The medical management of abnormal uterine bleeding in reproductive-aged women

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In the treatment of women with abnormal uterine bleeding, once a thorough history, physical examination, and indicated imaging studies are performed and all significant structural causes are excluded, medical management is the first-line approach. Determining the acuity of the bleeding, the patient's medical history, assessing risk factors, and establishing a diagnosis will individualize their medical regimen. In acute abnormal uterine bleeding with a normal uterus, parenteral estrogen, a multidose combined oral contraceptive regimen, a multidose progestin-only regimen, and tranexamic acid are all viable options, given the appropriate clinical scenario. Heavy menstrual bleeding can be treated with a levonorgestrel-releasing intrauterine system, combined oral contraceptives, continuous oral progestins, and tranexamic acid with high efficacy. Nonsteroidal antiinflammatory drugs may be utilized with hormonal methods and tranexamic acid to decrease menstrual bleeding. Gonadotropin-releasing hormone agonists are indicated in patients with leiomyoma and abnormal uterine bleeding in preparation for surgical interventions. In women with inherited bleeding disorders all hormonal methods as well as tranexamic acid can be used to treat abnormal uterine bleeding. Women on anticoagulation therapy should consider using progestin-only methods as well as a gonadotropin-releasing hormone agonist to treat their heavy menstrual bleeding. Given these myriad options for medical treatment of abnormal uterine bleeding, many patients may avoid surgical intervention.

Key words: abnormal uterine bleeding, heavy menstrual bleeding, International Federation of Gynecology and Obstetrics classification, medical treatment, premenopausal women

Abnormal uterine bleeding (AUB) is a common clinical problem, affecting up to 14% of women during their reproductive years and impairing their quality of life by creating significant physical, emotional, sexual, social, and financial burdens.[1-3]

AUB is the preferred term to describe a spectrum of symptoms, such as heavy menstrual bleeding (HMB), intermenstrual bleeding, and a combination of both heavy and prolonged menstrual bleeding.[4] 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.

The goal of this review was to provide an updated reference of the medical therapeutic options available for treatment of patients with AUB, with a view toward reducing the need for major surgical intervention. Treatment of AUB in selected clinical scenarios is described in Table 1.

The normal menstrual cycle

A solid understanding of the normal menstrual cycle is essential to effectively evaluate and treat women with irregularities. 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] Cycle length varies most during the years immediately succeeding menarche (age <20 years) and during the perimenopausal transition (age >40 years) because these age ranges have the highest prevalence of anovulatory cycles.[5-7]

The normal menstrual cycle is a manifestation of coordinated interplay within the hypothalamic-pituitary-ovarian axis. During the follicular phase of the menstrual cycle, follicle-stimulating hormone (FSH) causes the ovarian follicles to produce estrogen from granulosa cells. A dominant follicle emerges on days 5−7, leading to another rise in the estrogen level and further growth of the endometrium.

The rise in estrogen triggers negative feedback to FSH at the same time that it stimulates a surge in luteinizing hormone (LH), triggering ovulation. The remaining corpus luteum produces

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Received May 13, 2015; revised June 28, 2015; accepted July 30, 2015.

L.D.B. has a research grant from Bayer and is currently the principal investigator of a clinical trial entitled Assess safety and efficacy of vilaprisanin women with uterine fibroids. She is also on the advisory panel for Bayer, Boston Scientific, and PCORI. She is on the data safety monitoring board for Gynesonics and has stock in Cooper Surgical/Endosee. Lastly, she receives royalties from the textbook, Hysteroscopy: office evaluation and management of the uterine cavity, published by Elsevier, as well as up to date chapters on operative hysteroscopy, hysteroscopic fluid management, and office hysteroscopy. N.-A.G. reports no conflict of interest.

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0002-9378/$36.00 • • http://dx.doi.org/10.1016/j.ajog.2015.07.044

TABLE 1
Medical management recommendations for abnormal uterine bleeding (choice of therapy depends on the need for contraception and the contraindications)

Clinical scenarios	Medical treatment options
Acute AUB[a] (normal uterus without underlying systemic cause)	1. IV CEE 2. Oral tranexamic acid 3. Multidose combined monophasic OC 4. Multidose oral progestin 5. GnRH agonist with aromatase inhibitor or antagonist (to prevent initial estrogen flare)[b] Note: Consider 3 or 10 mL intrauterine Foley balloon for tamponade during acute period
HMB (normal uterus without underlying systemic cause)	A. Ovulatory AUB 1. LNG-IUS 2. Tranexamic acid 3. Combined OC (cyclic, extended, or continuous) 4. Cyclic or continuous oral progestin (eg, norethisterone), starting on day 5 for 21 d 5. Injectable progestin (DMPA) 6. NSAIDs 7. GnRH agonist 8. Danazol B. AUB with ovulatory dysfunction 1. Combined OC 2. MPA (take for 2 wks every 4 wks) Note: Consider using an NSAID in combination with any of the previously listed therapies
Symptomatic leiomyomas	1. LNG-IUS (approved by the FDA in women with an undistorted uterine cavity size) 2. Combined OCs 3. NSAIDs 4. Danazol 5. Tranexamic acid Note: If medical therapy fails, consultation for surgical intervention, uterine fibroid embolization, MRI-focused ultrasound may be offered
Inherited bleeding disorder	1. Tranexamic acid 2. Combined OC 3. LNG-IUS 4. DMPA 5. Danazol 6. GnRH agonist 7. Desmopressin (vWD)
Anticoagulation therapy	1. LNG-IUS 2. Oral progestins 3. Depo-Lupron

AUB, abnormal uterine bleeding; *CEE*, conjugated equine estrogen; *DMPA*, depot medroxyprogesterone acetate; *FDA*, Food and Drug Administration; *GnRH*, gonadotropin-releasing hormone; *HMB*, heavy menstrual bleeding; *IV*, intravenous; *LNG-IUS*, levonorgestrel-releasing intrauterine system; *MPA*, medroxyprogesterone acetate; *MRI*, magnetic resonance imaging; *NSAID*, nonsteroidal antiinflammatory drug; *OC*, oral contraceptive; *vWD*, von Willebrand's disease.

[a] American College of Obstetricians and Gynecologists. Management of acute abnormal uterine bleeding in nonpregnant reproductive-aged women. ACOG Committee opinion no. 557. Obstet Gynecol 2013;121:891-6; [b] Bedaiwy MA, Mousa NA, Casper RF. Aromatase inhibitors prevent the estrogen rise associated with the flare effect of gonadotropins in patients treated with GnRH agonists. Fertil Steril 2009;91(Suppl 4):1574-7.

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progesterone, stimulating a secretory endometrium. If fertilization does not occur, progesterone and estrogen levels fall rapidly, leading to synchronous shedding of the endometrial lining approximately 14 ± 1 day after ovulation has occurred.

Fifty percent of the endometrial lining is shed during the first 24 hours of menstrual flow.[5] Vasoconstriction of the denuded spiral arterioles in the basal layer of the endometrium (and, potentially, the radial arteries in the surface of the myometrium) brings about the end of menses. Endothelins and prostaglandins are highly concentrated in the endometrium and are responsible for the intense vasoconstriction of the spiral arterioles that leads to the cessation of bleeding. The duration of the follicular phase is highly variable, ranging from 10.3 to 16.3 days,[8] whereas the luteal phase remains fairly constant at a mean of 14.13 days ($\pm$1.41 days).[9]

A synchronous rise and fall in estrogen and progesterone levels throughout the cycle is the most important determinant of normal menses. This synchronization leads to the organized growth of the endometrial epithelium, stroma, and microvasculature as well as subsequent controlled endometrial shedding.[5]

In women who have chronic anovulatory AUB, the cyclic stimulation and withdrawal of estrogen and progesterone are lost because of the persistent follicular and proliferative state. After a prolonged period of undisturbed estrogen-primed endometrial proliferation, without the influence of progesterone on its stability and organization, unpredictable sloughing of the endometrial lining occurs.

Women with ovulatory AUB without any anatomical causes have regular menses that occur every 24–35 days, accompanied by either of the following:

- large volumes of blood loss (ie, $>$ 80 mL), 90% of which is lost within the first the first 3 days of menstruation[10] or
- menses lasting longer than 7 days.

The hypothalamic-pituitary-ovarian axis and steroid hormone production are normal in ovulatory women with AUB.[10,11] The cause of AUB in these

women is the dysregulation of the hemostatic and vasoconstrictive capabilities of the endometrial lining. There is a rise in the total prostaglandin (PG) production, with a significant increase in PGE_2 (promoting vasodilation) as well as a rise in PGE_2 (a potent vasodilator) and PG_{I2} (an inhibitor of platelet aggregation) receptors.[12,13] This disproportionate rise in PG production is well documented to disrupt the body's ability to control the quantity of menstrual blood loss in women with ovulatory AUB.

Evaluation of AUB

The first step in evaluating a patient with AUB is to determine whether the bleeding is acute or chronic. This goal can be achieved through a directed history, physical examination, and laboratory testing. The history should elicit the nature of the bleeding and the associated symptoms as described in Table 2 as well as a detailed sexual and reproductive history. It is important to determine whether the patient has any signs or symptoms of anemia, including pallor, headache, shortness of breath, dizziness, fatigue, and pica.

It is also important to elicit any personal or family history of chronic

TABLE 2
Focused assessment of abnormal uterine bleeding

History

1. Bleeding pattern
   Quantity, frequency of changing pads or tampons, presence of clots, timing during menstrual cycle, impact on quality of life
2. Symptoms of anemia
   Headache, palpitations, shortness of breath, dizziness, fatigue, pica
3. Sexual and reproductive history
   Use of contraception, sexually transmitted infections, cervical screening, possibility of pregnancy, desire for future pregnancy, known infertility
4. Associated symptoms
   Fever, chills, increasing abdominal girth, pelvic pressure or pain, bowel or bladder dysfunction, vaginal discharge or odor
5. Symptoms associated with a systemic cause for AUB
   Overweight, obesity, PCOS, hypothyroidism, hyperprolactinemia, hypothalamic or adrenal disorder
6. Chronic medical illness
   Inherited bleeding disorders (coagulopathy, blood dyscrasias, platelet functional disorders), systemic lupus erythematosus or other connective tissue diseases, liver disease, renal disease, cardiovascular disease
7. Medications
   Hormonal contraceptives, anticoagulants, SSRIs, antipsychotics, tamoxifen, herbals (eg, ginseng)
8. Family history
   Coagulation or thromboembolic disorders, hormone-sensitive cancers

Physical examination

Vital signs: blood pressure, pulse, orthostatics as clinically indicated, weight, BMI

Neck: thyroid examination

Abdomen: tenderness, distension, striae, palpable mass, hepatomegaly

Skin: pallor, bruising, petechia, signs of hirsutism (male hair pattern distribution, acanthotis nigricans) Pelvic examination/inspection: vulva, vagina, cervix, anus, and urethra

Bimanual examination of uterus and adnexal structures

Rectal examination if bleeding from rectum suspected or risk of concomitant pathology

Testing: Papanicolaou smear, cervical cultures if risk for sexually transmitted infection

Laboratory

Beta hCG

Complete blood count with platelets

Other laboratory testing as clinically indicated

- TSH
- Free testosterone
- Prolactin
- PTT/PT/fibrinogen or thrombin time or von Willebrand diagnostic panel if available at your laboratory
  Imaging

TVS or SIS

Office endometrial sampling (as clinically indicated)

Office hysteroscopy (as clinically indicated)

AUB, abnormal uterine bleeding; *BMI*, body mass index; *hCG*, human chorionic gonadotropin; *PCOS*, polycystic ovary syndrome; *PT*, prothrombin time; *PTT*, partial thromboplastin time; *SIS*, saline infusion sonography; *SSRI*, selective serotonin reuptake inhibitor; *TSH*, thyrotropin; *TVS*, transvaginal sonography.

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medical illnesses that are associated with or can lead to AUB (ie, inherited bleeding disorders such as coagulopathy, blood dyscrasias, platelet functional disorders, etc; hypothyroidism; hyperprolactinemia; hypothalamic or adrenal disorder; systemic lupus erythematosus or other connective tissue diseases; liver disease; or renal disease).

A detailed personal and family history should also elucidate possible coagulation or thromboembolic disorders, hormone-sensitive cancers, and heart disease and should also be obtained to help tailor potential treatment options.

In addition, women who are obese are at risk for menstrual aberrations and have a higher incidence of polycystic ovarian syndrome (PCOS).[14] Thirty-five to 60% of women with chronic anovulation and PCOS are obese.[15-17] Obese women suffer from ovulatory dysfunction because they have persistently elevated estrogen levels through increased peripheral androgen aromatization; they have elevated free circulating estradiol and testosterone as a result of a reduction in sex hormone-binding globulin; and their insulin levels are elevated as a result of insulin resistance, which stimulates androgen production in the ovarian stroma and disrupts normal follicular development.[18]

Weight loss in these women is imperative, and counseling must be a component in addressing treatment of their menstrual dysfunction. It can lead to the restoration of normal menses by reducing their levels of free insulin and androgen concentrations.[19-22]

The targeted physical examination and laboratory assessments are detailed in Table 2. It is in our opinion to reserve transvaginal sonography (TVS), saline infusion sonography, or office hysteroscopy for patients with a normal pelvic examination and laboratory evaluation who do not respond to routine medical management. TVS is more widely available and often utilized first in the search for an anatomic cause of AUB. However, it is important to remember that 1 of 6 intracavitary lesions can be missed on TVS in women with AUB. Therefore, we believe that when it is possible, it is preferable to perform saline infusion sonohysterography (SIS) instead of TVS,[23] given its higher sensitivity in detecting submucosal myomas and endometrial polyps in premenopausal women.[24] If SIS is not available, we believe that a diagnostic hysteroscopy should be considered if available.

Also recommended is endometrial sampling in all women with unrelenting AUB who are older than 45 years as well as in younger women in whom medical therapy has failed or who have risk factors for endometrial cancer. These risk factors include anovulation with long-term exposure to unopposed estrogen (ie, PCOS or obesity), nulliparity, diabetes, and hereditary nonpolyposis colorectal cancer.[4] Endometrial biopsies can be limiting based on the size and location of endometrial pathology, size of the endometrial cavity, presence of congenital malformations, focal or global endometrial process, and sample size obtained with office endometrial sample devices.[25,26]

Acute AUB is defined as a discrete episode of bleeding that, in the clinician's judgment, requires immediate medical attention to prevent subsequent bleeding, given an abnormal volume, duration, and/or frequency.[4,27,28] In such cases, the priorities are determining the patient's volume status and hemodynamic stability and proceeding with appropriate volume resuscitation. Transvaginal imaging also should be used to evaluate pelvic pathology. When available, SIS should be performed to evaluate for endometrial pathology. Once the patient is stabilized, the clinician must swiftly identify the cause of the AUB.

Patients with chronic AUB have abnormal volume, duration, and/or frequency of uterine bleeding for at least 6 months and can safely be evaluated on an outpatient basis.[4] Women with intermenstrual bleeding have regular menstrual cycles with random or predictable uterine bleeding between each cycle,[4] commonly owing to a structural abnormality.

Classification of AUB

A classification system developed by the FIGO Menstrual Disorders Working Group and supported by the American College of Obstetricians and Gynecologists facilitates investigation into the etiology of AUB.[4] Under the FIGO system, AUB can be described as either heavy menstrual bleeding (AUB/HMB) or intermenstrual bleeding (AUB/IMB).

The causes of AUB are divided into 2 groups: those related to uterine structural abnormalities and those unrelated to such abnormalities. The first group consists of polyps, adenomyosis, leiomyoma, malignancy and hyperplasia and the second consists of coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not otherwise classified (Figure). The goals of this new classification system are to provide a uniform and clear communication modality for physicians, scientists, and patients and to facilitate optimal patient care by fostering a common language for research.

A recent study showed 38% of women < 40 years of age have unsupported pathology at the time of hysterectomy performed for AUB, uterine fibroids, endometriosis, or pelvic pain.[29] In addition, overall, up to 38% of the women who underwent a hysterectomy were never offered an alternative treatment option. Therefore, it is crucial to review the medical options available and to reduce the reliance on major surgical interventions, when possible. Among women in whom medical therapies have failed, who do not desire future fertility, and who do not desire a hysterectomy, endometrial ablation can be considered.

Medications used in the treatment of AUB, as well as their dosages, contraindications, and side effects, are listed in Table 3. The specific treatment of AUB due to ovulatory dysfunction based on age groups is outlined in Table 4.

Hormonal therapies

Estrogen and progestin contraceptives

Combination contraceptive methods in the form of a pill,[30,31] the vaginal ring,[32] and the transdermal patch[33] have all been shown to afford cycle control, reducing menstrual blood loss significantly as well as the incidence of irregular bleeding.

The estrogen component in combination estrogen-progestin oral contraceptives (OCs) prevents FSH secretion and development of a dominant follicle. It also provides endometrial stability and

growth and enhances the progestational impact. The progestin prevents the LH surge and ovulation and creates an atrophic endometrial lining, thereby reducing overall blood loss at the time of withdrawal bleeding.[5]

Dienogest/estradiol valerate (Natazia) is the only combination OC that was approved by the US Food and Drug Administration (FDA) for the treatment of HMB (March 2012). In a randomized controlled trial (RCT), Jensen et al[34] found this OC to be very effective in reducing menstrual blood loss, compared with placebo.

In addition, all forms of monophasic combination OCs are readily used to successfully treat acute and chronic AUB, despite a lack of data from RCTs supporting this use.[35] One small RCT demonstrated the utility of short-term administration of a multidose monophasic OC (norethindrone 1 mg and ethinyl estradiol 35 μg 3 times daily for 1 week, followed by daily dosing for 3 weeks), compared with oral medroxyprogesterone acetate (MPA) 20 mg with the same dosing schedule.[28] Bleeding stopped within 3 days of the drug administration in 88% and 76% of women, respectively, when given to treat acute AUB in hemodynamically stable patients.[28]

A triphasic combination OC (norgestimate/ethinyl estradiol) successfully treated HMB and intermenstrual bleeding in women with ovulatory dysfunction.[36]

When a combination OC, transdermal patch, or vaginal ring is used in an extended (12 week cycle) or continuous (365 days) fashion, the amount of blood loss per cycle and the number of bleeding episodes per year, compared with cyclic combined OCs, decrease.[33,37,38] An extended or continuous regimen also may be beneficial in the treatment of women with dysmenorrhea and pelvic pain.

Parenteral estrogen

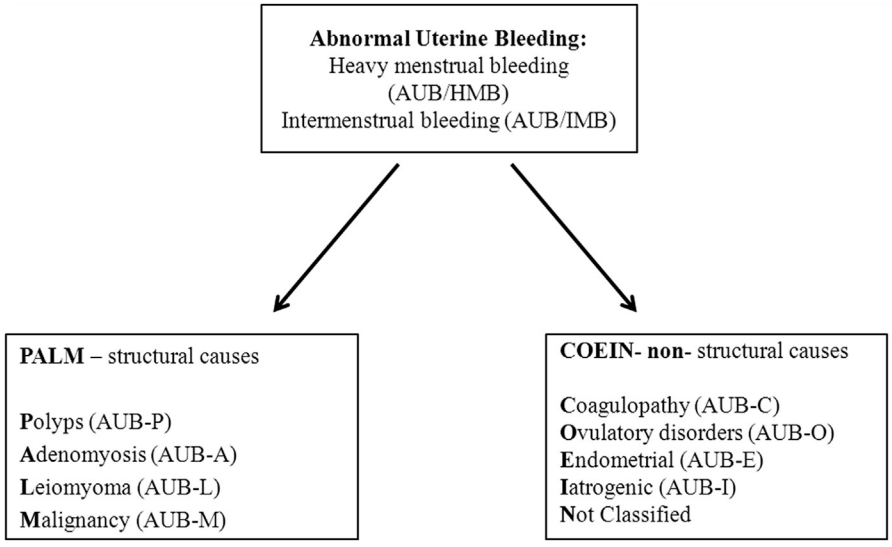
Intravenous (IV) conjugated equine estrogens (CEE) were approved by the FDA in November 2009 for the treatment of acute AUB. High-dose estrogen quickly treats acute AUB by causing rapid growth of the endometrial epithelium and stroma; stimulating vasospasm of uterine arteries; promoting platelet aggregation and capillary clotting[5]; increasing fibrinogen, factor V and factor XI; and increasing the production of both estrogen and progesterone receptors.

In 1982 DeVore et al conducted a randomized double-blinded study (n = 34), in which the parenteral administration of CEE led to the cessation of uterine bleeding in 72% of patients, compared with 38% who received placebo, even with the presence of uterine pathology such as polyps, hyperplasia, and endometritis.[27]

In hemodynamically unstable women with acute AUB, a 25 mg dose of IV CEE can be administered every 4–6 hours for up to 24 hours, followed by progesterone alone or a combination OC for 10–14 days. Patients should receive CEE for no longer than 24 hours before transitioning to OCs to reduce the duration of exposure to unopposed estrogen.[4] If acute AUB is not reduced within 24 hours, further evaluation of the endometrial cavity should be done through operative hysteroscopy with targeted removal of intracavitary pathology. Also consider a work-up for an inherited bleeding disorder, when appropriate.

FIGURE

FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding



AUB, abnormal uterine bleeding; *COEIN*, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not otherwise classified; *HMB*, heavy menstrual bleeding; *PALM*, polyps, adenomyosis, leiomyoma, malignancy and hyperplasia.

Reproduced, with permission, from Munro et al.[4]

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Progestogen-only formulations

Progestational agents are an ideal alternative for women who have a contraindication to estrogen. Progesterone quickly treats AUB by stabilizing endometrial fragility; inhibiting the growth of the endometrium by triggering apoptosis; inhibiting angiogenesis; and stimulating the conversion of estradiol to the less active estrone.[5] It prevents ovulation and ovarian steroidogenesis, interrupting the production of estrogen receptors and the estrogen-dependent stimulation of the endometrium, leading to an atrophic endometrium.

Oral progestins. Ovulatory status determines the regimen for oral progestin use. For example, in women with ovulatory AUB, oral MPA (2.5–10 mg daily), norethindrone (2.5–5 mg daily), megestrol acetate (40–320 mg daily), or micronized progesterone (200–400 mg daily) taken cyclically (starting on menstrual day 5 for 21 days) or continuously provides cycle control and reduction of menstrual blood loss.[39,40]

The use of a luteal-phase progestin alone has not proved to be successful

TABLE 3
Medical options for treatment of abnormal uterine bleeding

Medication	Regimen	Efficacy	Contraindications (select list)	Side effects (select list)	Contraception
Hormonal					
Combined contraceptives	Acute: monophasic pill 35 μg estradiol 3 times daily for 1 week, then daily dosing for 3 wks HMB: cyclic monophasic or triphasic oral contraceptive pills, extended or continuous monophasic oral contraceptive pill, transdermal patch or vaginal ring	High	Pregnant, smoking (aged ≥ 35 years and ≥ 15 cigarettes/d), history of malabsorptive bariatric surgery, multiple risk factors for arterial cardiovascular disease (ie, older age, smoking, diabetes, and hypertension), hypertension (systolic ≥ 160 mm Hg or diastolic ≥ 100 mm Hg), active or previous venous or arterial thromboembolic disease, known thrombogenic mutations, current or past ischemic heart disease, stroke, complicated valvular heart disease, SLE with vascular disease, nephritis, or antiphospholipid antibodies, headaches with aura, current or past history of breast cancer, diabetic nephropathy, retinopathy, neuropathy, or diabetes for > 20 y, liver cirrhosis, or tumor[a]	Spotting, nausea, headache, breast tenderness, breakthrough bleeding, VTE, stroke, MI	Yes
Conjugated equine estrogen	Acute: 25 mg IV every 4–6 h for 24 h	High	Pregnant, active or previous venous or arterial thromboembolic disease, breast cancer Use with caution in obese women	Spotting, nausea, headache, breast tenderness, breakthrough bleeding, VTE, stroke, MI	No
Oral progestins	Acute: MPA 20 mg 3 times a day for 7 days HMB: oral MPA (2.5–10 mg), norethindrone (2.5–5 mg), megestrol acetate (40–320 mg), or micronized progesterone (200–400 mg) Without ovulatory dysfunction, take 1 tablet daily starting day 5 for 21 d With ovulatory dysfunction, take 1 tablet daily for 2 wks every 4 wks	High	Pregnant, history of malabsorptive bariatric surgery, liver disease or tumor, breast cancer, current or past ischemic heart disease[a]	Irregular bleeding	No
LNG-IUS	HMB: intrauterine placement every 5 y, releases 20 μg/d	High	Pregnant, unexplained abnormal vaginal bleeding, untreated cervical or uterine cancer, large or distorted cavity should sound to a depth of 6–10 cm,[b] breast cancer, cervix or uterus abnormalities, pelvic inflammatory disease within 3 mo, STI such as chlamydia or gonorrhea within 3 mo, liver disease or tumor	Irregular bleeding and spotting, cramping, breast tenderness, mood changes, acne, nausea, decreased libido	Yes
DMPA	HMB: 150 mg IM injection every 12 wks	Low	Pregnant, multiple risk factors for arterial cardiovascular disease (ie, older age, smoking, diabetes, and hypertension), current or past ischemic heart disease, stroke, hypertension with vascular disease, CAD, CVD, current or previous history of breast cancer, liver disease or tumor[a]	Decreased bone mineral density, irregular (reversible) bleeding, weight gain, amenorrhea, bloating, breast tenderness, and fluid retention	Yes

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TABLE 3
Medical options for treatment of abnormal uterine bleeding *(continued)*

Medication	Regimen	Efficacy	Contraindications (select list)	Side effects (select list)	Contraception
Leuprolide acetate	HMB: 3.75 mg IM monthly or 11.25 mg IM every 3 mo	High	Pregnant	Hot flashes, sweating, and vaginal dryness (effects minimized with add-back therapy with estrogen and progestins), trabecular bone loss with use for longer than 6 mo (reversible)	No
Danazol	HMB: 100–400 mg orally daily (in divided doses)	Low	Pregnant, unexplained vaginal bleeding, impaired hepatic, renal, or cardiac function	Weight gain, acne, androgenic effects	No
Nonhormonal					
NSAIDs	HMB: Meclomen: 100 mg 3 times daily Ibuprofen 600-800 mg every 6-8 h, respectively (best if used in combination with other medication)	Moderate	Pregnant, gastrointestinal bleeding, inflammatory bowel disease, severe asthma, use after CABG procedure, renal disease, CVD, CHF	Gastrointestinal adverse effects (bleeding, ulceration, and perforation), worsening of asthma, effect on platelet function	No
Tranexamic acid	Acute: 1.3 g orally every 8 h for 5 d (indicated in ovulatory women with excessive menstrual bleeding)	High	Current or past thromboembolic disease, acquired impaired color vision (cannot be used with combined oral contraceptives)[c]	Headaches, nausea, vomiting, diarrhea, muscle pain, dysmenorrhea	No

CABG, coronary artery bypass graft; *CAD*, coronary artery disease; *CVD*, cardiovascular disease; *CHF*, chronic heart failure; *DMPA*, depot medroxyprogesterone acetate; *HMB*, heavy menstrual bleeding; *IM*, intramuscularly; *IV*, intravenously; *LNG-IUS*, levonorgestrel-releasing intrauterine system; *MI*, myocardial infarction; *MPA*, medroxyprogesterone acetate; *VTE*, venous thromboembolism.

[a] World Health Organization. Medical eligibility criteria for contraceptive use: a WHO family planning cornerstone. 4th ed. Geneva (Switzerland): World Health Organization; 2010; [b] Mirena (levonorgestrel-releasing intrauterine system) [package insert]. Whippany (NJ): Bayer HealthCare Pharmaceuticals Inc; 2014; [c] Lysteda (tranexamic acid) [package insert]. Parsippany (NJ): Ferring Pharmaceuticals Inc; 2013.

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in the treatment of ovulatory HMB.[41,42] In women with anovulatory bleeding, a cyclic progestin (ie, MPA, norethindrone, or norethisterone), given for 12–14 days each month, leads to regulation of the menstrual cycle in 50% of women.[43] In patients presenting with acute AUB, a multidose progestin (ie, MPA 20 mg 3 times daily for 1 week, followed by daily dosing for 3 weeks)[28] can significantly reduce menstrual blood loss.

Injectable progesterone. Depot medroxyprogesterone acetate (DMPA), a reliable contraceptive, produces amenorrhea in more than 50% of users after 1 year. However, many women report unscheduled bleeding during the first few months of use.[44] In large clinical trials that included about 3900 women, 57.3% experienced abnormal bleeding at 12 months and 32.1% at 24 months, and 37.7% of women also experienced weight gain of more than 10 pounds at 24 months.[45] Discontinuation because of side effects occurred in at least 2% of the patients (8.2% abnormal bleeding, 2.0% weight gain).[45] Overall, there is a lack of clinical data on the utility of DMPA for the treatment of acute or chronic AUB.

Intrauterine progestogen-releasing systems. The levonorgestrel-releasing intrauterine system (LNG-IUS; Mirena) administers 20 μg of the progestin every 24 hours locally to the endometrium, reducing endometrial thickness and the mean uterine vascular density.[46-48] The LNG-IUS was approved by the FDA in October 2009 for the treatment of HMB in women who also require contraception. It remains effective as a contraceptive and treatment for AUB for as long as 5 years.[49] Lethaby et al[50-52] demonstrated a reduction in menstrual blood loss of 86% after 3 months and 97% at 12 months of use in the treatment of HMB. Other studies have produced similar findings.[50-52]

The LNG-IUS is superior to luteal phase oral MPA; norethindrone for 21 days[42,53]; oral progestin (norethisterone in extended use)[54]; DMPA[55]; combination OCs[56,57]; and mefenamic acid.[58] Hemoglobin and serum ferritin levels are significantly improved after insertion of an LNG-IUS in women with iron deficiency anemia.[59,60]

In women with HMB, quality of life is improved remarkably when the LNG-IUS is used. In a multicenter randomized trial of 571 women with HMB, patients were randomized to the LNG-IUS or the usual medical treatment (tranexamic acid, mefenamic acid,

TABLE 4
Medical treatment of AUB-O based on age groups

Age groups	Causes	Management
13–18 y	Immature HPO axis, PCOS, obesity, inherited bleeding disorder	Acute AUB: parenteral estrogen[a] HMB: 1. Low-dose combination hormonal contraceptive (20–35 μg ethinyl estradiol) 2. Weight loss[b]
19–39 y	PCOS, obesity, premalignant or malignant endometrial pathology (if risk factors are present)	Acute AUB:[a] 1. Parenteral estrogen 2. Multidose oral progestins HMB: 1. Cyclic or continuous low-dose combined hormonal contraceptive 2. Progestins including LNG-IUS 3. Weight loss[b]
40 y to menopause	Intermittent anovulation, premalignant or malignant endometrial pathology	Acute AUB:[a] Multidose progestin-only regimen HMB: 1. Cyclic progestin therapy 2. LNG-IUS 3. Cyclic combined hormone therapy 4. Weight loss[b]

AUB, abnormal uterine bleeding; *HMB*, heavy menstrual bleeding; *HPO*, hypothalamic-pituitary-ovarian; *LNG-IUS*, levonorgestrel-releasing intrauterine system; *PCOS*, polycystic ovary syndrome.

[a] American College of Obstetricians and Gynecologists. Management of acute abnormal uterine bleeding in nonpregnant reproductive-aged women. ACOG Committee opinion no. 557. Obstet Gynecol 2013;121:891-6; [b] Guzick DS, Wing R, Smith D, Berga SL, Winters SJ. Endocrine consequences of weight loss in obese, hyperandrogenic anovulatory women. Fertil Steril 1994;61:598-604.

Adapted from American College of Obstetricians and Gynecologists.[122]

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combination estrogen-progesterone, or progesterone alone) over 2 years. The Menorrhagia Multi-Attribute Scale domains of practical difficulties, social life, family life, work and daily routine, psychological well-being, and physical health were significantly higher among women using the LNG-IUS, as were the domains for quality of life. Surgical rates and sexual activity were comparable between the 2 groups.[61]

Many clinical studies have compared the efficacy and acceptability of the LNG-IUS to those of surgical treatments for AUB. When menstrual loss and quality of life were compared between the LNG-IUS and endometrial ablation, the LNG-IUS was either superior to[62] or comparable with[52] ablation. When the LNG-IUS was compared with hysterectomy for the treatment of HMB, most trials showed a similar quality of life years later as well as lower cost for the LNG-IUS.[63-65]

Danazol

Danazol is a synthetic steroid ethisterone that inhibits pituitary secretion of FSH and LH and has a weak androgenic influence, causing thinning or atrophy of endometrial tissue.[66,67] In the treatment of HMB, danazol is superior to luteal-phase oral progestins (ie, norethindrone)[38,41,64,68] and mefenamic acid.[69] In clinical trials, danazol reduced menstrual blood loss by as much as 80%.[66,70] However, danazol is associated with significantly more adverse effects, including weight gain, acne, and androgenic effects, than other medical therapies.[71]

Low-dose vaginal danazol is an alternative being considered as a way to preserve the benefits of the drug while reducing systemic side effects, although few data are currently available.[72] Larger studies are needed to determine the utility of lower-dose danazol in the treatment of AUB.

GnRH agonists

Gonadotropin-releasing hormone (GnRH) agonists down-regulate GnRH receptors, thereby inhibiting gonadotropin secretion and creating a hypogonadic state that leads to endometrial atrophy. In the treatment of HMB caused by leiomyoma-associated hormonal imbalance, GnRH agonists have proved to be effective, but menopausal side effects, including vasomotor symptoms, vaginal atrophy or dryness, depression,[73] and trabecular bone loss, limit their long-term use.[74,75]

Add-back therapy with low-dose estrogen and norethindrone helps minimize adverse effects and should be considered if therapy is expected to exceed 6 months.[76] Short-term and long-term use should be considered in clinical scenarios that have strong contraindications to all other medical or surgical interventions.

Few RCTs have explored the efficacy of GnRH agonists in the treatment of AUB. Leuprolide acetate is FDA approved for short-term use in the preoperative treatment of uterine leiomyomata to delay surgery and, potentially, reduce intraoperative blood loss. Uterine volume can be reduced by 30–60%, and anemia is improved in women with HMB and fibroids.[77,78] Subcutaneous goserelin acetate also has FDA approval for the induction of endometrial atrophy prior to ablation for AUB. Atrophy and amenorrhea usually occur among premenopausal women within 3–4 weeks of the drug's administration.[79]

Nonhormonal therapies

Nonsteroidal antiinflammatory drugs (NSAIDs)

NSAIDs suppress prostaglandin synthesis by inhibiting cyclooxygenase.[80] They may also alter the equilibrium between thromboxane A2 (which causes vasoconstriction and platelet aggregation) and prostacyclin (which causes vasodilation and prevents platelet aggregation).[13,81] Because prostaglandin E_2 and prostaglandin F_{2a} are highly concentrated at the menstrual endometrium in women with HMB,[82,83] treatment with an NSAID increases thromboxane A2, thereby increasing platelet aggregation

and vasoconstriction and reducing menstrual blood loss.

Overall, treatment with an NSAID may reduce blood loss by as much as 40%.[84-86] In a Cochrane metaanalysis of 18 RCTs involving women with HMB, treatment with an NSAID was more effective than placebo in reducing menstrual blood loss.[87] In comparison, tranexamic acid, danazol, and the LNG-IUS were associated with greater menstrual blood loss. When treatment with an NSAID was compared with oral luteal-phase progestogen, ethamsylate, an older progesterone-releasing intrauterine system (Progestasert), and an OC, no difference was found in the amount of menstrual blood loss, although these studies were largely underpowered.[87]

Mefenamic acid and naproxen are the 2 most widely studied NSAIDs in the treatment of HMB and appear to be equivalent in efficacy.[84,86] A well-designed study by Vargyas et al[88] examined the efficacy of meclofenamate sodium (100 mg 3 times daily) in a double-blind, placebo-controlled, crossover study in women with unexplained HMB. Menstrual blood loss was measured by the alkaline hematin method, and 26 of 29 patients experienced a significant reduction in blood loss (42.4% ± 3.0% to 55.8% ± 8.3%) during their treatment cycles.

NSAIDs are fairly underutilized in the treatment of HMB but could be beneficial in combination with other medical therapies to further reduce menstrual blood loss while treating the dysmenorrhea that often accompanies HMB.[89] These NSAIDs also have a low side-effect profile.

Tranexamic acid

Oral tranexamic acid is FDA approved for the treatment of ovulatory AUB; an IV formulation is approved for use in hemophilia. This medication works by competitively blocking plasminogen-binding sites, preventing plasma formation, fibrin degradation, and clot degradation.[90,91] Women with HMB appear to have higher numbers of endometrial plasminogen activators and more local fibrinolytic activity than women with normal menses.[92-94]

In the treatment of HMB, tranexamic acid has proved to be superior to placebo,[94-100] mefenamic acid,[101] and luteal-phase progestins.[102] In a double-blind, placebo-controlled study of 115 women with HMB, Lukes et al[103] treated patients with oral tranexamic acid 3.9 g/d or placebo for a maximum of 5 days over 6 cycles. All women in the treatment group experienced a significant drop in menstrual blood loss (−69.6 mL [40.4%]), compared with the 72 women taking placebo (−12.6 mL [8.2%]). In addition, the women taking tranexamic acid believed that the reduction in menstrual blood loss was meaningful enough to improve their overall quality of life, including social, leisure, and physical activities, as well as work inside and outside the home.[103] The most commonly prescribed and studied treatment regimen is oral tranexamic acid 1 g to 1.3 g every 6−8 hours during menstruation.

Desmopressin

This drug, a synthetic analog of vasopressin, promotes the release of von Willebrand factor from endothelial cell storage sites.[5] It is used to treat patients with bleeding disorders, notably, von Willebrand's disease, during episodes of acute AUB. It should be utilized only when all other hormonal and nonhormonal therapies have failed. Collaboration with a hematologist is strongly encouraged before treatment of AUB with desmopressin.

Special considerations

Symptomatic leiomyomas

In women who have symptomatic fibroids, it can initially be unclear whether the fibroids are a passenger or the problem. The location of the leiomyoma(s) and the patient's clinical history can provide clues as to whether the leiomyoma is involved in AUB. For example, submucosal fibroids often cause unpredictable and heavy uterine bleeding because of unsteady vasculature of the endometrium with inadequate rebuilding and healing, increased endometrial surface area, and inadequate uterine contraction to compress the vessels on the surface of the endometrium.[104]

The medical treatment of HMB has variable effects based on a multitude of factors. GnRH agonists are approved by the FDA to reduce the size and volume (30−50%) of leiomyomas in preparation for surgical intervention[105-107] and to potentially reduce intraoperative bleeding.

The following medications have been shown to help reduce menstrual blood loss in women with fibroids and prolong the time to surgery or prevent the need for surgical intervention altogether:

- LNG-IUS (approved by the FDA for the treatment of HMB in women with an undistorted uterine cavity)
- Combined OCs
- NSAIDs
- Danazol
- Tranexamic acid (helps significantly reduce menstrual blood loss[86,98,108] and causes fibroid necrosis and infarction[109]).

Many other medications, such as mifepristone, asoprisnil, ulipristal acetate, and epigallocatechin gallate, are currently under investigation for their ability to shrink leiomyomas and improve symptoms.[110]

Ulipristal acetate is used readily in Canada and has been shown to be effective in treating HMB in 3 phase 3 studies from Europe.[111-113] It is a selective progesterone receptor modulator that induces apoptosis and prevents cell proliferation and neovascularization.[114]

It is important to note that medical therapies are most successful in the absence of a submucosal myoma.[115] In the clinical scenario in which all the appropriate medical options have been tried and failed for the treatment of AUB in women with leiomyomas, the recommendation is to proceed with either uterine artery embolization, focused ultrasound surgery, radiofrequency ablation, or surgical management.[115] If the patient desires future fertility, she can preserve her uterus and undergo a myomectomy to treat her symptoms of AUB.[116] If a patient does not desire fertility but prefers uterine preservation a

TABLE 5
Screening criteria for inherited bleeding disorders for women with AUB

Adolescents
Menses last longer than 7 days, bleeding through a pad or tampon in 1 hour, with clots greater than 1 inch in diameter, resulting in anemia or low iron level
Bleeding requiring blood transfusion
Refractory heavy menstrual bleeding
Family history of bleeding disorder
History of heavy or prolonged bleeding after a procedure or surgical intervention (ie, tooth extraction, surgery, delivery)
Prolonged bleeding from small wounds, lasting more than 15 minutes or recurring spontaneously during the 7 days after the wound (NIH)
Adults
Extremely heavy bleeding since menarche
Bleeding requiring blood transfusion
• One of the following conditions: Postpartum hemorrhage
Surgery-related bleeding
Bleeding associated with dental work
• Two or more of the following conditions: Epistaxis, 1-2 times per month (requiring more than 10 min to stop or needing medical attention)
Frequent gum bleeding
Family history of bleeding symptoms

AUB, abnormal uterine bleeding; *NIH*, National Institutes of Health.

Reproduced, with permission, from Dean et al. von Willebrand disease in a pediatric-based population: comparison of type 1 diagnostic criteria and use of the PFA 100 and a von Willebrand factor/collagen-binding assay. Thromb Haemost 2000;3:401-9.

Reproduced, with permission, from Drews et al. Screening questions to identify women with von Willebrand disease. J Am Med Womens Assoc 2002;57:217-8.

Reproduced, with permission, from Laffan et al. The diagnosis of von Willebrand disease: a guideline from the UK Haemophilia Centre Doctors' Organization. Haemophilia 2004;10:199-217 (http://www.nhlbi.nih.gov/health-pro/guidelines/current/von-willebrand-guidelines/full-report/3-diagnosis-evaluation).

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myomectomy, uterine artery embolization,[117] magnetic resonance imaging guided focused ultrasound surgery,[118] or radiofrequency ablation[119] can be offered. Otherwise, a hysterectomy can be performed, preferably in the most minimally invasive method possible, based on the practitioner's training and the experience and the clinical scenario.[120]

Inherited bleeding disorders

AUB is the most common symptom of an inherited bleeding disorder in women. Eighty-four percent of women with von Willebrand disease present with HMB, but only 10−20% of all women with AUB have an inherited bleeding disorder. Von Willebrand disease is the most common inherited bleeding disorder (70% of all cases) and therefore is the most common cause of acute AUB or HMB after menarche.

It is imperative to have a high index of suspicion in adolescents with HMB, given that 50% will be diagnosed with a coagulopathy.[104] The screening of adults and adolescents with a suspected bleeding disorder is based on the historical criteria described in Table 5.

The treatment of acute AUB and HMB in women with a bleeding disorder is similar to that in women without a bleeding disorder except that the use of NSAIDs is contraindicated, given their antiplatelet effects. The estrogen component of OCs aids in enhancing von Willebrand factor and factor VIII activity.[121,122] Therefore, oral estrogen in combined OCs is efficient in treating HMB as well as parenteral estrogen in the treatment of acute AUB.

If standard medical treatments for AUB fail, consider consultation with a hematologist and initiation of desmopressin. Desmopressin should be used as needed during the 2 or 3 heaviest days of the menstrual cycle.[123,124]

Anticoagulation therapy

Women who require anticoagulation for a diagnosis such as deep venous thrombosis, pulmonary embolism, artificial heart valves, atrial fibrillation, etc often have some form of menstrual disorder, most commonly AUB. These women often have heavier and longer menses, even if menses were normal prior to the initiation of anticoagulation. Huq et al[125] found that 70% of women on oral anticoagulation therapy experienced changes in their menstrual cycle after starting therapy. Of these women, 50% experienced a greater number of days of menstruation, and 66% experienced HMB. Therefore, it is crucial to provide pharmacological options for these women without further increasing their risk for thrombosis.

The management of women with active or prior thrombotic disease is challenging. Tranexamic acid is

contraindicated in women with active thrombosis or a history of thrombosis. The World Health Organization has advised against the use of any combined contraceptives in this population.[126] The data on the use of progestin-only methods in women with an elevated risk of thrombosis also are scarce, but the overall risk of thrombosis is lower than in women using tranxenamic or combined contraceptives.

Women on progestin-only methods should be monitored very closely because they face a higher risk of thrombosis than nonusers of hormonal medication. The LNG-IUS remains the superior method to control and significantly reduce menstrual blood loss in this group of patients,[127] but few studies are available to clarify whether it poses further risks to the patient. Leuprolide acetate should also be considered in patients on anticoagulation therapy.

Conclusion

AUB is a common complaint and disorder that is encountered often and can be complex and challenging. This document provides guidance for the medical treatment of AUB and demonstrates the importance of obtaining the correct diagnosis and individualizing treatment. In this new age of technology and the Internet, there are many online applications that can be used by our patients to record their menstrual history, which is often crucial in guiding one's diagnostic path.

The use of FIGO's universal terminology and diagnosis schema provides great guidance for physicians, but one must always keep in mind that there might be more than one cause for the AUB in each patient and that each condition should be addressed appropriately. It also is important to select medical therapy by fully assessing the patient's medical history, age, desire for fertility, and risk factors. The ultimate goal in the management of AUB is to identify the cause and prevent recurrence, to create a long-term clinical plan, to prevent and treat anemia, to treat underlying systemic or anatomic causes, to decrease unnecessary surgical intervention, and to improve a woman's quality of life. ■

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