

The Adolescent with Menorrhagia: Diagnostic Approach to a Suspected Bleeding Disorder

Rudi-Ann Graham, MD,*[†] Joanna A. Davis, MD,^{†‡} Fernando F. Corrales-Medina, MD*^{†‡}

**Department of Pediatrics, Holtz Children's Hospital–Jackson Memorial Medical Center, Miami, FL*

†Division of Pediatric Hematology-Oncology, Department of Pediatrics, University of Miami–Miller School of Medicine, Miami, FL

‡University of Miami–Hemophilia Treatment Center, Miami, FL

Practice Gaps

1. To deliver comprehensive care to the adolescent with menorrhagia, clinicians should recognize patterns of menstrual loss that are atypical of that associated with physiologic hormonal changes. There remains a need for consideration of possible underlying bleeding diatheses when screening the adolescent with heavy menstrual bleeding.
2. Clinicians should be aware of the treatment modalities available to the adolescent with menorrhagia and an underlying bleeding disorder and understand when referral to a hematologist is indicated.

Objectives After completing this article, readers should be able to:

1. Define menorrhagia.
2. Use validated screening tools to identify menorrhagia.
3. Identify cases of menorrhagia in the adolescent that warrant further hematologic evaluation based on predictors noted on history and physical examination.
4. Review the most common bleeding disorders associated with menorrhagia in the adolescent and the diagnostic approach to each disorder.
5. Identify the hormonal and hematologic treatment modalities available for use in the adolescent with menorrhagia and understand the limitations of using each treatment in this age group.
6. Recognize when a referral to a pediatric hematologist/oncologist is indicated.

OVERVIEW

Adolescent girls and young women often seek medical attention because of menorrhagia, or heavy menstrual bleeding (HMB). Menorrhagia is defined as menstrual bleeding lasting for more than 7 days, sanitary product use greater than

AUTHOR DISCLOSURE Dr Graham has disclosed no financial relationships relevant to this article. Dr Davis has disclosed that she is a medical advisory board member for Bayer Pharmaceuticals, Genentech, CSL Behring, Novo Nordisk, Bioverativ, and Octapharma and a phase III trial study coordinator for CSL Behring and Bayer Pharmaceuticals. Dr Corrales-Medina has disclosed that he has grant awards from Bayer and Shire and is an advisory board member for Bayer, Genentech, Octapharma, and Shire. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

| | |
|---------|---|
| ACOG | American Academy of Obstetrics and Gynecology |
| COCp | combined oral contraceptive pill |
| DDAVP | 1-deamino-8-D-arginine vasopressin |
| FVIII | factor VIII |
| FIX | factor IX |
| GnRH | gonadotropin-releasing hormone |
| HMB | heavy menstrual bleeding |
| LNG-IUS | levonorgestrel-releasing intrauterine system |
| LTA | light transmission aggregometry |
| PBAC | pictorial bleeding assessment calendar |
| PFD | platelet function defect |
| TA | tranexamic acid |
| vWD | von Willebrand disease |
| vWF | von Willebrand factor |

7 per day, and greater than 80 mL of blood loss per menstrual cycle. (1) Estimated prevalence may be as high as 37%. (2)(3) Menorrhagia can be a significant issue for young women at a time of life characterized by dramatic physical and psychological changes. Patients may not discuss HMB with their health-care provider due to a skewed perception of what constitutes normal menstrual bleeding, particularly if other family members have the same menstrual pattern. In 2006, the American College of Obstetricians and Gynecologists (ACOG), in association with, the American Academy of Pediatrics, issued a committee consensus report emphasizing the need for clinicians to not only recognize patterns of normal and abnormal menstruation but also to thoroughly evaluate the adolescent girl with abnormal bleeding.

In the first few years after menarche most cases of abnormal bleeding in adolescent girls can be attributed to anovulatory cycles and the immaturity of the hypothalamic-pituitary-ovarian axis. However, this dysfunctional uterine bleeding is a diagnosis of exclusion. Menorrhagia should be investigated. Although it may be comforting to parents, patients, and physicians that most cases of adolescent HMB can be considered physiologically normal, clinicians must pursue other diagnoses that may significantly affect long-term health outcomes and quality of life. Menorrhagia is well recognized as a common bleeding manifestation in women, with a documented inherited bleeding disorder. However, in adolescents without a known personal or family history, the potential link between HMB and a coagulopathy is sometimes forgotten. If an underlying bleeding disorder is considered, the diagnostic evaluation becomes much more extensive, involving the input of a pediatric hematologist. Adolescent girls with inherited bleeding disorders are more likely to have menorrhagia and are more likely to develop iron deficiency anemia, a need for blood transfusions, endometriosis, and hemorrhagic ovarian cysts. They may be at increased risk for miscarriage and postpartum hemorrhage. (4) Fifteen percent to 25% of women with iron deficiency anemia are found to have an undiagnosed bleeding disorder. (5) This statistic underscores the importance of a thorough evaluation performed earlier rather than later. The public health impact is significant. Diagnosing a bleeding disorder improves management, especially when menorrhagia has been inadequately controlled by standard hormonal interventions. In this article, we provide a review of the most common inherited bleeding disorders associated with menorrhagia in the adolescent. We provide an outline for diagnostic evaluation and an overview of current management strategies available for this age group.

EPIDEMIOLOGY OF BLEEDING DISORDERS IN ADOLESCENTS WITH MENORRHAGIA

An estimated 20% of American women with menorrhagia have an underlying bleeding disorder (approximately 2.5–3 million American women). (1) Historically, the most common inherited bleeding disorder is von Willebrand disease (vWD), with an estimated population prevalence of 1% to 2%, regardless of sex, race, or ethnicity. (6) Von Willebrand disease has increased prevalence in women with menorrhagia, particularly white women, with estimates as high as 10% to 20%. (5) Platelet function defects (PFDs) account for the next most common bleeding disorder in women and girls with HMB, with an estimated prevalence of 4% to 44%. (7) As recognition of and ability to diagnose PFDs improve, there is evidence that these defects may be as common as vWD. (7) Other less common bleeding disorders include mild hemophilia A or B (formerly referred to as symptomatic carrier states) and rare coagulation factor deficiencies. The prevalence of menorrhagia in women with bleeding disorders is high. Menorrhagia affects 32% to 100% of women with vWD, up to 51% of women with platelet dysfunction, 10% to 57% of women with symptomatic hemophilia, and 35% to 70% of women with rare factor deficiencies. Additional uncommon disorders associated with menorrhagia include plasminogen activator inhibitor-1 deficiency, connective tissue disorders (such as Ehlers-Danlos syndrome), and hereditary hemorrhagic telangiectasia.

SCREENING FOR BLEEDING DISORDERS

The Healthy People 2020 initiative in the United States included, among its targets, increasing the proportion of physicians who refer for further evaluation of women and girls with symptoms suggestive of an inherited bleeding disorder. (8)(9) Menorrhagia in early adolescence is commonly reported in women with bleeding disorders, often associated with acute hemorrhage and severe anemia requiring hospitalizations and blood transfusions. This typically occurs within the first few years after menarche. (4)(10) Menorrhagia was common in affected female members of the family 'S' of the Aland Islands, first described by Dr. Erik von Willebrand in the 1920s. His index case, Hjordis, bled to death with her fourth menstrual period at 14 years old. (11)(12) Several studies have highlighted the need to evaluate women for an underlying bleeding disorder if they develop HMB throughout their menstrual life. The most recent ACOG guidelines state that health-care providers should screen all adolescents with

menorrhagia for bleeding disorders. (8)(13) Quantifying menstrual bleeding can be challenging in clinical practice. Warner et al (14) identified characteristics of the menstrual bleed that are strong predictors of blood loss greater than 80 mL per cycle: flooding (soaking a pad or tampon in less than an hour) and/or impairment of daily activities with most periods, soaking through night clothes, passing clots greater than 1 inch in diameter, and low serum ferritin level. One proposed method to objectively quantify menstrual blood loss includes the use of a pictorial bleeding assessment calendar (PBAC) (Fig 1). (15)(16) The PBAC score has been validated in women with greater than 80% sensitivity and specificity for scores greater than 100. A menstrual score greater than 100 was associated with blood loss of greater than 80 mL. (15) The PBAC score is simple to use and can be readily incorporated into the initial history. A thorough bleeding history documents easy bruising or bleeding with minor injuries, a history of frequent or difficult-to-control epistaxis, or excessive bleeding after surgeries such as tonsillectomy or dental extractions. A coagulopathy is suggested by iron deficiency anemia, a history of blood transfusions, a family history positive for a diagnosed bleeding disorder, HMB, early hysterectomy, or challenges with bleeding during or after childbirth. (17)

Pertinent physical findings include skin bruising, petechiae, ecchymoses, and pallor, although the absence of these features does not exclude a bleeding disorder. (15)

INHERITED BLEEDING DISORDERS ASSOCIATED WITH MENORRHAGIA

Von Willebrand Disease

Von Willebrand disease is the most common bleeding disorder identified in women with HMB. It affects 1% to 2% of the general population (6) and 3% to 36% of girls with menorrhagia. (4)(15) Von Willebrand factor (vWF) is a large glycoprotein synthesized by megakaryocytes and endothelial cells. It is stored in the Weibel-Palade bodies in endothelial cells and in α -granules of platelets. It is released into the circulation on stimulation by endothelial cell damage. (11)(18) It exists in plasma as a multimeric dimer configuration ranging in size from small (500 kD) to very large (>10,000 kD) high-molecular-weight multimers. (19) Its function in primary hemostasis is to promote platelet adhesion to the subendothelium at the site of vascular injury. High-molecular-weight vWF multimers adhere to platelets better than do small ones. Also, vWF participates in platelet-platelet interactions and, along with fibrinogen, promotes thrombus growth and stabilization. (19) It has a role in secondary hemostasis, serving as a carrier protein for

| Surname, First Name | | Start Date: | | Total: | | | | | |
|---------------------|--|-------------|---|--------|---|---|---|---|---|
| Towel | | Day | | | | | | | |
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| | | | | | | | | | |
| | | | | | | | | | |
| | | | | | | | | | |
| Clots/Overflow | | | | | | | | | |
| Tampon | | Day | | | | | | | |
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| | | | | | | | | | |
| | | | | | | | | | |
| | | | | | | | | | |
| Clots/Overflow | | | | | | | | | |

Interpretation:

A score of >100 points indicates menstrual loss >80ml/cycle

Figure 1. Pictorial bleeding assessment calendar (PBAC). Adapted with modifications from Higham JM, O'Brien PM, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. *Br J Obstet Gynaecol.* 1990;97(8):734–739. (16)

| PADS | |
|-------------------|------------|
| Lightly Soaked | +1 Point |
| Moderately Soaked | +5 Points |
| Heavily Soaked | +20 Points |
| TAMPONS | |
| Lightly Soaked | +1 Point |
| Moderately Soaked | +5 Points |
| Heavily Soaked | +20 Points |
| CLOTS | |
| Small | +1 Point |
| Large | +5 Points |
| FLOODING | |
| Any | +5 Points |

coagulation factor VIII (FVIII), protecting it from early proteolytic degradation, and increasing its half-life by 5- to 10-fold. (19) A quantitative deficiency or qualitative abnormality of vWF results in vWD. Von Willebrand disease is classified as type 1 or type 3, which describe partial and near-complete quantitative deficiencies of vWF, respectively, and as type 2, which is characterized by various qualitative defects. (18) Type 1 disease, an autosomal dominant disorder, accounts for 70% to 80% of all cases of vWD. (18)(20) Type 2 disease encompasses subtypes 2A, 2B, 2M, and 2N, which, due to mutations in the vWF gene, cause abnormalities in the interactions between vWF and its ligands. (18) Subtypes are determined by assessment of vWF multimers, measures of interaction of vWF protein with platelets, and measures of FVIII levels. (18) Qualitative or quantitative deficiencies of vWF may manifest as mucocutaneous bleeding: epistaxis, bruising without recognized trauma, gastrointestinal bleeding, oropharyngeal bleeding after brushing or flossing, and prolonged bleeding after trauma and surgery. (18)(20) Severe deficiencies, as in type 3, may also present with hemarthroses and deep muscular hematomas, similar to that seen in hemophilia A or B. (20) Women are disproportionately affected because of menstruation and childbirth. Menorrhagia is the most prevalent symptom in women with vWD (6) and may often be the only symptom in mild type 1 disease. Women with vWD more often bleed through protection and report a longer duration of bleeding compared with controls. They are more likely to develop anemia than women without a bleeding disorder. (6) Severe menorrhagia resulting in blood transfusion was reported in 7% to 22% of women with type 1 vWD. (6)

There is no single definitive test that confirms the diagnosis of vWD. The Table highlights the panel of tests to be requested when there is suspicion of underlying vWD.

An activated partial thromboplastin time will often be normal in vWD because most patients with type 1 disease can maintain adequate FVIII levels. Thrombocytopenia may be seen in type 2B vWD. A complete blood cell count may also show a microcytosis, suggestive of iron deficiency anemia. Initial vWF assays should include vWF antigen, ristocetin cofactor activity, and FVIII assays. (15)(12) The normal level of vWF antigen is generally accepted to be between 50 and 200 IU/dL. (20) A vWF antigen level less than 50 IU/dL is considered to be low and when associated with bleeding is usually diagnostic, although false-positives can occur. A diagnostic dilemma can exist because there can be considerable variation in vWF levels in any individual at any given time. Protein assays may be affected by genetic, physiologic, and pharmacologic factors. The vWF protein is an acute phase reactant. Levels of vWF and FVIII may rise

acutely with infection, inflammation, vigorous exercise, hyperthyroidism, and increased levels of estrogen during pregnancy or with the use of hormonal contraceptives. (4) (12) Even the stress associated with laboratory draws can increase protein levels. (4) It is well known that individuals with blood group type O exhibit a 20% decrease in vWF levels compared with individuals with blood type A or B. (21)

Levels of vWF have been shown to vary during the menstrual cycle, although this is not well defined. Limited evidence suggests that levels drawn on days 1 to 4 of the menstrual cycle are least likely to be affected by endogenous hormones. (4) Repeated testing is often necessary to establish or exclude the diagnosis and should be considered if the degree of bleeding and the family history are suggestive of disease. Ideally, on-site sample collection and real-time analysis of samples should be performed to avoid sample degradation and subsequent false-positive results. (12) Interpretation of abnormal laboratory test results is best performed with a hematologist.

Genetic testing for vWD is technically challenging. Von Willebrand factor is a very large polymorphic gene that spans 178 kb of DNA, contains 52 exons, and has more than 300 single nucleotide polymorphisms. (20) This makes gene sequencing difficult and of relevant clinical utility in only very specific situations. For example, identifying large deletions in patients with vWD type 3 suggests an increased risk of developing neutralizing antibodies and anaphylactic reactions on treatment. (18) Identifiable mutations are useful for prenatal diagnosis or carrier analysis. (20) Genetic testing may also be justified if molecular diagnosis will help guide treatment, such as for types 2N and 2B. In these variants, mutations are usually clustered in specific areas of the gene, making sequencing and interpretation less difficult. (18)

Inherited PFDs

Platelet function disorders are increasingly recognized as an underlying etiology of unexplained menorrhagia in adolescents. A retrospective review of medical records performed by Amesse et al (22) identified menorrhagia in 41% of adolescents with a documented PFD. Philipp et al (23) found that in a cohort of multiracial women 17 to 55 years old with previously unexplained menorrhagia, platelet dysfunction was more common than vWD. In this study, compared with white women, black women were more likely to have a PFD associated with menorrhagia. (23) This supports testing for PFDs in adolescents with menorrhagia and a negative evaluation for vWD, especially if the patient is of African descent. Platelet function defects encompass a heterogeneous cluster of disorders that may not be detected until

TABLE. Laboratory Panel for vWD

| DIAGNOSTIC TEST | FUNCTION | TYPE OF VWD | | | | | |
|---|--|--|--|---|--|---|--|
| | | 1: PARTIAL QUANTITATIVE DEFICIENCY | 2A: QUALITATIVE DEFICIENCY WITH ABSENCE OF HIGH- AND INTERMEDIATE- WEIGHT VWF MULTIMERS | 2B: QUALITATIVE DEFICIENCY WITH INCREASED AFFINITY FOR PLATELET GLYCOPROTEIN IB; ASSOCIATED WITH MILD THROMBOCYTOPENIA | 2M: QUALITATIVE VARIANT WITH DECREASED PLATELET- DEPENDENT VWF ACTIVITY | 2N: QUALITATIVE VARIANT WITH DECREASED AFFINITY FOR FVIII | 3: COMPLETE DEFICIENCY OF VWF |
| vWF antigen | Measures the concentration of vWF protein in the plasma | ↓ | ↓ or N | ↓ | ↓ | N | ↓↓↓ |
| vWF ristocetin cofactor activity | Quantitates agglutination of platelets after addition of ristocetin to plasma (function of vWF activity) A ratio of vWF ristocetin cofactor to vWF antigen differentiates between quantitative and qualitative defects <ul style="list-style-type: none"> • A ratio >0.6 is seen in quantitative defects (vWD types 1 and 3) • A ratio <0.6 is seen in qualitative defects (vWD type 2) | ↓ | ↓↓ | ↓↓ | ↓ | N | ↓↓↓ |
| FVIII assay | Measures the concentration of FVIII in plasma; individuals with type 1 or type 2 may have lower levels of FVIII concentrate | ↓↓ | ↓ or N | ↓ or N | ↓ or N | ↓↓ | ↓↓↓ |
| vWF multimers | High-molecular-weight multimers are the most hemostatically active; distribution of multimer sizes in patient plasma will affect hemostatic phenotype | N | ↓↓ | ↓ | N | N | ↓↓↓ |
| Ristocetin-induced platelet aggregation | Quantitates platelet aggregation at varying concentrations of ristocetin in the presence of patient-rich plasma | ↓ or N | ↓ | ↑ | ↓ | N | ↓↓↓ |
| Type and screen | ABO blood group affects vWF levels and influences interpretation | | | | | | |

FVIII=factor VIII; N=normal; vWD= von Willebrand disease; vWF= von Willebrand factor.

after a bleeding event. Platelets aid in clot formation by adhering to the exposed subendothelium at the site of vascular damage. Platelets subsequently become activated and secrete the contents of intracellular granules, which creates a cascade of adhesion, aggregation, and clot formation. Disorders of platelet function can take place at any step in the cascade, although these steps are so closely intertwined that the classification of platelet function disorders by any single system is challenging. A proposed classification scheme is provided in Fig 2. Platelet defects may be inherited or acquired. Acquired disorders are commonly seen with medications (such as nonsteroidal anti-inflammatory drugs, penicillin antibiotics, and anticonvulsants),

immune-mediated disorders, and chronic illnesses such as uremia and liver disease. (7) The most common inherited disorders include dysfunctional adhesion as in Bernard-Soulier syndrome, which is due to a defect of glycoprotein Ib, and Glanzmann thrombasthenia, due to defective glycoprotein IIb/IIIa. These disorders are considered major inherited PFDs and can be associated with significant menorrhagia. (7)(24) Defects of platelet granules, known as storage pool disorders, include α -granule disorders such as gray platelet syndrome and abnormalities in dense granules, as seen in Chediak-Higashi syndrome. Inherited microthrombocytopenia can be seen in Wiskott-Aldrich syndrome. These platelet defects may manifest a mild to

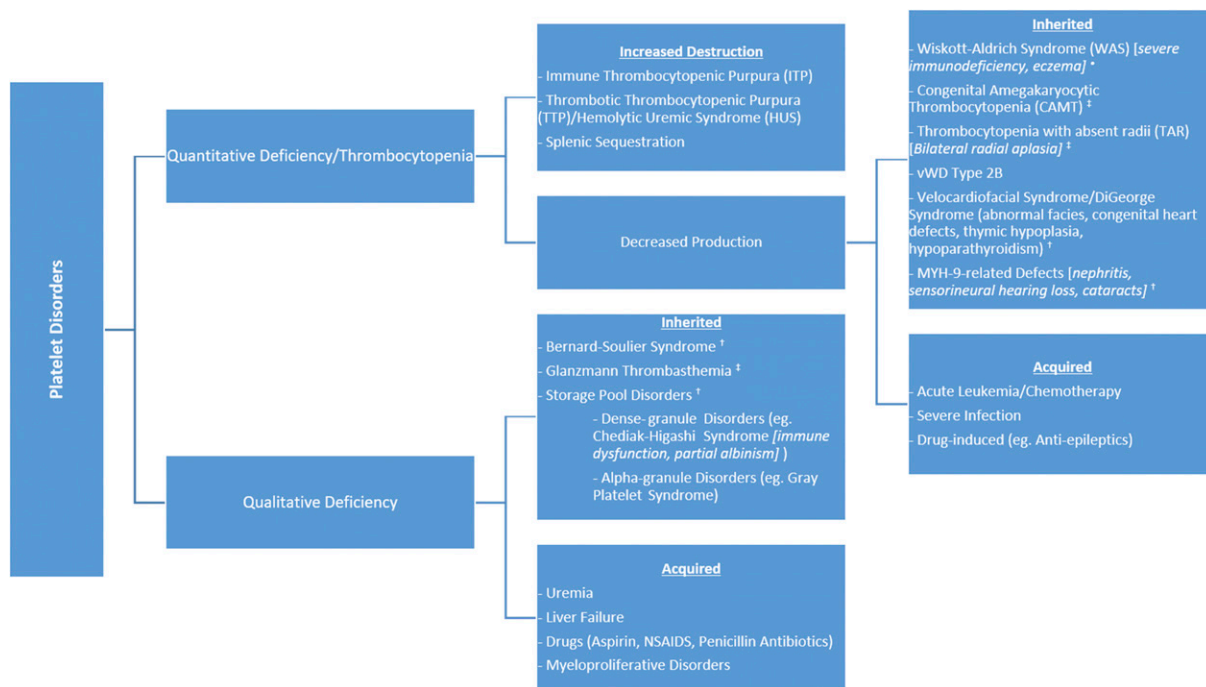


Figure 2. Classification of platelet disorders. This proposed scheme for the classification of platelet disorders includes characteristic features associated with some platelet disorders. [†]Large-sized platelets. ^{*}Small-sized platelets. [‡]Normal-sized platelets. vWD= von Willebrand disease.

moderate bleeding phenotype and can be associated with HMB. In the MYH-9 group of disorders, defects of the platelet cytoskeleton result in macrothrombocytopenia and platelet dysfunction. These disorders can cause severe menorrhagia and other mucocutaneous bleeding symptoms, usually in association with sensorineural hearing loss and renal disease. (7)(25)

Evaluation of a potential platelet disorder begins with a platelet count and peripheral smear. Macrothrombocytopenia, characteristic of Bernard-Soulier syndrome and other giant platelet syndromes, or small platelets, characteristic of Wiskott-Aldrich syndrome, may be obvious by light microscopy.

Platelet aggregometry is the gold standard investigation for PFDs and is usually ordered once vWD and thrombocytopenia have been ruled out. Tests of aggregometry have widely replaced bleeding time. Light transmission aggregometry (LTA), the most widely used method, measures light conduction through plasma thick with platelets; light conduction increases as platelets aggregate in the presence of specific agonists. (7) The test measures the rate and the maximal height of the aggregation response, known as the maximal aggregation. Agonists most commonly used are collagen, adenosine-5'-diphosphate, arachidonic acid, and epinephrine. (7) Nonsteroidal anti-inflammatory drugs, antiplatelet agents such as aspirin and clopidogrel, antihistamines, and some antibiotics

(β -lactam antibiotics, sulphonamides) may interfere with platelet aggregation. (7) The general life span of circulating platelets is 10 days. These medications should be held for at least 7 to 10 days before having LTA performed. (7) Combined oral contraceptive pills (COCPs) may also affect platelet aggregation; however, many patients require oral contraceptives to manage HMB. Experts recommend performing LTA during a placebo week. Repeated testing is recommended before a diagnosis of platelet dysfunction is confirmed or refuted. Philipp et al (23) used platelet aggregometry to assess aggregation induced by ristocetin, adenosine-5'-diphosphate, arachidonic acid, epinephrine, and collagen. In this study, statistically significant defects in ristocetin-induced platelet aggregation were found to be more prevalent in black women with menorrhagia compared with black control women. (23)

The platelet function analyzer may be used as a screening test of abnormal platelet function. This test measures the time to plug formation (the closure time) when whole blood is introduced to membranes lined with epinephrine and collagen. (7) The utility of the platelet function analyzer as a tool for evaluating underlying bleeding disorders in women with menorrhagia is controversial. (26) The platelet function analyzer has good sensitivity to identify disorders of primary hemostasis, including PFDs and vWD, but has low specificity.

More detailed analysis of a suspected platelet disorder might include platelet electron microscopy and flow cytometry. Electron microscopy identifies platelet granules and cytoskeleton defects. Flow cytometry to analyze glycoprotein defects may confirm the presence of Bernard-Soulier syndrome and Glanzmann thrombasthenia by demonstrating decreased glycoprotein Ib and IIb/IIIa levels, respectively. (7)

Hemophilia Carrier States

Hemophilia A and B, deficiencies of FVIII and factor IX (FIX), respectively, are rare X-linked disorders characterized by the potential for spontaneous life-threatening bleeding and recurrent musculoskeletal hemorrhage leading to chronic arthropathy and disability. (27) The disorder typically affects men, and women are often categorized as being obligate carriers or possible carriers. Obligate carriers include all daughters of a father with hemophilia, mothers of 1 son with hemophilia and at least 1 other affected family member, or mothers of at least 2 affected sons. Possible carriers include daughters of a carrier, mothers of 1 son with hemophilia and no other family history, or female first- or second-degree relatives of a known carrier. (28) Factor levels may vary from one carrier to another; some carriers have levels low enough to exhibit a bleeding phenotype. This results from variable expression of the gene due to the random inactivation of 1 X chromosome seen in lyonization. The reference range of FVIII and FIX is 50 to 150 IU/dL. Bleeding manifestations typically occur when factor levels are less than 50 IU/dL. However, hemophilia carriers may manifest bleeding symptoms even with FVIII or FIX levels within the reference range. It is important that baseline levels are established so that appropriate anticipatory guidance or active management can be provided. Carriers with lower factor levels are at increased risk for severe bleeding episodes. (29)

Levels of FVIII are variable because they may increase transiently with stressful events and certain physiologic states, such as pregnancy, for which results interpretation should be conducted with caution. Certain FVIII gene mutations (intron 22 inversions, nonsense mutations, and large deletions) carry a high risk of inhibitor (antibody) formation. Inhibitors are antibodies (primarily immunoglobulin G) directed against the specific deficient factor; these antibodies bind to infused FVIII molecules, resulting in clearance from the circulation and continued bleeding. Gene sequence analysis may be indicated in cases in which FVIII replacement might need to be used.

The hallmark of hemophilic bleeding is hemarthrosis, but female carriers of hemophilia face the additional

challenges of reproductive bleeding. Carriers are at increased risk for bleeding from hemorrhagic ovarian cysts. (29) Compared with women with normal clotting factor levels, women with factor levels less than 0.4 IU/mL more often reported menorrhagia and iron deficiency anemia. (29)

In the United States, males with hemophilia have access to insurance coverage and comprehensive health-care, including factor infusion. Females may not be eligible for insurance coverage if diagnosed as a symptomatic carrier. (28) This disparity has resulted in elimination of the diagnosis of symptomatic carrier in favor of mild hemophilia. Most female carriers maintain factor levels that qualify to classify them as having mild hemophilia. Mild hemophilia is defined as a FVIII or FIX level of 5 to 40 IU/dL. However, few females qualify as having moderate (FVIII or FIX levels of 1–5 IU/dL) or severe (FVIII or FIX levels <1 IU/dL) hemophilia, depending on the extent of lyonization. Changing International Classification of Diseases coding to mild hemophilia is sufficient to allow third-party payers to cover the medical care of the mild hemophilic female.

Factor XI Deficiency and Other Rare Bleeding Disorders

Rare bleeding disorders, including deficiency of fibrinogen (FI), FII, FV, FVII, FX, FXI, FXIII, as well as combined factor deficiencies, represent 3% to 5% of all inherited coagulation disorders. (28) Rare bleeding disorders are characterized by a variety of symptoms, ranging from mild to severe, which can vary significantly from one disorder to another and among patients with the same disorder. The bleeding phenotype is often expressed in patients who are homozygous or compound heterozygous. The correlation between the factor level and the bleeding tendency can also vary markedly between deficiencies and between patients affected by the same deficiency. Factor XI deficiency is increasingly recognized as a cause of reproductive bleeding. Factor XI deficiency, also called hemophilia C, or Rosenthal syndrome, was first recognized in 1953 in patients who experienced severe bleeding after dental extractions. The incidence is 1 in 100,000 persons in the general population. (30) It is increased among persons of Ashkenazi Jewish descent. It is an autosomal recessive disorder. In plasma, FXI circulates in association with high-molecular-weight kininogens and plays an important role in contact activation of the coagulation cascade. A deficiency of FXI may manifest as injury-related bleeding but has also been associated with epistaxis and easy bruising. (30) A review published by Wiewel-Verschueren et al (31) revealed that women with inherited FXI deficiency were at increased risk for HMB and bleeding complications after miscarriage, termination of

pregnancy, and delivery. Heavy menstrual bleeding was reported in 7% to 67% of women observed. (31) Studies related exclusively to adolescents are limited.

Additional laboratory evaluation of all adolescent females with a suspected bleeding disorder should include a pregnancy test, tests of thyroid function (thyrotropin and free thyroxine levels), a prolactin level, a dehydroepiandrosterone-sulfate level, and a total testosterone level. Irregular bleeding can occur with dysthyroid states, hyperprolactinemia, and polycystic ovarian syndrome.

Referral to a hematologist is recommended if there is suspicion of a bleeding disorder from history, physical examination, or laboratory test findings. Figure 3 provides an algorithm for the diagnostic evaluation of the adolescent with menorrhagia and a suspected bleeding disorder.

MANAGEMENT STRATEGIES FOR THE ADOLESCENT WITH MENORRHAGIA AND AN INHERITED BLEEDING DISORDER

A multidisciplinary approach to patient management involving hematologists, obstetrician/gynecologists, and adolescent medicine specialists is appropriate. Bleeding is best managed in the context of the acuity and severity of blood loss. Life-threatening blood loss and severe anemia warrant hospital admission, intravascular fluid repletion, blood product transfusions, and replacement of clotting factor concentrates when indicated. Long-term goals should include reducing the morbidity associated with HMB and improving the patient's health-related quality of life. Therapy

should aim to regularize the menstrual cycle or halt bleeding entirely, correct anemia, and limit the occurrence of problematic bleeding episodes. (32) In older patients, endometrial ablation or hysterectomy may become options, but for women in their reproductive years, where the need to preserve fertility is a priority, medical management forms the mainstay of therapy. Available treatment options include those recommended for women and girls without bleeding disorders but with heavy menstrual flow. Hormonal and hemostatic treatment options are available. Generally, hormonal treatments are used first, with the addition of hemostatic agents as necessary to control bleeding. For women with an identified bleeding disorder, treatment may be more patient-specific. For example, documentation of an appropriate response to desmopressin allows for this medication to be used in vWD or hemophilia A. A combination of therapies is often required. To date there have been no large randomized trials to specifically address treatment of HMB secondary to bleeding disorders in the adolescent population. A general approach to treatment is provided in Fig 4. Explaining the benefits and potential adverse effects of treatment is essential to optimize adherence to a prescribed regimen.

Hormonal Methods of Management

Hormonal modalities include COCPs, levonorgestrel-releasing intrauterine systems (LNG-IUS), oral progestins, injected progestogens, and short courses of gonadotrophin-releasing hormone (GnRH) analogues. These medications inhibit endometrial proliferation, which decreases the potential for extensive bleeding. The COCPs are most often

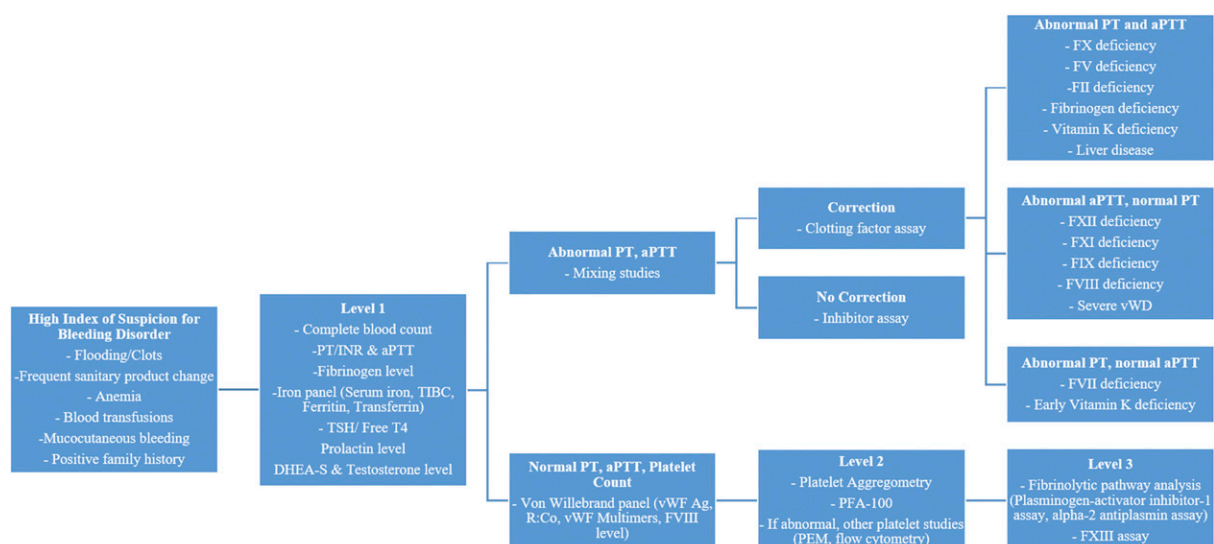


Figure 3. Diagnostic algorithm for the evaluation of the adolescent with menorrhagia. aPTT=activated partial thromboplastin time; FII/V/VI/VIII/IX/X/XI/XII/XIII=Factors II/V/VI/VIII/IX/X/XI/XII/XIII; PEM=platelet electron microscopy; PFA=platelet function analyzer; R:Co: ristocetin cofactor; TIBC=total iron binding capacity; TSH=thyroid stimulating hormone; T4=thyroxine; vWF Ag= von Willebrand factor antigen; vWD= von Willebrand disease.

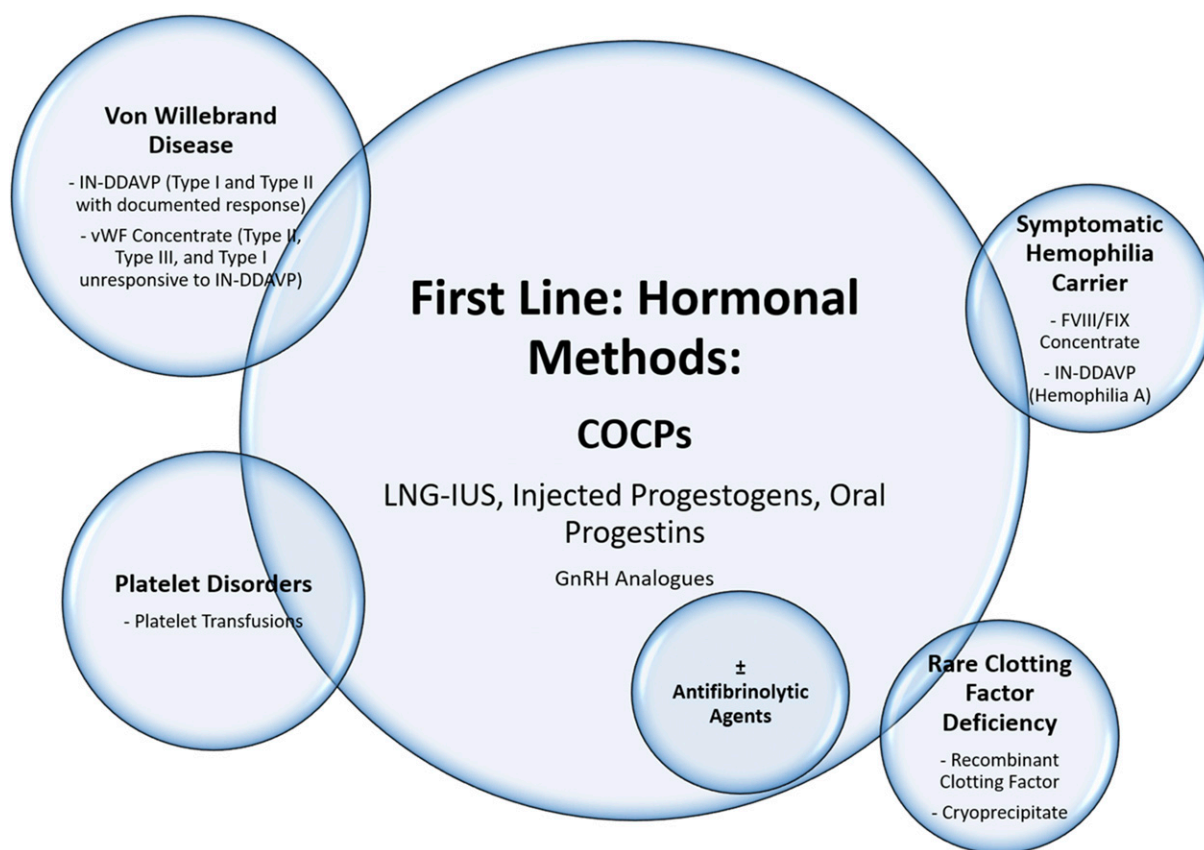


Figure 4. Approach to the management of menorrhagia in the adolescent.
COCP=combined oral contraceptive pill; GnRH=gonadotropin-releasing hormone; IN-DDAVP=intranasal 1-deamino-8-D-arginine vasopressin; FVIII/FIX=factors VIII/IX; LNG-IUS=levonorgestrel-releasing intrauterine system; vWF= von Willebrand factor.

the method of choice for adolescents and have been shown to reduce menstrual loss, correct iron deficiency anemia, and improve quality of life. (24)(32) Multiple formulations are available with varying estrogen concentrations, which allows for augmentation of treatment if initial low doses fail to control HMB. Therapy is often initiated at high doses in the immediate period after achieving hemodynamic stability to gain control of or to prevent hemorrhage. In the long-term, COCPs are useful for cycle regulation and improvements in dysmenorrhea and premenstrual tension. (32) Use of COCP has the added advantage of suppressing ovulation bleeding. Extended or continuous cycles of COCPs for 3 months or more can induce temporary amenorrhea in adolescents and reduce the frequency and severity of menstrual bleeding. (32) This regimen allows control of the timing of bleeding. In a retrospective review by Chi et al, (33) one-third of girls on this regimen experienced breakthrough bleeding, which was generally light and well tolerated. A potential complication of COCP use is an increased risk of thrombosis. The risk is very low in adolescent girls in general, especially in those with a bleeding diathesis. (32)

Smoking, malignancy, and autoimmune conditions increase the hypercoagulability risk. Screening for these risk factors should be a part of the initial history. A personal or family history suggestive of thrombophilia, particularly in first-degree relatives, may be a contraindication to COCP use. Other common adverse effects of COCPs include headache, bloating, breast tenderness, weight gain, and nausea and vomiting. (32) The severity of these symptoms tends to decline with use over time. In a study by Amesse et al, (22) the use of COCPs in adolescents with vWD type 1 was evaluated and it was found that COCPs alleviated menstrual blood loss in 86% of patients, as determined by the PBAC score.

An LNG-IUS is a hormonal reservoir inserted into the uterus. Similar to the COCP, the LNG-IUS reduces menstrual bleeding by limiting proliferation of the endometrium, but with a steady intrauterine delivery of levonorgestrel at a rate of 20 µg/24 hours. An LNG-IUS is effective in managing menorrhagia in women with bleeding disorders. The hypercoagulable potential is minimal. Chi et al (33) studied the effects of an LNG-IUS on women with bleeding disorders, including

13 women with vWD, all of whom reported a significant improvement in their quality of life and a decrease in blood flow. Previously, the lack of evidence of safety in adolescents, possible increased risk of device expulsion, and hesitancy to use in the vaginal female account for less frequent use of this method. (33) The 2011 ACOG Clinical Management Guidelines confirmed the safety of intrauterine devices for women, including adolescent girls. There have been no studies demonstrating an increased risk of pelvic inflammatory disease with LNG-IUS use in the nulliparous female, and there is no evidence that its use is associated with subsequent infertility. (34) Oral progestins, injected progestogens, and GnRH analogues have been less studied in adolescents, but there have been reports of their use in the literature. (33) Oral progestins have a particular role in the management of patients with inherited or acquired thrombophilic disorders, who have an increased risk of thrombosis with estrogen-containing agents. Analogues of GnRH are very effective in controlling menorrhagia; but because of the potential adverse effects of hypogonadism and subsequent osteopenia they are generally not prescribed for young adolescent girls. The GnRH analogues with add-back therapy can be considered as a final medical option for girls with severe bleeding not controlled by other measures. (33)

Hemostatic Therapy

Hemostatic agents demonstrated to be effective in controlling menorrhagia in women with bleeding diatheses include desmopressin, antifibrinolytic medications (tranexamic acid [TA] and aminocaproic acid), and clotting factor concentrates. These methods may be used alone but are more often used in combination or in addition to the hormonal methods already described.

Desmopressin (1-deamino-8-D-arginine vasopressin [DDAVP]), a synthetic analogue of antidiuretic hormone, releases endothelial stores and increases plasma vWF and FVIII levels transiently in healthy individuals, in individuals with vWD, and in persons with mild hemophilia A. (12)(29) (35) It is most effective in patients with type 1 vWD, who have normal vWF available for release from storage sites, and is ineffective in patients with type 3 disease. Response is variable in type 2 vWD, depending on the dysfunction. It may also be used in some mild PFDs. It is important to document patient response to a DDAVP challenge before prescribing this medication. The DDAVP can be administered intravenously or subcutaneously at a dose of 0.3 µg/kg or as an intranasal spray by a metered-dose inhaler at a fixed dose of 150 or 300 µg. (10)(32)(35) The intranasal spray is convenient for outpatient, in-home use. The use of DDAVP for menorrhagia associated with vWD has been extensively studied in adults, but experience is limited in adolescent

girls. Studies to evaluate the effectiveness of intranasal DDAVP in controlling HMB in adolescents with bleeding disorders, including vWD, platelet dysfunction, and symptomatic mild hemophilia A, have demonstrated significant reduction in bleeding assessment scores from baseline. (12) (36)(37)

A limitation of DDAVP use is tachyphylaxis, secondary to depletion of available endothelial stores of vWF, (35) which typically occurs after 2 or 3 days of consecutive use. These stores replenish after 10 to 14 days. It is generally recommended not to take more than 2 doses in a 2-week period. Other adverse effects include facial flushing, headaches, and nausea. (6)(32)(35) Perhaps the most critical albeit infrequent complication is the risk of dilutional hyponatremia, secondary to water retention, which may lead to seizures. (35) It is important to counsel patients against using DDAVP more frequently than 2 administrations daily at 12-hour intervals (15) and to limit excessive free water intake during periods of use.

Higher levels of fibrinolysis occur in the endometrium and menstrual fluid of women with HMB than in controls. (6) Antifibrinolytic therapy can be used alone or in addition to other therapies for the prevention and management of menorrhagia. There have been no large systematic trials demonstrating the efficacy of these agents in adolescents with an underlying bleeding disorder. However, beneficial effects on quality of life and bleeding assessment scores have been documented. Aminocaproic acid is a strong competitive inhibitor of both plasminogen activator and plasmin itself. It may be administered orally or intravenously to control menorrhagia. Tranexamic acid, a synthetic lysine derivative, adheres to the lysine receptor binding sites on plasmin, inhibiting attachment of fibrin monomers and slowing clot disintegration. (38) A prospective crossover study compared the ability of intranasal DDAVP and TA to reduce menstrual blood loss. The study demonstrated a statistically significant decrease in PBAC scores for both treatments, although the decrease in PBAC score was greater for TA than for intranasal DDAVP. (39) A similar study of oral TA versus COCPs demonstrated significant improvement by both TA and COCPs in menstrual blood loss, but no significant difference was noted between the 2 interventions. (40)

Antifibrinolytic medications are generally well tolerated. Nausea, emesis, and diarrhea have been the most frequently reported adverse effects. (38)(40) Prolonged use of TA has rarely been associated with changes in color vision. (29)

Most managed patients have improved long-term outcomes. A small percentage of women with vWD will require the use of vWF replacement because of failure to respond to

DDAVP, or when DDAVP is contraindicated, such as patients who have either severe type 1 vWD or type 2 or 3 vWD. In these patients with intractable menorrhagia, virally inactivated plasma-derived vWF concentrates can be administered. These concentrates often contain varying amounts of FVIII. The typical dose is 20 to 40 U/kg of vWF ristocetin cofactor unit for menorrhagia. (12)(41) A recombinant vWF concentrate has recently become commercially available. Use of this product eliminates the risk of accumulating potentially thrombogenic FVIII. (12) Although recombinant factor concentrates are available for FVII, FVIII, FIX, and FXIII, the use of these agents to exclusively control HMB in the adolescent has not been systemically studied.

CONCLUSION

Menorrhagia secondary to underlying bleeding disorders is common among adolescent females. Bleeding disorders in adolescents and young women, when unrecognized, pose challenges for patients and their families and also carry significant public health implications. There remains a need for consideration by clinicians of a possible diagnosis of a bleeding disorder in patients with HMB. Comprehensive evaluation and management is best accomplished with a multidisciplinary team involving a hematologist, a gynecologist, an adolescent medicine specialist, and a primary care physician. Controlling menorrhagia in these adolescent girls often requires a combination of treatment modalities. The mainstay of managing menorrhagia is hormonal therapy, with the addition of hemostatic agents as needed. Management should aim to reduce the frequency and severity of bleeding episodes and increase health-related quality of life. Well-designed clinical trials focused on the adolescent patient to provide high-quality evidence for optimal diagnostic and therapeutic approaches are essential.

Summary

- On the basis of epidemiologic studies and expert opinion, the adolescent female presenting with menorrhagia should be evaluated for a bleeding disorder. (8)(13)
- On the basis of expert opinion and consensus guidelines, menorrhagia is defined as menstrual bleeding lasting for more than 7 days, sanitary product use greater than 7 per day, and a greater than 80-mL blood loss per menstrual cycle. (1)
- On the basis of observational studies and expert opinion, a history of flooding and/or impairment of daily activities with periods, soaking through night clothes, passing clots greater than 1 inch in diameter, and iron deficiency anemia often identify patients with menorrhagia. (14)
- On the basis of observational studies, the pictorial bleeding assessment calendar and the bleeding assessment questionnaire can be used to objectively quantify menstrual losses. (15)(42)
- A thorough diagnostic evaluation includes studies for von Willebrand disease, platelet function defects, hemophilia A and B, and rarer clotting factor deficiencies. On the basis of observational studies, it is now appreciated that female carriers of factor deficiency often have symptomatic menorrhagia, even when factor levels are normal. (29) African American females investigated for menorrhagia more often have platelet function disorders than do white females. (23)
- On the basis of observational studies and expert opinion, hormonal and hematologic treatment options are effective in controlling HMB in adolescents. (22)(24)(12)(33)(32)(40)(39) A combination of treatment modalities is often required to control menorrhagia.
- On the basis of expert opinion, comprehensive management is best achieved when it involves a hematologist/oncologist, an obstetrician/gynecologist, and a primary care physician.

References for this article are at <http://pedsinreview.aappublications.org/content/39/12/588>.

PIR Quiz

There are two ways to access the journal CME quizzes:

1. Individual CME quizzes are available via the blue CME link under the article title in the Table of Contents of any issue.
2. To access all CME articles, click "Journal CME" from Gateway's orange main menu or go directly to: <http://www.aappublications.org/content/journal-cme>.
3. To learn how to claim MOC points, go to: <http://www.aappublications.org/content/moc-credit>.

1. An almost 13-year-old girl presents to the clinic with a 6-month history of heavy menstrual bleeding. The patient had her first menstrual period 8 months ago. Her periods have been occurring irregularly at approximately 18- to 28-day intervals, each lasting 7 to 10 days with heavy flow soaking approximately 7 pads per day during each period. Her last menstrual period was 2 weeks ago. There is no history of gum bleeds or easy bruising. She takes no medications except for a total of 3 doses in the past 6 months of nonsteroidal anti-inflammatory drugs for menstrual pain. She is not taking oral contraceptive pills and is not sexually active. On physical examination she appears to have Tanner 3 breasts and slightly pale conjunctivae. Her parents are worried about the cause of the heavy bleeding. Which of the following is the most appropriate next step in the management of this patient?
 - A. Discontinue nonsteroidal anti-inflammatory drug use.
 - B. Order a coagulation evaluation.
 - C. Pelvic ultrasonography.
 - D. Reassurance and watchful waiting.
 - E. Start oral contraceptive pills and follow up in 1 to 2 months.
2. For the patient in question 1, laboratory studies were obtained and results are pending. On family history, her father reports a history of epistaxis. Her mother describes her own menses as being normal. Which of the following is the most likely underlying potential hematologic cause of menorrhagia in this patient?
 - A. Hemophilia A.
 - B. Hemophilia B.
 - C. Immune thrombocytopenic purpura.
 - D. Inherited platelet function defect.
 - E. Von Willebrand disease.
3. A 12-year-old girl develops menorrhagia with her first 4 menstrual cycles. There is no history of abdominal pain, fevers, vomiting, or vaginal discharge. She has a history of epistaxis several times in the past. The patient is seen in the clinic, and laboratory studies are ordered. Which of the following laboratory tests is most likely to identify the underlying cause of her heavy menstrual bleeding?
 - A. Bleeding time.
 - B. Complete blood cell count.
 - C. Partial thromboplastin time.
 - D. Platelet function studies.
 - E. Von Willebrand factor assays.
4. A 15-year-old African American girl has had menorrhagia since menarche at 13 years of age. Complete blood cell count showed a hemoglobin level of 9 g/dL (90 g/L) and a mean corpuscular volume of $65 \mu\text{m}^3$ (65 fL) with normal white blood cell and platelet counts. She was started on oral iron therapy, which resulted in increasing her hemoglobin level to 11.3 g/dL (113 g/L) 3 weeks later. Von Willebrand factor assay results were all above the mean. Which of the following is the most appropriate follow-up study to investigate the possible cause of her menorrhagia?
 - A. Factor IX levels.
 - B. Flow cytometry examining glycoprotein defects.
 - C. Platelet aggregometry.
 - D. Platelet electron microscopy.
 - E. Platelet function analyzer.

REQUIREMENTS: Learners can take *Pediatrics in Review* quizzes and claim credit online only at: <http://pedsinreview.org>.

To successfully complete 2018 *Pediatrics in Review* articles for AMA PRA Category 1 Credit™, learners must demonstrate a minimum performance level of 60% or higher on this assessment. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved.

This journal-based CME activity is available through Dec. 31, 2020, however, credit will be recorded in the year in which the learner completes the quiz.



2018 *Pediatrics in Review* now is approved for a total of 30 Maintenance of Certification (MOC) Part 2 credits by the American Board of Pediatrics through the AAP MOC Portfolio Program. Complete the first 10 issues or a total of 30 quizzes of journal CME credits, achieve a 60% passing score on each, and start claiming MOC credits as early as October 2018. To learn how to claim MOC points, go to: <http://www.aappublications.org/content/moc-credit>.

5. A 16-year-old girl reports heavy menstrual bleeding. Her menses usually last 7 or 8 days and often require 8 or 9 sanitary products per day on the day of heaviest flow. A diagnostic evaluation revealed the diagnosis of platelet function defect. She has a mild microcytic anemia, which responds to oral administration of ferrous sulfate. Which of the following is the most appropriate initial therapy to reduce blood loss in this patient?
- A. Combined oral contraceptive pills.
 - B. Desmopressin.
 - C. Gonadotrophin-releasing hormone analogues.
 - D. Levonorgestrel-releasing intrauterine system.
 - E. Monthly platelet transfusions.

The Adolescent with Menorrhagia: Diagnostic Approach to a Suspected Bleeding Disorder

Rudi-Ann Graham, Joanna A. Davis and Fernando F. Corrales-Medina

Pediatrics in Review 2018;39;588

DOI: 10.1542/pir.2017-0105

Updated Information & Services

including high resolution figures, can be found at:
<http://pedsinreview.aappublications.org/content/39/12/588>

References

This article cites 35 articles, 2 of which you can access for free at:
<http://pedsinreview.aappublications.org/content/39/12/588.full#ref-list-1>

Subspecialty Collections

This article, along with others on similar topics, appears in the following collection(s):
Medical Education
http://classic.pedsinreview.aappublications.org/cgi/collection/medical_education_sub
Journal CME
http://classic.pedsinreview.aappublications.org/cgi/collection/journal_cme
Gynecology
http://classic.pedsinreview.aappublications.org/cgi/collection/gynecology_sub
Menstrual Disorders
http://classic.pedsinreview.aappublications.org/cgi/collection/menstrual_disorders_sub
Hematology/Oncology
http://classic.pedsinreview.aappublications.org/cgi/collection/hematology:oncology_sub
Blood Disorders
http://classic.pedsinreview.aappublications.org/cgi/collection/blood_disorders_sub

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
<https://shop.aap.org/licensing-permissions/>

Reprints

Information about ordering reprints can be found online:
<http://classic.pedsinreview.aappublications.org/content/reprints>



The Adolescent with Menorrhagia: Diagnostic Approach to a Suspected Bleeding Disorder

Rudi-Ann Graham, Joanna A. Davis and Fernando F. Corrales-Medina

Pediatrics in Review 2018;39;588

DOI: 10.1542/pir.2017-0105

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pedsinreview.aappublications.org/content/39/12/588>

Pediatrics in Review is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1979. Pediatrics in Review is owned, published, and trademarked by the American Academy of Pediatrics, 345 Park Avenue, Itasca, Illinois, 60143. Copyright © 2018 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0191-9601.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®

