting vasoconstriction, estrogen acutely decreases uterine bleeding related to asynchronous shedding [47].

8.45 Oral High-Dose Combined Hormonal Therapy

With heavy, non-emergent bleeding or when bleeding has decreased to a level consistent with heavy menses or less, an oral contraceptive therapy taper can be initiated (Table 8.5). This approach may be utilized for women with heavy bleeding in the outpatient setting who do not require hospitalization. As with intravenous estrogen, nausea is a common side effect, and oral antiemetics should be provided to optimize compliance.

Table 8.5 "Taper" oral contraceptive regimen for treatment of AUB using low-dose (30 μg ethinyl estradiol), monophasic oral contraceptive pills

Day	Frequency
1–2	One tablet 4 times daily
3–4	One tablet 3 times daily
5–19	One tablet daily
20–25	Expect menses
26	Start oral contraceptives at standard dosage

8.46 Women at Increased Risk for Cardiovascular Disease or Venous Thrombosis

In women at increased risk for cardiovascular disease, venous or arterial thromboembolism, estrogen-containing oral contraceptives may be relatively or absolutely contraindicated. This includes women with a history of thromboembolic disease and woman over 35 years of age who have additional risk factors for thromboembolism (e.g., cigarette smoking, hypertension, diabetes). Although no studies have been published using short-term, high-dose intravenous or oral estrogen in these patients, at least one case of fatal pulmonary thromboembolism has been reported with intravenous therapy [48]. Certainly, high-dose estrogen therapy should be used in these patients in the acute setting only if the benefits outweigh the risks. The Medical Eligibility Criteria for Contraception provides evidence-based guidelines for use of hormonal agents in the setting of various medical comorbidities and can be an important reference in the management of high-risk patients, particularly when considering options for long-term therapy [49].

8.47 Women with a Coagulopathy

Women with menorrhagia secondary to von Willebrand's disease may be successfully treated with long-term oral contraceptive therapy, as described below. Other medical treatments used by hematologists for acute episodes include desmopressin acetate, antifibrinolytic agents, and plasma-derived concentrates of von Willebrand factor.

8.48 Long-Term Treatment of AUB

The most appropriate long-term management of AUB depends on the underlying etiology of AUB as well as a patient's reproductive desires. Women who do not desire pregnancy may initiate combined oral contraception or other hormonal therapies, such as cyclic progestins or a progestin-containing intrauterine device. Additionally, non-hormonal therapy with tranexamic acid, an anti-fibrinolytic agent, may be a therapeutic option. For anovulatory women wishing to become pregnant, ovulation induction is usually the most appropriate treatment. Two important considerations, endometrial synchronization and subclinical endometritis, deserve mention, because they may serve to optimize medical management of AUB.

8.49 Endometrial Synchronization

For women with chronic irregular bleeding, synchronizing the endometrium prior to the initiation of cyclic hormones may be a helpful first step, as synchronization can reduce breakthrough bleeding encountered with subsequent therapy. Two approaches to synchronization include the use of a potent progestin or an oral contraceptive taper. Medroxyprogesterone acetate, in the dose of 10 mg per day for 14 days, usually improves the presenting bleeding episode within 2–3 days and serves to thin the endometrial lining prior to withdrawal bleeding. Patients should be counseled that they may experience moderately heavy bleeding within 1–2 days of stopping the medroxyprogesterone. Oral contraceptives should be started on the Sunday following this withdrawal bleeding. Alternately, taper therapy with oral contraceptives (Table 8.4) can be used for women presenting with heavy prolonged bleeding.

8.50 Antibiotics for Subclinical Endometritis

While few studies have evaluated the impact of subclinical endometritis on the clinical presentation of AUB, an emerging body of literature supports a relationship between these clinical diagnoses. A recent study demonstrated that chronic endometritis is the most frequent histologic finding in endometrial biopsies performed on women with AUB [50]. In another study, 81% of patients with irregular bleeding or vaginal discharge had positive endometrial cultures for *Mobiluncus*, and treatment with metronidazole resolved their irregular bleeding [51]. In a study of 100 hysterectomies performed for irregular bleeding or fibroids, 25% of the endometrial cavities were found to harbor organisms, including *Gardnerella vaginalis*, *Enterobacter* and *Streptococcus agalactiae* [52]. Finally, a study of college-age women presenting with abnormal bleeding while on oral contraceptives found that 29% were infected with *Chlamydia* [29].

These studies suggest that subclinical endometritis may impact the clinical presentation of AUB. Therefore, when apparently anovulatory AUB does not respond to standard medical management with hormonal therapy, subclinical endometritis may be a coexisting disorder to address. Cervical evaluation for common pathogens (chlamydia and gonorrhea) followed by appropriate antibiotic therapy is important. In women with negative cultures who do not respond to cyclic hormonal therapy, empiric therapy with a broad-spectrum antibiotic (e.g., metronidazole or a cephalosporin) may be considered. However, to date, prospective trials assessing the impact of treatment of clinical endometritis on AUB outcomes have not been conducted.

8.51 Ovulation Induction

Restoration of ovulation for women desiring fertility is of paramount importance. Accomplishing regular ovulatory cycles may occur with the 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 pregnancy. In the case of PCOS, recent studies have demonstrated that insulin

sensitizing agents, such as metformin, can promote ovulation (see ▶ Chap. 8). However, a recent randomized clinical trial did not demonstrate an improvement with live birth rates when adding metformin to clomiphene citrate [53].

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 or injectable medications should be considered (see ▶ Chap. 7).

8.52 Oral Contraceptives

For decades, combined oral contraceptive pills have been the first-line therapy for managing AUB, and studies have demonstrated that combined oral contraceptives decrease the duration and amount of menstrual flow as well as dysmenorrhea [54]. In addition, extending the number of consecutive days of active pills and decreasing the annual number of menses may further minimize menstrual-related symptoms [55]. 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 [56].

8.53 Progestins

Progestins represent 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 hyperplasia and cancer. Side effects of progestin therapy include mood changes or depression, nausea, breast tenderness, and bloating. Luteal phase progestin therapy has been demonstrated to be less efficacious in ovulatory AUB (menorrhagia) when compared with nonsteroidal antiinflammatory drugs (NSAIDs), tranexamic acid, or a progesterone-releasing intrauterine system [57].

8.54 Levonorgestrel-Containing Intrauterine Device

While originally developed for contraception, the levonorgestrel intrauterine device (IUD) represents a highly effective treatment of both menorrhagia and dysmenorrhea. The local release of levonorgestrel into the uterine cavity suppresses endometrial growth and has been shown to decrease menstrual blood loss by as much as 97% [58]. While many women will experience irregular or intermenstrual bleeding in the first 6 months of use, approximately 50% will have amenorrhea by 24 months [59]. While most of the progestin acts locally within the uterus, levonorgestrel can be detected in the systemic circulation among IUD users [60]. Therefore, other side effects, such as hirsutism, acne, weight change, nausea, headache, mood changes, and breast tenderness, may occur. Although the initial costs of the levonorgestrel IUD may be higher than other medical treatment options, they provide very cost-effective long-term therapy of AUB.

8.55 GnRH Analogues

Administration of a GnRH agonist results in pituitary down-regulation, hypoestrogenemia, and complete cessation of menses. GnRH agonists initially increase ovarian stimulation, called a "flair," prior to suppression of the hypothalamic–pituitary–ovarian axis. GnRH antagonists avoid this flair, but have only recently become available, and their clinical utility remains to be determined. Symptoms of estrogen deprivation, most notably hot flashes, mood alterations, and bone loss, result from the use of all GnRH analogues. These side effects may be averted with the use of "add-back" therapy with daily administration of norethindrone 5 mg orally. While GnRH analogues play an important role in the initial management of AUB, they are rarely used for long-term therapy given the expense and side effect profile.

8.56 Tranexamic Acid

Tranexamic acid, an anti-fibrinolytic agent, is an emerging therapy for the treatment of AUB. Recent Cochrane analysis has confirmed efficacy and patient tolerance of tranexamic acid in the treatment of menorrhagia, and in Europe this medication has become the preferred treatment for women with heavy menstrual bleeding [61]. Recently, the FDA approved tranexamic acid for use in the treatment of menorrhagia. This therapy is administered orally at a dose of 1300 mg three times daily for 5 days, initiated with onset of menses. To date, studies have not demonstrated an increased risk of venous or arterial thromboembolism [62]. However, tranexamic acid should not be concomitantly administered with combined oral contraception or in women with an increased risk of thromboembolism.

8.57 Nonsteroidal Antiinflammatory 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 20–40% [63]. While naproxen has been the most extensively studied NSAID, no member of the drug class offers distinct advantages for AUB [64]. Additionally, NSAIDs provide an effective treatment for dysmenorrhea, which is often present in those with AUB.

8.58 Surgical Treatment

For women with AUB refractory to medical management who do not desire childbearing, surgical treatment modalities, including endometrial ablation or hysterectomy, should be considered. Endometrial ablation is a minimally invasive surgical procedure that has been demonstrated to have less morbidity, shorter recovery, and greater cost-effectiveness than hysterectomy in the short term. Importantly, endometrial ablation does not provide reliable contraception, and patients who become pregnant after ablation have markedly increased risks of adverse pregnancy outcomes, such as PPROM or abnormal placentation. Therefore, reliable contraception is necessary, and permanent sterilization should be considered [65].

Hysterectomy remains a reasonable option for some women with AUB who fail medical management. As many as 20% of women who initially undergo endometrial ablation will require hysterectomy within 5 years, and some studies have demonstrated a higher satisfaction rate in women who initially underwent hysterectomy rather than endometrial ablation [66].

References

1. Fraser IS, Langham S, Uhl-Hochgraeber K. Health-related quality of life and economic burden of abnormal uterine bleeding. Exp Rev Obstet Gynecol. 2009;4:179–89.
2. 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.
3. Frick KD, Clark MA, Steinwachs DM, Langenberg P, Stovall D, Munro MG, Dickersin K, STOP-DUB Research Group. Financial and quality-of-life burden of dysfunctional uterine bleeding among women agreeing to obtain surgical treatment. Womens Health Issues. 2009;19:70–8.
4. 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.
5. 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.
6. Carlson KJ, Nichols DH, Schiff I. Indications for hysterectomy. N Engl J Med. 1993;328:856–60.
7. Chiazze L, Brayer FT, Macisco JJ, Parker M, Duffy BJ. The length and variability of the human menstrual cycle. JAMA. 1968;203:377–80.
8. 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.
9. Fraser IS. Menorrhagia–a pragmatic approach to the understanding of causes and the need for investigations. Br J Obstet Gynaecol. 1994;101(Suppl 11):3–7.
10. Bayer SR, DeCherney AH. Clinical manifestations and treatment of dysfunctional uterine bleeding. JAMA. 1993;269(14):1823–8.
11. 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.

12. Falco P, Zagonari S, Gabrielli S, Bevini M, Pilu G, Bovicelli L. Sonography of pregnancies with first-trimester bleeding and a small intrauterine gestational sac without a demonstrable embryo. Ultrasound Obstet Gynecol. 2003;21(1):62–5.
13. Barnhart K, Esposito M, Coutifaris C. An update on the medical treatment of ectopic pregnancy. Obstet Gynecol Clin N Am. 2000;27:653–67.
14. Soto-Wright V, Bernstein M, Goldstein DP, Berkowitz RS. The changing clinical presentation of complete molar pregnancy. Obstet Gynecol. 1995;86(5):775–9.
15. Eschenbach DA. Acute pelvic inflammatory disease: etiology, risk factors and pathogenesis. Clin Obstet Gynecol. 1976;19(1):147–69.
16. Heatley MK. The association between clinical and pathological features in histologically identified chronic endometritis. J Obstet Gynaecol. 2004; 24(7):801–3.
17. 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.
18. Gotz HM, van Bergen JE, Veldhuijzen IK, Broer J, Hoebe CJ, Richardus JH. A prediction rule for selective screening of Chlamydia trachomatis infection. Sex Transm Infect. 2005;81(1):24–30.
19. Marrazzo JM, Handsfield HH, Whittington WL. Predicting chlamydial and gonococcal cervical infection: implications for management of cervicitis. Obstet Gynecol. 2002;100(3):579–84.
20. Jones H. Clinical pathway for evaluating women with abnormal uterine bleeding. Obstet Gynecol Surv. 2002;57:22–4.
21. 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.
22. 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.
23. 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.
24. Clevenger-Hoeft M, Syrop CH, Stovall DW, Van Voorhis BJ. Sonohysterography in premenopausal women with and without abnormal bleeding. Obstet Gynecol. 1999;94:516.
25. 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.
26. Sorosky J. Endometrial cancer. Obstet Gynecol. 2008;112(1):186–7.
27. Young RH, Clement PB. Pseudoneoplastic glandular lesions of the uterine cervix. Semin Diagn Pathol. 1991;8(4):234–49.
28. 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.
29. 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.
30. 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.
31. Brenner PF. Differential diagnosis of abnormal uterine bleeding. Am J Obstet Gynecol. 1996;175(3 Pt 2): 766–9.
32. Tsilchorozidou T, Overton C, Conway GS. The pathophysiology of polycystic ovary syndrome. Clin Endocrinol. 2004;60(1):1–17.
33. Zawadski JK, Dunaif A. Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. Polycystic ovary syndrome. Boston: Blackwell Scientific; 1992. p. 377–84.
34. 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;96:1043–7.
35. Pugeat M, Ducluzeau PH. Insulin resistance, polycystic ovary syndrome and metformin. Drugs. 1999;58(Suppl 1):41–6.
36. Chang RJ. A practical approach to the diagnosis of polycystic ovary syndrome. Am J Obstet Gynecol. 2004;191(3):713–7.
37. Holley JL. The hypothalamic-pituitary axis in men and women with chronic kidney disease. Adv Chronic Kidney Dis. 2004;11(4):337–41.
38. Falcone T, Desjardins C, Bourque J, Granger L, Hemmings R, Quiros E. Dysfunctional uterine bleeding in adolescents. J Reprod Med. 1994;39:761–4.
39. Committee ACOG. Opinion no. 451: Von Willebrand disease in women. Obstet Gynecol. 2009;114:1439–43.
40. 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.
41. 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.
42. Kouides PA. Menorrhagia from a haematologist's point of view. Part I: initial evaluation. Haemophilia. 2002;8(3):330–8.
43. 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.
44. Kouides PA. Evaluation of abnormal bleeding in women. Curr Hematol Rep. 2002;1(1):11–8.
45. 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.
46. DeVore GR, Owens O, Kase N. Use of intravenous premarin in the treatment of dysfunctional uterine bleeding—a double-blind randomized control study. Obstet Gynecol. 1982;59:285.

47. Hestinger M, Stockenhuber F, Schneider B, Pabinger I, Brenner B, Wagner B, et al. Effect of conjugated estrogens on platelet function and prostacyclin generation in CRF. Kidney Int. 1990;38:1181.
48. Zreik TG, Odunsi K, Cass I, Olive DL, Sarrel P. A case of fatal pulmonary thromboembolism associated with the use of intravenous estrogen therapy. Fertil Steril. 1999;71(2):373–5.
49. Tepper N, Curtis KM, Jamieson DJ, Marchbanks PA, Centers for Disease Control and Prevention (CDC). Update to CDC's U.S. medical eligibility criteria for contraceptive use, 2010: revised recommendations for the use of contraceptive methods during the postpartum period. Morb Mortal Wkly Rep. 2011;60:878–83.
50. Ferenczy A. Pathophysiology of endometrial bleeding. Maturitas. 2003;45(1):1–14.
51. Larsson PG, Bergman B, Forsum U, Pahlson C. Treatment of bacterial vaginosis in women with vaginal bleeding complications or discharge and harboring Mobiluncus. Gynecol Obstet Investig. 1990;29(4):296–300.
52. Moller BR, Kristiansen FV, Thorsen P, Mogensen SC. Sterility of the uterine cavity. Acta Obstet Gynecol Scand. 1995;74:216–9.
53. 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.
54. Sulak PJ. The career woman and oral contraceptive use. Int J Fertil. 1991;36(Suppl 2):90–7.
55. Sulak PJ, Cressman BE, Waldrop E, Holleman S, Kuehl TJ. Extending the duration of active oral contraceptive pills to manage hormone withdrawal symptoms. Obstet Gynecol. 1997;89(2):179–83.
56. Anderson FD, Hait H. A multicenter, randomized study of an extended cycle oral contraceptive. Contraception. 2003;68:89–96.
57. Lethaby A, Irvine G, Cameron I. Cyclical progestogens for heavy menstrual bleeding. Cochrane Database Syst Rev. 2008;1:CD001016.
58. 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.
59. Hidalgo M, Bahamondes L, Perrotti M, Diaz J, Dantas-Monteiro 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.
60. Nilsson CG, Lahteenmaki PL, Luukkainen T, Robertson DN. Sustained intrauterine release of levonorgestrel over five years. Fertil Steril. 1986;45(6):805–7.
61. Cooke I, Lethaby A, Farquhar C. Antifibrinolytics for heavy menstrual bleeding. Cochrane Database Syst Rev. 2000;2:CD000249.
62. 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.
63. Speroff L, Fritz MA. Clinical gynecologic endocrinology and. infertility. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2005.
64. Lethaby A, Augood C, Duckitt K, Farquhar C. Nonsteroidal anti-inflammatory drugs for heavy menstrual bleeding. Cochrane Database Syst Rev. 2007;4:CD000400.
65. ACOG Committee on Practice Bulletins—Gynecology. ACOG practice bulletin no. 81: endometrial ablation. Obstet Gynecol. 2007;109:1233–48.
66. 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.