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Diagnosis and Management of Heavy Menstrual Bleeding and Bleeding Disorders in Adolescents

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IMPORTANCE Heavy menstrual bleeding is a common cause of anemia and reduced quality of life in adolescents. There is a higher prevalence of bleeding disorders in girls with heavy menstrual bleeding than in the general population. Pediatricians should be comfortable with the initial evaluation of heavy menstrual bleeding and the indications for referral to subspecialty care.

OBSERVATIONS The most common cause of heavy menstrual bleeding in adolescents is ovulatory dysfunction, followed by coagulopathies. The most common inherited bleeding disorder is von Willebrand disease, and its incidence in adolescents with heavy menstrual bleeding is high. Distinguishing the etiology of heavy menstrual bleeding will guide treatment, which can include hemostatic medications, hormonal agents, or a combination of both. Among hormonal agents, the 52-mg levonogestrel intrauterine device has been shown to be superior in its effect on heavy menstrual bleeding and is safe and effective in adolescents with bleeding disorders.

CONCLUSIONS AND RELEVANCE Anemia, need for transfusion of blood products, and hospitalization may be avoided with prompt recognition, diagnosis, and treatment of heavy menstrual bleeding, especially when in the setting of bleeding disorders. Safe and effective treatment methods are available and can greatly improve quality of life for affected adolescents. A multidisciplinary approach to the treatment of girls with bleeding disorders and history of heavy menstrual bleeding is optimal.

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Supplemental content

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Achieving menarche and having regular menstrual periods are critical developmental milestones in the life of an adolescent girl. However, for many teenagers, menses can be a source of distress and medical morbidity, particularly when menses is excessively heavy, frequent, or prolonged. This is especially true when heavy menstrual bleeding (HMB) is associated with a congenital or acquired bleeding disorder (BD). The etiology and management of HMB in adolescents, with and without a BD, has been understudied. This review will explore what is known about HMB in adolescents, as well as the coincidence of a BD with HMB, and how diagnostic work up and management should vary accordingly.

Heavy menstrual bleeding is a common problem in adolescent girls and a frequent reason for visits to primary care physicians, as well as referrals to hematology, adolescent medicine specialists, and gynecologists. Reported prevalence of HMB ranges from 34% to 37%.[1,2] Quality of life (QOL) can be significantly affected, manifested in missed school days, physical activity limitations, and need for prolonged periods of rest.[1]

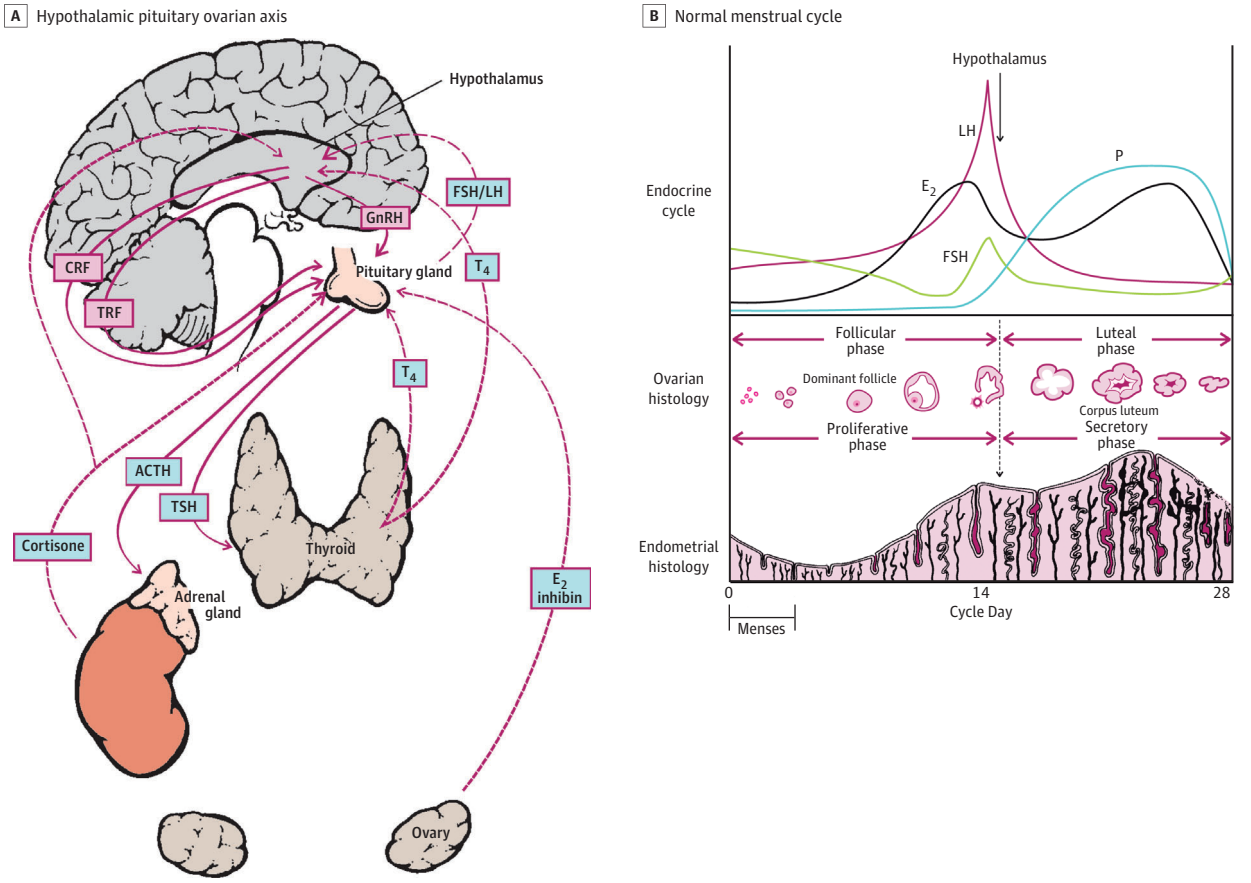
The American College of Obstetricians and Gynecologists (ACOG) has endorsed the use of the menstrual cycle as a vital sign[3]; ie, a normal menstrual cycle is an essential element of overall health, while an abnormal menstrual cycle can reflect medical illness, iatrogenic problems, or hypothalamus-mediated stress. Heavy menstrual bleeding, especially when associated with prolonged or frequent menses, can lead to anemia, fatigue, and hemodynamic instability. These may result in associated emergency department visits, hospitalizations, the need for transfusion of blood products, and the use of oral and intravenous therapies to stop blood loss. Bleeding disorders are not uncommon in female adolescents, and prevalence of BD among girls with HMB is much higher than that for the general population.[4,5]

Normal Menstrual Cycle and Abnormalities in Menstruation: Definitions and Terms

Normal Menstrual Cycle

The normal menstrual cycle (**Figure 1**)[6] depends on the feedback loops of estrogen and progesterone on the production of luteinizing hormone and follicle-stimulating hormone by the pituitary gland and on the hypothalamus's normal function as metronome for the hypothalamic-pituitary-ovarian axis.[7] According to ACOG, the mean age for menarche in the United States remains around 12.5 years; cycle intervals range from 21 to 45 days (averaging 32 days); menstrual flow is 7 days or less; and normal daily menstrual product use ranges from 3 to 6 regular pads or tampons.[3] Normal cycles may vary up to 9 days in length, although parameters for teenagers have not been well characterized.[8]

Figure 1. Hypothalamic Pituitary Ovarian Axis and Normal Menstrual Cycle[a]



ACTH indicates adrenocorticotropic hormone; CRF, corticotropin-releasing hormone; E_2, estradiol; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; TRF, thyrotropin-releasing factor; T4, thyroxine; TSH, thyrotropin.

[a] Reproduced with permission from Berek, 2012.[6]

Abnormal Uterine Bleeding

Abnormal uterine bleeding (AUB) is a term recently favored over the previously used *dysfunctional uterine bleeding* (DUB), and per ACOG refers to "menstrual flow outside of normal volume, duration, regularity, or frequency."[9] In 2011, the Federation of International Gynecology and Obstetrics (FIGO) proposed a new classification system for causes of AUB, PALM-COEIN[10] (Polyp, Adenomyosis, Leiomyoma, Malignancy and hyperplasia, Coagulopathy, Ovulatory dysfunction, Endometrial, Iatrogenic, and Not yet classified) (**Figure 2**), which was endorsed by ACOG in 2012[9] and revised in 2018.[8]

Although HMB, one symptom of AUB, has previously been defined as a quantification of hemoglobin or an estimation of menstrual blood loss by volume (>80 mL),[11] the newer FIGO recommendations[8] endorse the UK National Institute for Health and Care Excellence (UK NICE) clinical definition: "excessive menstrual blood loss, which interferes with the woman's physical, emotional, social and material QOL, and which can occur alone or in combination with other symptoms."[12] This definition relies on the patient's lived experience, rather than rigid criteria involving difficult measurements, and should be applied when treating adolescents.

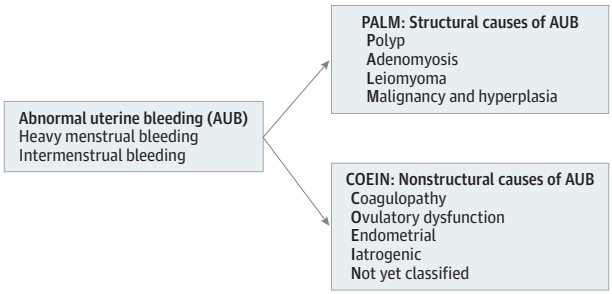
Simultaneous to proposing its new classification system, FIGO issued a recommendation on the nomenclature used to describe menstrual function, in which confusing, previously used terms such as *menorrhagia*, *metrorrhagia*, *polymenorrhea*, and *menometrorrhagia* are discarded in favor of the terms used in Figure 2: *HMB* and *intermenstrual bleeding*, as well as *heavy and prolonged menstrual bleeding*.[13] The Federation of International Gynecology and Obstetrics also suggested parameters for normal/abnormal menses for the midreproductive years (eTable in the Supplement); parameters for the perimenarchal years are not specified.

Primary and Secondary Hemostasis

A woman's monthly menstruation takes a large toll on the hemostatic system. To avoid excessive bleeding, the interaction of procoagulants and anticoagulants must be balanced. Any quantitative or qualitative disruption of the hemostatic system can lead to increased menstrual bleeding.

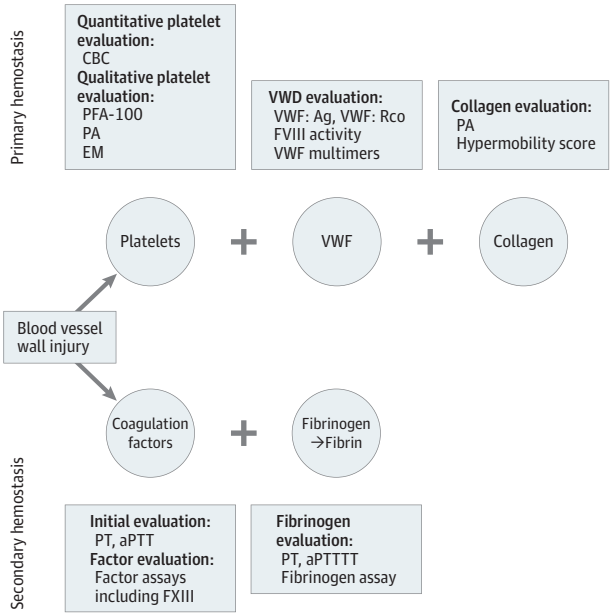
Primary hemostasis involves the integration of platelets and a glycoprotein called von Willebrand factor (VWF). Initiation of primary hemostasis begins with injury to the blood vessel wall. This injury allows exposure of collagen, elastin, and VWF,[14] which

Figure 2. Federation of International Gynecology and Obstetrics Classification for Causes of Abnormal Uterine Bleeding: PALM-COEIN[a]



[a] Adapted from Munro et al, 2011.[10]

Figure 3. Diagnostic Testing for Disorders of Primary and Secondary Hemostasis



Abbreviations: aPTT, activated thromboplastin time; CBC, complete blood cell count; EM, electron microscopy; FXIII, factor XIII; PA, platelet aggregation; PFA-100, platelet function assay; PT, prothrombin time; VWD, von Willebrand disease; VWF:Ag, von Willebrand factor antigen; VWF:Rco, ristocetin co-factor activity.

causes platelets to activate and bind to VWF (**Figure 3**). Platelets are activated to signal further platelet activation and aggregation, which leads to the formation of the primary hemostatic plug.

Secondary hemostasis involves coagulation proteins called factors, the blood vessel wall, and fibrin. Endothelial wall injury causes the release of tissue factor, which activates factor (F) VII to the activated form, FVIIa.[15] The tissue factor/FVIIa complex activates the remainder of the coagulation cascade and the formation of thrombin. The final step is the activation of FXIII, which crosslinks fibrin chains to form the fibrin clot. Anticoagulants, such as protein C, S, and antithrombin, as well as plasmin, help balance this procoagulant state and prevent excessive thrombus formation.

Heavy Menstrual Bleeding: Pathophysiology and Diagnostic Evaluation

Differential Diagnosis

Ovulatory Dysfunction

In adolescents up to approximately age 19 years, the most common causes of HMB/AUB are the nonstructural or *functional* causes, or the COEIN side of the FIGO mnemonic, with ovulatory dysfunction being the most common.[10] Anovulation is commonly seen in adolescents in association with ovulatory dysfunction, and owing to the lack of a functional corpus luteum, there is an absence of progesterone and a relative excess of estrogen acting on the endometrium. This imbalance leads to excessive and uncontrolled bleeding. Hypothalamic-pituitary-ovarian axis immaturity or dysfunction, a diagnosis of exclusion, is a frequent cause of such anovulatory bleeding and occurs most commonly in the first 2 to 3 years after menarche; however, longitudinal studies have shown that most cycles do fall within normal and predictable limits by year 3.[16,17] Ovulatory dysfunction can also occur as a result of numerous endocrinologic abnormalities, including thyroid disease, hyperprolactinemia, and hyperandrogenemia/polycystic ovarian syndrome (PCOS), as well as obesity.[18] These must be considered in the diagnostic work up for HMB, and risk for pregnancy must also be assessed.

Coagulopathies

Inherited BD are diagnosed in 10% to 17% of women[19-22] and in 21% to 46% of adolescents with HMB.[4,5] Almost half of adolescents diagnosed as having a BD have had HMB since menarche and 12% have required hospitalization secondary to anemia.[23,24] The mean age of menarche for adolescents with a BD does not differ from those without a BD; some adolescents with BD will initially have a normal menstrual flow and do not present with HMB until later in life.

von Willebrand Disease

von Willebrand disease (VWD) is the most common inherited BD, with an estimated prevalence of 1% of the population and an incidence of 36% in those with HMB.[19,25-27] von Willebrand disease is caused by either a quantitative deficiency or a qualitative functional defect of VWF. Mucocutaneous bleeding, such as HMB, epistaxis, bruising, gastrointestinal bleeding, and surgical bleeding, are the most common manifestations. Patients with more severe forms of VWD can also have joint and muscle bleeding. Owing to ACOG recommendations, there has been increased awareness and evaluation of VWD in women presenting with HMB.[28] Nevertheless, less than 20% of adolescents with HMB are screened for VWD.[29] There are 3 types of VWD, type 1 being the most common and mildest; it is inherited in an autosomal dominant pattern. Type 3, the most severe, is inherited in an autosomal recessive pattern. Diagnosing VWD can be complicated, owing to preanalytical variables as well as the associated high coefficients of variation, especially for the ristocetin cofactor assay (VWF:Rco).[30] Initial screening for VWD begins with a VWF:Ag, VWF:Rco, FVIII (FVIII) activity and VWF multimers. Depending on the results of these 4 assays, VWD can be ruled out, a VWD subtype can be identified, or more specific VWD testing can be ordered.

Inherited Coagulation Factor Deficiencies

An inherited deficiency in any of the coagulation factors can lead to HMB. Patients with a family history of hemophilia should be evaluated for a deficiency in either FVIII or FIX, known as hemophilia A or B, respectively. Hemophilia is inherited in an X-linked recessive pattern; men are most commonly affected. Women who carry 1 copy of the hemophilia gene mutation are known as carriers, and typically have mucocutaneous, surgical, and/or postpartum bleeding.

Rare factor deficiencies can also cause HMB, other mucocutaneous bleeding, and intracranial bleeding. These factors include II, V, VII, X, XI and XIII and are inherited in an autosomal recessive pattern.[31] The incidence is rare, with a higher incidence of FXI deficiency seen in those from Ashkenazi Jewish decent.[32] For most factor deficiencies, a screening for prothrombin time (PT) and activated partial thromboplastin time (aPTT) can guide the clinician, in consultation with a hematologist, as to which factor-specific assay to obtain. Factor XIII deficiency must be diagnosed with a quantitative assay because neither the PT nor aPTT will be prolonged.

Disorders of Fibrinogen

Fibrinogen is the final backbone of the normal clot that is formed after endothelial injury, as described in previous sections. Patients can have either decreased production of fibrinogen (hypofibrinogenemia), a complete lack of fibrinogen (afibrinogenemia), dysfunctional fibrinogen (dysfibrinogenemia), or a combination (hypodysfibrinogenemia).[33] Patients present with mucocutaneous bleeding, including HMB, as well as joint bleeding and central nervous system bleeding; severity of bleeding can vary. Laboratory assays will reveal a prolongation of the PT and aPTT, as well as the thrombin time (TT). Confirmatory testing includes a functional fibrinogen assay.

Platelet Disorders

The most common platelet disorder affecting adolescents with HMB is immune thrombocytopenia purpura (ITP), an autoantibody-mediated, acquired disorder.[34] A single-center, retrospective review found that 7% of adolescents with HMB were diagnosed with ITP.[20] Immune thrombocytopenia purpura can be secondary to other autoimmune disorders, such as systemic lupus erythematosus or Hashimoto thyroiditis, as well as immunodeficiencies. Patients with ITP present with mucocutaneous bleeding such as HMB, bruising, petechiae, epistaxis, and gastrointestinal bleeding. Immune thrombocytopenia purpura is a diagnosis of exclusion and should be considered in patients with thrombocytopenia and otherwise normal complete blood cell count (CBC) and differential.

Inherited disorders of platelet function are rare, although up to 28% to 49% of women with unexplained HMB have a qualitative platelet disorder.[35,36] Symptoms include mucocutaneous bleeding as well as intracranial, postpartum, and postsurgical bleeding. Diagnostic workup should include a CBC and smear to evaluate platelet number and size as well as platelet aggregation (PA) and granule release.[37] Second-tier testing of platelets can include flow cytometry and electron microscopy (EM).

The most well characterized inherited platelet dysfunction disorders are Glanzmann thrombasthenia and Bernard-Soulier syndrome, both of which are inherited in an autosomal recessive pattern and typically manifest with severe mucocutaneous bleeding. These disorders can be diagnosed via PA. Other rarer inherited platelet disorders include platelet storage defects and defects in signal transduction, which can be diagnosed using PA and EM.

Connective Tissue Disorders

Connective tissue disorders are caused by abnormalities in collagen, fibrin, and matrix proteins.[38] These various syndromes are sometimes overlooked when evaluating a patient with a possible BD. The most common are the joint hypermobility syndromes, Ehlers-Danlos syndrome, and Marfan syndrome. These patients can have mucocutaneous bleeding, such as HMB, bruising, and gastrointestinal bleeding, as well as a history of joint pain and instability.[39] On physical examination, patients can have striae, signs of poor wound healing, and skin laxity. A bleeding workup may be normal, although some patients with these disorders can have abnormal PA.

Other Causes of HMB

The "EIN" of the PALM-COEIN system for AUB can occur in adolescents with HMB, although with less frequency than ovulatory dysfunction and coagulopathy. Endometrial (E), includes conditions such as sexually transmitted infections causing endometrial friability, and endometriosis.[40] Iatrogenic (I) includes medication induced menstrual bleeding; the most common are breakthrough bleeding owing to hormonal agents such as CHCs, or anticoagulation.[41] Not yet classified (N) refers to possible causes that do not fall into the other categories and have not yet been characterized. Occasionally, structural (PALM) causes, such as rare benign uterine tumors,[42] malignancy,[43] or vascular malformations, may present with AUB in adolescents. Intrauterine or ectopic pregnancy can cause abnormal and unexpected bleeding. Lastly, trauma to the vagina and cervix can cause intermenstrual/irregular bleeding, and patients should be carefully evaluated for history of vaginal foreign bodies and/or sexual assault.

Diagnostic Evaluation

Menstrual History

To determine whether a patient's bleeding is excessive, a focused history of a patient's menses, beginning with menarche, should be obtained (**Table**).[44] To help standardize menstrual blood loss, the Pictorial Blood Assessment Chart score was created.[45,46] The Phillips Bleeding Assessment Tool has also been shown to be useful as a screening tool for women with HMB, with a high sensitivity and specificity (95%) for hemostatic disorders, especially when combined with the Pictorial Blood Assessment Chart.[47,48] Clinicians are encouraged to use these tools to guide them in assessing for abnormal menstrual flow in their adolescent patients. Additionally, numerous mobile device period tracker apps have been developed, which are extremely helpful for recall of bleeding days during follow-up visits.

Quality-of-life measures[49,50] should be considered in clinics treating adolescents with HMB. Adolescents with HMB miss more days of school with each menses and have decreased sports participation and increased disruption of their hobbies and leisure activities owing to menses compared with their typically menstruating counterparts.[51]

Bleeding History

A detailed history should be taken regarding other bleeding symptoms. Generalized bleeding assessments tools have been created to help standardize quantitative scores for bleeding symptoms, assess bleeding severity, and guide clinicians as to which patients require further workup. Bleeding symptoms most worrisome for an underlying BD are listed in the Table.[44]

Other Medical History

Hyperthyroid or hypothyroid disease and autoimmune diseases can cause HMB through hypothalamic dysfunction and/or thrombocytopenia. Hair loss, temperature dysregulation, weight changes, rashes, fever, arthralgia, and arthritis should be discussed. History and review of symptoms for hypermobility syndromes should be assessed in patients. A 5-point self-administered questionnaire to help assess flexibility and hypermobility can be used.[52]

Family History

Family history of bleeding, especially that of first-degree relatives, is an important factor when assessing for inherited BD or autoimmune disorders. Similar questioning regarding family history of bleeding (mucocutaneous, joint or muscle, postpartum, or surgical bleeding) and a detailed family menstrual history, including associated hysterectomies and blood transfusions, is important to ascertain from family members. Because many adolescents will need hormonal management to control HMB, a family history of arterial and venous thrombosis should be obtained, given the increased risk of thrombosis in patients on systemic hormonal therapy.

Physical Examination

When determining whether a patient has a BD, certain aspects of the PE should be focused on. Thoroughly examine the skin for bruising, hematomas, and petechiae and inspect the nares and oral cavity for signs of allergic rhinitis, bleeding, or wet purpura. A Beighton 9-point joint hypermobility score should be used to evaluate any patient with a concern for increased bleeding and hypermobility.[53]

Patients should be examined for signs of thyroid disease, such as hair loss, dry skin for hypothyroidism or excessive sweating, and tachycardia for patients with hyperthyroidism. Signs of excessive androgen production, such as hirsutism, acne, and hair loss, as well as signs of insulin resistance, should be evaluated.

Although outflow tract abnormalities are unusual in patients presenting with HMB, if menses is associated with severe pelvic pain not typical for primary dysmenorrhea, an external genital examination should be performed, and evaluation for patency of the vaginal orifice with a cotton swab should be considered. A more comprehensive gynecological examination should be performed in patients who have a history of sexual activity, particularly if review of systems is suggestive of genitourinary tract infection.

Laboratory Testing

In addition to a thyrotropin level to evaluate for thyroid disease, any adolescent with a concern for HMB should have a CBC with smear, ferritin test, and a pregnancy test if sexually active.[9] The CBC will evaluate for both (1) anemia, a possible consequence of HMB, and (2) thrombocytopenia, a possible cause of HMB. A ferritin test will assess for iron deficiency, which may be present without anemia or microcytosis.[54] Depending on a patient's history and PE, further coagulation tests can be performed, preferably under the guidance of a hematologist (Figure 3).

Table. Menstrual and Bleeding History: Indications for Possible Bleeding Disorder

Menstrual History Elements	Bleeding Symptoms[a]
Heavy bleeding at menarche	Spontaneous episodes of epistaxis lasting >10 min (in absence of allergic rhinitis)
Prolonged menstrual bleeding lasting >8 d	Gingival/oral bleeding lasting >10 min (in absence of gingivitis)
Frequent menstrual bleeding, cycles <24 d	Prolonged cutaneous bleeding from superficial lacerations or abrasions lasting >10 min
Severe iron deficiency anemia, especially if resulting in pRBC transfusion	Excessive or unexpected bleeding from surgeries or dental extractions
Flooding, heavy leakage onto clothing, or gushing of blood	Muscle or joint bleeding
Passage of clots, especially if >2 cm in size	Postpartum hemorrhage
Increased menstrual hygiene product use, saturating/changing every 120 min or less	Any excessive bleeding requiring blood transfusion

Abbreviation: pRBC, packed red blood cells.

[a] Adapted from the ISTH BAT.[44]

Concern for excessive androgen production and anovulatory cycles secondary to PCOS should prompt a laboratory evaluation. Although numerous testing strategies have been suggested, there is lack of consensus about diagnostic criteria for PCOS in adolescents.[55,56] We suggest starting with free and total serum testosterone levels. If history/PE reveal significant hirsutism or signs of virilization, dehydroepiandrosterone sulfate, androstenedione, and morning 17-OH progesterone should also be obtained. Clinicians should note that patients who are taking combination hormonal contraceptives (CHCs) at the time of testing will have iatrogenically decreased serum testosterone levels owing to both suppressed ovarian steroid production and increased sex hormone–binding globulin production stimulated by estrogen in the CHC.[57]

Radiological testing

Although diagnostic imaging is frequently performed in the evaluation of HMB, structural abnormalities are accountable for only a small minority of cases of HMB in adolescents. Clinical evaluation should therefore guide its inclusion; if a patient presents with (1) menstrually associated pelvic pain (dysmenorrhea) refractory to first-line medical therapy (ie, nonsteroidal anti-inflammatory drugs or CHCs) or (2) PE findings suggestive of pelvic mass or uterine/outflow tract abnormality, then imaging should be considered. Pelvic ultrasonography is generally the initial modality used, and although transvaginal ultrasonography is more sensitive in the detection of small ovarian cysts, large masses and clinically significant mullerian anomalies should be detectable on transabdominal studies.

Heavy Menstrual Bleeding

Management

Acute heavy and prolonged menstrual bleeding can be an extremely traumatic event for a teenager and can result in hospitalization and transfusion of blood products. However, these can of-

ten be prevented with proactive outpatient management. All clinicians are encouraged to take time alone with adolescents presenting with HMB and to be familiar with consent and confidentiality laws regarding reproductive health in their respective state/jurisdiction. Evaluation for confidential issues such as sexual activity, potential sexually transmitted infection exposure, sexual trauma, and pregnancy must be considered and should be conducted with the adolescent alone. If other endocrinologic or bleeding symptoms are identified in the history, review of systems, or PE, then laboratory testing should be considered, as outlined in previous sections.

Once the diagnosis of heavy and/or prolonged menstrual bleeding has been established, priorities in evaluation and management of acute HMB include:

1. Assessment of hemodynamic status: history of syncope, presyncope, or positional dizziness must be obtained, followed by office-based orthostatic blood pressure and heart rate measurements, if indicated.
2. Accurate medication history, particularly if hormonal agents have already been used by the patient, or any drugs that inhibit platelet function.
3. Physical examination, including assessment of briskness of vaginal bleeding and pelvic examination to evaluate for trauma (if appropriate).
4. Measurement of hemoglobin/hematocrit, as well as platelet count.

The management of chronic, heavy, and prolonged menstrual bleeding varies according to etiology. Hormonal management is almost always indicated and beneficial. The use of hemostatic agents is indicated in the presence of a BD and can supplement or replace the use of hormones, particularly if hormones are not well tolerated.

Hormonal Agents

If the patient is hemodynamically stable and anemia is not severe (hemoglobin levels >8.0 g/dL but <12 g/dL, per WHO definition [to convert to grams per liter, multiply by 10]),[58] outpatient treatment with iron supplementation and hormonal management should be initiated. Numerous hormonal regimens have been shown to be effective, and little evidence to support the use of one over another exists for the adolescent population. Progestagens or progestins (synthetic forms of progesterone) form the foundation of hormonal management of HMB[59]; they exert their effect by downregulating endometrial estrogen receptors, thereby reducing glandular proliferation and inducing endometrial atrophy. They can be administered orally, by injection, or via intrauterine device, although in the setting of acute bleeding, they are most commonly given orally. They can be combined with estrogen, typically in the form of CHCs (available in oral, transdermal, and transvaginal formulations), which helps to establish regular and predictable cycles, if desired. However, particularly in the setting of anemia, menstrual suppression is recommended, at least temporarily, to allow the patient to avoid further blood loss and recuperate her normal hematologic status, as well as improve her QOL.[60]

Stand-alone oral progestins available in the United States include medroxyprogesterone acetate (MPA) and norethindrone; 2.5 mg to 5 mg is a common starting dose for either in the management of HMB, and some patients may require titration to 10 mg or 20 mg daily. They can be given at these doses either cyclically for those desiring menstrual cycles or continuously for those desiring menstrual suppression.[61] We do not recommend use of lower-dose progestin-only oral contraceptives (also known as the mini-pill) because they are more frequently associated with breakthrough bleeding.

Dozens of combination oral contraceptives (COC) formulations are available in the United States, most commonly containing ethinyl estradiol with one of numerous progestins, and are most commonly packaged as 28-day cycles, with some extended-use formulations available. While COCs containing the first-generation and second-generation progestins norethindrone and levonogestrel are frequently used for the control of HMB, there is a lack of randomized clinical trials comparing efficacy of different COC formulations; any COC may be used.[62,63] However, those with very low ethinyl estradiol dosages (ie, 10 µg) are more likely to be associated with breakthrough bleeding; therefore, we also recommend avoiding such ultralow estrogen-dose pills for the management of HMB.[60] A newer COC formulation, estradiol valerate plus dienogest, has been shown in some studies to be significantly more effective than standard COCs for control of menstrual bleeding, and is in fact the only COC that is approved by the US Food and Drug Administration for the management of HMB.[64]

Placebo-free regimens can be used in both the short- and long-term to safely suppress menses; duration of use must be weighed against adverse effects of different medications used.[60] Breakthrough bleeding is not uncommon with such regimens, and in the absence of BD, discontinuing medication after 6 to 12 months can be attempted if desired by the patient. For patients who have never used hormonal medications and in whom rapid cessation of bleeding is needed, a tapering regimen of oral agents with higher starting doses may be prescribed. Again, although many tapering regimens are used in practice, there is little evidence in the literature to support one over another.[65]

Intravenous conjugated estrogen can be used for the management of acute HMB, rapid blood loss, and severe anemia because it acutely induces vasospasm in the endometrium, in addition to causing follicular suppression; it should be considered when a patient has failed outpatient treatment with other hormonal regimens. It should be given along with antiemetics and eventually transitioned to oral agents. Though this approach is frequently relied on in the inpatient setting, evidence to support its use instead of oral combination or progestin-only regimens is also lacking, as is evidence to support the use of one oral regimen over another in this setting, particularly for adolescents. The **Box**[66,67] includes intravenous and oral regimens that may be used to control acute HMB.

The gonadotropin-releasing hormone agonist leuprolide acetate may also be used to abort HMB. However, it will induce menopauselike symptoms, including hot flashes and vaginal dryness, reducing its tolerability. It is infrequently used in adolescents solely for the indication of HMB. Surgical modalities are typically also avoided in adolescents because they may pose a threat to future fertility; use of a Foley balloon uterine tamponade may be considered for bleeding resistant to less invasive therapies.

Studies have indicated that the 52-mg levonogestrel intrauterine system is highly superior to other hormonal methods in its effect on HMB[4,68,69] and that it is well tolerated in adolescents, including those with BD.[70,71] Although insertion requires a vaginal speculum examination and cervico-uterine instrumentation, intra-

Box. Medication Regimens Used to Control Acute Heavy Menstrual Bleeding

Intravenous Regimens
- Conjugated equine estrogen: 25 mg every 4-6 h for 24 h
- Tranexamic acid: 10 mg/kg: (max 600 mg) every 8 h for 2-8 d
- Aminocaproic acid: 100-200 mg/kg (max 30 g/d) every 4-6 h

Oral Regimens
- Combined oral contraceptive containing 30-50 µg EE
  - Three times per d for 7 d, then taper to daily dosing
- Medroxyprogesterone acetate: 20 mg three times per d for 7 d, then taper to daily dosing
- Norethindrone acetate: 10 mg three times per d for 7 d, then taper to daily dosing
- Tranexamic acid: 1300 mg three times per d for 5 d
- Aminocaproic acid: 100-200 mg/kg (max 30 g/d) every 4-6 h

Adapted from ACOG Committee Opinion No. 557,[62] Moon et al,[66] and Haamid et al.[67]

uterine devices (IUDs) are considered to be safe in nulliparous women and have been recommend by both the American Academy of Pediatrics and ACOG as first-line contraceptive agents for teenagers, without a minimum age limit.[72,73] Although unscheduled bleeding is a common adverse effect, especially in the first 3 to 6 months of use, amenorrhea is common thereafter; once placed, ease of use is another advantage. While best practices for pain management during IUD insertion have not been established, in the authors' experience, even precoital teens can successfully tolerate it with good support and use of verbal counseling without sedation or anesthesia; distraction techniques have also been successfully used to reduce patient pain and anxiety.[74] Some small studies have suggested that IUD expulsion and malposition rates may be higher in recipients with BD, but more data are needed.[75]

Hemostatic Agents

Antifibrinolytics, such as tranexamic acid and aminocaproic acid, are an effective and generally well-tolerated therapy for adolescents with HMB[76,77] and can be used in both the acute and chronic setting. They block the conversion of plasminogen into plasmin and inhibit excessive fibrin breakdown. Tranexamic acid is approved specifically for HMB and can be taken orally every 8 hours for 5 days of the menstrual period.[78] These medications can be used for patients with or without an identified BD.

Desmopressin, or 1-desamino-8-D-arginine vasopressin (DDAVP), is the synthetic analog of the naturally occurring vasopressin, and releases stored VWF and FVIII. Desmopressin can be used to treat or prevent HMB in patients with type 1 VWD and some type 2 VWD, as well as those with mild FVIII deficiency. Desmopressin can also help with bleeding in some patients with platelet dysfunction and hypermobility syndromes.[79] To prevent tachyphylaxis, patients should avoid taking more than 1 dose per day or more than 2 doses per week during their menstrual period.[80,81] Desmopressin can be administered parentally, via subcutaneous injection or intranasally. Caution should be taken with overhydration because DDAVP can cause water retention and hyponatremia. Both tranexamic acid and DDAVP have been shown to cause statistically significant decreases in HMB and improved QOL when used during menses.[82]

Factor concentrates are available for many of the factor deficiencies, including VWF. They are only available as intravenous formulations and therefore are usually reserved for HMB unresponsive to other treatment. Factor VII replacement is also used to treat GT.

Medications to Avoid

Patients diagnosed as having a BD should try to avoid repeated and frequent doses of aspirin and nonsteroidal anti-inflammatories (NSAIDs) such as ibuprofen, naproxen, and ketorolac, owing to their interference with platelet function.[83] Other therapies, such as acetaminophen and heat, should be attempted first for the treatment of dysmenorrhea or pain after IUD placement. Some selective serotonin reuptake inhibitors (SSRIs) have been shown to cause increased bleeding in patients owing to decreased platelet serotonin content,[84] and unfortunately, many adolescents, including those with BDs, have depression and anxiety that requires pharmaceutical treatment.[85] Owing to the potential increased bleeding risk with SSRIs, alternative antidepressant agents should be considered when possible.

Treatment of HMB and BD: the Multidisciplinary Approach

Multidisciplinary clinics have been well established for patients with BD since the 1970s. These clinics were initially established for patients with hemophilia, named Hemophilia Treatment Centers. Over the past decade and a half, there has been increasing focus to also treat women and girls with HMB in such multidisciplinary clinics.[86]

Historically, the evaluation of HMB has been predominantly the role of a primary care clinician or gynecologist. Given that a high prevalence of female individuals (specifically adolescents) with HMB have underlying BDs, hematologists should also have a prominent role.[87] Likewise, given the complexity of diagnosing and managing these disorders, a multidisciplinary approach provides improved time to diagnosis and bleeding control as well as the most efficacious use of medical resources.[88] Individuals with HMB have shown high satisfaction rates of 90% with the multidisciplinary approach.[89] Ideal multidisciplinary clinics are comprised of a (1) hematologist, (2) pediatric and adolescent gynecologist or adolescent medicine specialist (3), nurse, and (4) psychologist or social worker. Given the excellent treatment options available for HMB and BD, adolescents receiving such coordinated care have the potential to live normal, healthy, and developmentally appropriate lives with few limitations.

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