Management of Abnormal Bleeding in the Adolescent

Julie Jaffray and Kristina Haley

Abstract

Heavy menstrual bleeding is the most common sign of an acquired or inherited bleeding disorder in females. For many young women, the manifestations of an inherited bleeding disorder do not surface until menarche, which can lead to a delay in diagnosis. Besides heavy menstrual bleeding, patients can have menstrual pain from bleeding into the corpus luteum, bleeding from trauma or procedures, easy bruising, and gastrointestinal bleeding. An undiagnosed bleeding disorder can lead to severe blood loss, chronic iron deficiency, and unnecessary surgical procedures, such as a hysterectomy. Therefore, identifying a possible bleeding disorder in these young women is crucial to allow an initiation of targeted therapy. Management of bleeding will depend on the diagnosis, as well as the severity and bleeding location. Many adolescent females with menorrhagia can be successfully managed with a combination of hormonal control and/or antifibrinolytics. Depending on the diagnosis, treatment can also include coagulation factor replacement, blood product transfusion, as well as specific therapies for acquired bleeding disorders, such as intravenous immune globulin, plasmapheresis, or corticosteroids.

Keywords

Menorrhagia • Adolescent • Von Willebrand disease • VWD • Factor deficiency • Hemophilia carrier • Platelet dysfunction • ITP • TTP

Contents

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1 Introduction

As many as 10–15% of premenopausal women have heavy menstrual bleeding (HMB) and account for 15% of all referrals to gynecologists and over 300,000 hysterectomies annually (James et al. 2006). HMB is secondary to an underlying bleeding disorder in up to 20% of premenopausal women, which translates to two to three million American women (James et al. 2006).

Approximately 40% of teenage girls have heavy periods, and anywhere from 10 to 40% of this group have an underlying bleeding disorder.

The most common underlying bleeding disorders are von Willebrand disease and qualitative platelet disorders. On average, there is an average 16-year delay between onset of symptoms and bleeding disorder diagnosis (Kirtava et al. 2004). It is difficult, based on history alone, to determine which girls with heavy periods have an underlying bleeding disorder.

In adolescent women, self-reports of periods as heavy and irregular, as well as greater than four heavy days out of each cycle, were each associated with being diagnosed with a bleeding disorder (Vo et al. 2013).

In adult women, concerning features for an underlying bleeding disorder include periods lasting >7 days, having leaking/soaking, passing large clots, a family history of a bleeding disorder, and a history of iron deficiency (James et al. 2006; James 2010). Additional signs and symptoms of bleeding disorders include frequent and prolonged (>15 min) epistaxis, excessive or spontaneous bruising, gum bleeding not related to dental problems, and excessive or unusual bleeding with surgical or dental procedures.

Bleeding disorders resulting in heavy periods can be due to deficiency or dysfunction at each level of hemostasis: primary hemostasis, secondary hemostasis, or fibrinolysis. Primary hemostatic dysfunction can come in the form of collagen dysfunction (as in Ehlers–Danlos syndrome), quantitative platelet disorders (acquired disorders like immune thrombocytopenia purpura or congenital platelet deficiency as in thrombocytopenia-absent radii or myosin heavy chain 9-related disorders), qualitative platelet disorders (as in Glanzmann's thrombasthenia or Bernard–Soulier syndrome), or in von Willebrand disease. Secondary hemostatic dysfunction is typically associated with deficiencies of one of the coagulation factors, such as female carriers of hemophilia, who are not infrequently symptomatic with heavy periods. The prevalence for bleeding disorders in adolescent and adult women is wide-ranging as symptoms often go unreported, unassessed, or uninvestigated.

Regardless of the cause, diagnosing an underlying bleeding disorder, if one is present, is important in order to guide adjunctive treatments for heavy periods, treat other symptoms associated with the bleeding disorder, plan for surgeries and other procedures, create emergency plans, and connect the patient with a bleeding disorder community. In general, though, treatment of the associated heavy periods is through some form of hormonal control, typically oral contraceptive pills (OCP's) or intrauterine devices (IUDs). Treatment is also aimed at managing associated symptoms, specifically iron deficiency anemia. In this chapter, the role of the hemostatic system and the contributions of deficiencies or dysfunction within the hemostatic system, as well as interventions, will be discussed.

2 Overview of Hemostasis

Hemostasis, which is the ability to slow and stop bleeding at the site of injury, is divided into two main components, primary and secondary hemostasis, which occur simultaneously (Fig. 1). Primary hemostasis involves the relationship between the blood vessel wall endothelium,

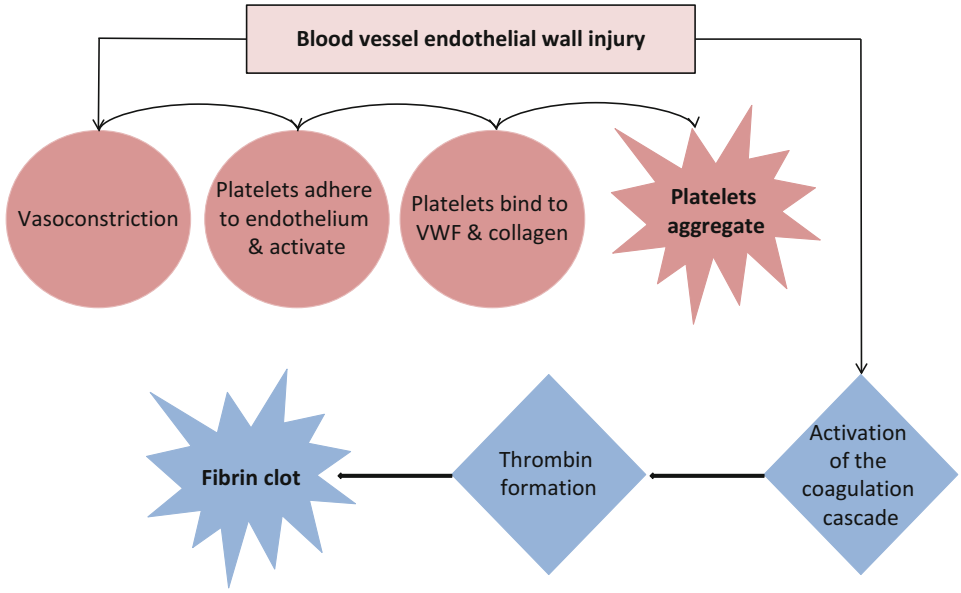

Fig. 1 Key steps in primary and secondary hemostasis, involving activation of platelets and the coagulation cascade to create a stable, cross-linked fibrin clot. *VWF=von Willebrand Factor

platelets, and von Willebrand factor (VWF). Secondary hemostasis also involves the blood vessel wall, as well as the coagulation proteins, mostly known as factors, and insoluble fibrin.

Primary hemostasis begins with injury to the endothelial lining of blood vessels, which exposes components of the subendothelial matrix to the blood (Gale 2011). These exposed components and receptors allow platelets to adhere to the blood vessel surface and become activated. The platelets bind to VWF and collagen and begin to aggregate to the site of injury. VWF is a multimeric protein which is synthesized in endothelial cells and megakaryocytes and helps with platelet adhesion and activation (Ruggeri 2007). Primary hemostasis also involves the constriction of the blood vessel to enable slowing of blood flow.

Endothelial damage also activates secondary hemostasis by exposing tissue factor and triggering the coagulation cascade (Wolberg and Mast 2012). The coagulation cascade consists of multiple coagulation proteins, or factors, that interact together to form a fibrin clot. These proteins include fibrinogen and factors II, V, VII, VIII, IX, X, XI, and XIII. There are several other factors (factor XII, prekallikrien, and high-molecular-weight kininogen), which are involved in the contact activation system that is currently not considered to be involved in hemostasis (but studies are further exploring their roles, especially with FXII). The most important role of the coagulation cascade is the formation of thrombin (FIIa) at the site of bleeding. Thrombin activates the main catalysts of the cascade, factors V and factor VIII, which generate even more thrombin. This large amount of thrombin then leads to the conversion of another protein, fibrinogen, into fibrin, which forms the structure of the clot. Thrombin also activates factor XIII and thrombin-activatable fibrinolysis inhibitor (TAFI), which help stabilize the fibrin clot. Thrombin also plays a role in promoting primary hemostasis by further activating platelets to the site of bleeding (Crawley et al. 2007).

3 Inherited Bleeding Disorders

3.1 Von Willebrand Disease

Von Willebrand disease (VWD) results from a quantitative or qualitative defect with the VWF protein. VWF is produced by endothelial cells and

by megakaryocytes and undergoes modifications during its synthesis that results in production of VWF arranged in various sizes of multimers. The VWF protein has three functions: (1) protect coagulation factor VIII (FVIII) from degradation, (2) mediate platelet adhesion at sites of vascular injury, and (3) assist in platelet adhesion.

VWD is the most common inherited bleeding disorder, and it is estimated that up to 1% of the entire population is affected by VWD (Rodeghiero et al. 1987). However, only about 1/1,000 are symptomatic.

It is not uncommon for mild VWD to not be diagnosed until adolescence or early adulthood as children may not have bleeding challenges that result in symptoms until they are older. Heavy menstrual bleeding (HMB) is a frequent symptom of VWD, and it is estimated that 5–24% of adult women with HMB have VWD and 3–36% of adolescent women have VWD (Seravalli et al. 2013). Other symptoms of VWD include mucocutaneous bleeding: epistaxis, gum bleeding, hematomas, as well as bleeding with invasive procedures.

A joint statement between the American Academy of Obstetricians and Gynecologists and the American Academy of Pediatrics (AAP) in 2006 advised that healthcare providers should consider the diagnosis of a bleeding disorder, especially VWD, in adolescents with HMB (Khamees et al. 2015).

Recently, the frequency of VWD screening was assessed in an Ohio-based study, and the researchers found that less than a quarter of subjects with severe HMB were screened (Khamees et al. 2015).

There are three main types of VWD. Type 1 VWD is a partial quantitative VWF deficiency and is the most common type of VWD accounting for about 75% of patients with VWD. Type 3 VWD is nearly a complete quantitative VWF deficiency and is the least common type of VWD. Type 2 VWD is further broken down into four subcategories. Type 2A VWD is a qualitative deficiency of VWF-dependent platelet adhesion, with an associated selective deficiency of high-molecular-weight VWF multimers. Type 2B VWD results from a qualitative abnormality in the VWF protein, which results in increased platelet binding, and the VWF deficiency is typically accompanied by thrombocytopenia. Type 2N VWD is characterized by decreased binding affinity of VWF for factor VIII, resulting in a lower than expected factor VIII activity. Type 2M VWD is also a qualitative deficiency of VWF-dependent platelet adhesion, but all VWF multimers are present. VWD is typically an autosomal-dominant disorder, but type 2N and type 3 VWD are inherited in an autosomal recessive manner.

VWD is evaluated through measurement of VWF antigen (a quantitative assessment of VWF protein), measurement of VWF activity (a qualitative assessment of VWF ability to bind platelets most often through the ristocetin activity assay), and measurement of factor VIII activity, which is a qualitative assessment to determine if VWF is adequately protecting factor VIII (Table 1). VWF multimers are measured when trying to differentiate between the various type 2 VWD diagnoses. Levels above 50 IU/dL are generally considered to be within normal limits. Levels above the upper limit of normal are not consistent with a diagnosis of VWD. Stress, estrogen, and acute illness can increase VWF levels. Hypothyroidism can decrease VWF levels. Previous recommendations indicated that patients should be off estrogen-containing contraception prior to testing, but current recommendations do not support this practice as the estrogen content in current oral contraceptives does not significantly impact VWD as to cause a missed diagnosis (Kouides 2008). Individuals with type O blood type have VWF levels that are 20–25% lower than individuals with non-O blood type. The criteria for VWD diagnosis, though, is the same regardless of blood type.

Table 1 Laboratory results and inheritance patterns between the types of von Willebrand disease diagnoses

	Type 1 VWD	Type 2A VWD	Type 2B VWD	Type 2M VWD	Type 2N VWD	Type 3 VWD
VWF activity	⇓	⇓	⇓	⇓	⇓	⇓⇓⇓
VWF antigen	⇓	⇓	⇓	⇓	⇓	⇓⇓⇓
Factor VIII activity	N or slight ⇓	N or slight ⇓	N or slight ⇓	N or slight ⇓	⇓	⇓
Multimers	N	⇓ HMWM	⇓ HMWM	N	N	Absent
Platelet count	N	N	⇓	N	N	N
Inheritance	AD	AD or AR	AD	AD or AR	AR	AR

N normal, *HMWM* high-molecular-weight multimer, *AD* autosomal dominant, *AR* autosomal recessive

3.2 Hemophilia Carriers

Hemophilia is an inherited x-linked recessive bleeding disorder due to the deficiency of either coagulation factor VIII or IX. Males are generally most affected by the disease due to it being X-linked, and females are known as hemophilia carriers. Persons with hemophilia are classified based on their plasma factor activity level, severe (<1%), moderate (1–5%), or mild (>5–40%) (Blanchette et al. 2014).

Hemophilia carriers typically have factor VIII or IX levels half that of non-hemophilia patients, although levels can range from very low to the lower limit of normal (Plug et al. 2006). Many hemophilia carriers do not experience any excessive bleeding, even during surgeries or postpartum, although some females can have increased bleeding, especially those affected by lyonization. Lyonization is X-inactivation, in which one of the copies of the X chromosome is randomly inactivated leading to lower factor VIII or IX levels. Hemophilia carriers are known as symptomatic carriers when they have bleeding symptoms and will follow the same severity classification based as males, based on their factor levels. Bleeding will usually be mucocutaneous, such as HMB, epistaxis, easy bruising, and gum bleeding, as well as bleeding from trauma, surgical procedures, or postpartum. Males with hemophilia can have mucocutaneous bleeding, as well as bleeding from trauma and surgeries, but bleeding into joints and muscles is the most common site, a problem that is rare in females.

Hemophilia carriers are usually diagnosed after a known family history of hemophilia.

> Factor assays (factor VIII or IX) should be tested on any potential female hemophilia carrier based on family pedigree.

Testing a female with a family history of hemophilia should be performed prior to menarche to avoid any possible severe menstrual bleeding. In a female who has already started her menses, the best time to test factor VIII activity is during the menstrual phase, when the factor level can be at its lowest (Knol et al. 2012). Factor IX activity does not fluctuate with the menstrual cycle, thus testing can be undertaken at any time. Since many carriers will have factor activity levels within the normal range, hemophilia gene mutation analysis is the ideal test to determine carrier status (Peake et al. 1993).

3.3 Rare Factor Deficiencies

Patients can have deficiencies in other coagulation factors such as factor II, V, VII, X, XI, or XIII. Patients with rare factor deficiencies represent 3–5% of all coagulation disorders, with an incidence of 1 in 500,000 to 1 in 2 million (Acharya et al. 2004; Palla et al. 2015). Patients with factors II, V, VII, X, XI, and XIII deficiency are inherited in an autosomal recessive pattern, and there is a higher incidence of factor XI deficiency in those

from Ashkenazi Jewish decent (Seligsohn 2009). Up to 4% of women with HMB have been found to have factor XI deficiency (Kadir et al. 1998). They can present with mucocutaneous bleeding, such as HMB, easy bruising, gastrointestinal bleeding, intracranial bleeding, prolonged bleeding from the umbilical stump, or bleeding after a surgery or trauma. Bleeding phenotype does not correlate well with some rare factor deficiencies, especially factor VII and XI deficiency (Mariani and Bernardi 2009; Seligsohn 2009).

Diagnosing rare factor deficiencies should begin with a PT and aPTT. An isolated prolongation of the PT is seen with factor VII deficiency, and an isolated prolongation of the aPTT is seen with factor XI deficiency (as well as factor VIII and IX deficiency, which was discussed earlier). Patients with factor II, V, or X deficiency will result in a prolongation of both the PT and aPTT. When a specific factor deficiency is suspected, confirmatory factor-specific assays should be performed. The PT and aPTT will be normal in those with factor XIII deficiency; thus, when suspected, a quantitative factor XIII assay should be sent.

3.4 Disorders of Fibrinolysis

Fibrinogen is converted to fibrin and provides the structural material for a blood clot during secondary hemostasis, as discussed above. Patients with disorders of fibrinolysis can either have decreased or lack of fibrinogen levels (hypofibrinogenemia, afibrinogenemia) or a dysfunctional fibrinogen (dysfibrinogenemia). Afibrinogenemia is inherited in an autosomal recessive pattern, where the heterozygous form is hypofibrinogenemia. Patients with disorders of fibrinolysis can present with intracranial bleeding or mucocutaneous bleeding, such as HMB, but will generally present earlier in life prior to menses (Acharya and Dimichele 2008). Patients can be diagnosed with hypo- or afibrinogenemia with a prolonged PT and aPTT. Confirmatory testing is a functional or antigenic fibrinogen assay.

3.5 Inherited Platelet Disorders

Platelets are tiny, cellular fragments that undergo a complex series of changes in response to bleeding, resulting in the initial cessation of blood flow from an injured area (primary hemostasis). As described previously, hemostasis is achieved through a series of coordinated events involving platelet-vessel, platelet-platelet, and platelet-protein interactions. These interactions occur in blood vessels under the shear stress of blood flow. Platelet disorders typically result in mucocutaneous bleeding, including epistaxis, gum bleeding, bruising, and HMB, and platelet dysfunction is found in 3–44% of adolescents with HMB (Seravalli). Platelet disorders can be secondary to qualitative or quantitative defects and can be acquired or inherited. In the adolescent population, the most common acquired platelet disorder is immune thrombocytopenia purpura (ITP). This section will focus on inherited disorders of platelet function and/or number; however, similar symptoms are present in adolescent women with ITP (see section on acquired bleeding disorders below).

Inherited platelet function disorders include a heterogeneous group of disorders. The most well-known platelet disorders are some of the rarer disorders, such as Bernard–Soulier syndrome (BSS) and Glanzmann thrombasthenia (GT). BSS results from a deficiency or defect in the platelet glycoprotein 1b, which impairs platelet binding to VWF. It is extremely rare, and only about 100 cases have been reported in the literature (Israels et al. 2010). GT is a defect in the platelet glycoprotein IIb/IIIa, the glycoprotein that mediates platelet-platelet aggregation. GT is also a rare disorder and is inherited in an autosomal recessive pattern (Israels et al. 2010). The mucocutaneous bleeding in GT can be severe, and menorrhagia and postpartum hemorrhage can be life-threatening. Other platelet disorders include disorders of platelet granule secretion, platelet signal transduction, and platelet receptor defects. These disorders do not all have specific names but result in characteristic patterns on

available platelet function testing. Both BSS and GT result in mucocutaneous bleeding present in early childhood; however, the more common and milder platelet disorders typically present in adolescents and adulthood following menarche and other bleeding challenges.

The best available test for diagnosing platelet disorders is platelet aggregometry. This testing method is difficult to perform, requires large volumes of blood, and does not adequately assess the steps prior to aggregation, such as platelet-vessel interactions, or the effects of flowing blood (Pai and Hayward 2009; Israels et al. 2011). As a result, platelet function disorders are challenging to diagnose, and patients presenting with mucocutaneous bleeding frequently go undiagnosed (James et al. 2006; Kouides 2008). The incidence of platelet disorders in adolescents is wide ranging, from 2% to 46%, but it is suspected that the true incidence of platelet function defects is unknown and that many patients presenting with mucocutaneous bleeding have platelet disorders that cannot be diagnosed with currently available tests (Philipp et al. 2011; Sokkary et al. 2012; Mills et al. 2014).

3.6 Connective Tissue Disorders

Disorders of the vessel wall or with the subendothelial matrix, which may affect platelet adhesion, can also cause menorrhagia (van Ommen and Peters 2012; Vo et al. 2013). Hereditary hemorrhagic telangiectasia (HHT) and Ehlers–Danlos syndrome (EDS) have been associated with HMB. Careful physical examination for telangiectasias (for HHT) or for joint or skin laxity (for EDS) can be helpful in the evaluation of an adolescent with HMB. The Beighton score, a quick physical assessment of joint laxity, can be easily incorporated into the physical exam. A score of 4 or higher is concerning for EDS and warrants further work up. The treatment of HMB in EDS is similar to other hemostatic disorders, primarily with hormonal interventions, IUD, or antifibrinolytics.

4 Acquired Bleeding Disorders

4.1 Immune Thrombocytopenia Purpura

Immune thrombocytopenia purpura (ITP) is an isolated thrombocytopenia (peripheral blood count $<100 \times 10^9$) in patients without other causes or disorders of thrombocytopenia (Rodeghiero et al. 2009). The pathogenesis is thought to be immune-mediated destruction against one's own platelets and megakaryocytes (Cooper and Bussel 2006). The exact etiology of the immune-mediated destruction is unknown but can occur secondary to a viral infection or some vaccinations. In children, ITP is usually a benign disorder that is self-limited and generally resolves prior to 12 months. In adolescents, ITP may have more of a chronic course, and other autoimmune diseases should be considered (British Committee for Standards in Haematology General Haematology Task 2003).

> Mucocutaneous bleeding is the hallmark of ITP, which includes HMB, epistaxis, easy bruising, and gastrointestinal bleeding.

Intracranial bleeding can also occur, but very rarely, with an estimated incidence of 0.2%–0.8% (Psaila et al. 2009). Laboratory assessment should include a complete blood count (CBC) with differential to evaluate all blood cell lines, reticulocyte count, and direct antibody assessment to determine Rh blood antigen status. Patients with ITP will normally have an isolated thrombocytopenia, unless their bleeding has led to iron deficiency anemia. Adolescents with ITP should also have a preliminary rheumatology and immunology work-up including immunoglobulin levels, antinuclear antibody (ANA), complement levels, and a complete metabolic panel (CMP) to evaluate liver and renal function.

Treatment based on platelet count alone remains controversial, and pharmacological treatment options to increase the platelet count and decrease the immune destruction are not always

successful, and in many circumstances, the effect is not long lasting. Many pediatric centers are opting toward an observational approach for patients with ITP, regardless of their platelet count (Witmer et al. 2016). Specific pharmacological treatment options include intravenous immune globulin (IVIG), corticosteroids, anti-D immunoglobulin (only if Rh blood antigen positive), rituximab, or splenectomy. Adolescents with HMB can be treated with one of these options in combination with specific treatments for menstrual bleeding as described in the treatment/management section.

4.2 Thrombotic Thrombocytopenia Purpura

Thrombotic thrombocytopenia purpura (TTP) is a serious and life-threatening disorder that leads to microangiopathic hemolytic anemia, thrombocytopenia, and neurological abnormalities. TTP can be acquired or congenital and leads to a deficiency of ADAMTS13, which is responsible for cleaving VWF multimers (Fujikawa et al. 2001). The ultra-large VWF multimers can cause excessive platelet aggregation and thrombosis. The acquired form is due to autoantibodies targeted against ADAMTS13, and the congenital form is due to mutations in the ADAMTS13 gene, leading to decreased production of ADAMTS13 (Levy et al. 2001). Luckily, TTP is very rare in the adolescent population, but can lead to severe mucocutaneous bleeding secondary to the thrombocytopenia.

When TTP is suspected, patients should have a CBC, with peripheral smear review reticulocyte count, CMP, as well as testing for ADAMTS13 activity and inhibitor levels. Until the thrombocytopenia resolves, adolescents with HMB can be treated with therapies listed in the treatment/management section of this chapter. Specific treatment for TTP involves plasma exchange to replace the ADAMTS13 and corticosteroids to target the autoimmune aspect of the disease.

4.3 Liver and Renal Failure

The liver is responsible for the synthesis of most pro- and anticoagulant proteins (except VWF), as well as the synthesis of thrombopoietin, the hormone that promotes platelet production. Therefore, a disruption in liver function can have a large impact on a person's coagulation and cause both hemorrhage and thrombosis. Adolescents with liver disease can present with HMB, extensive bruising, bleeding from blood draws, bleeding from peripheral or central intravenous catheters, intracranial bleeding, or bleeding from invasive procedures. Diseases that lead to liver failure in adolescents include drugs/toxins, viruses, metabolic disorders, and autoimmune hepatitis (Dhawan 2012). Coagulation testing abnormalities that are seen with liver failure are an elevated PT, aPTT, and d-dimer, decreased fibrinogen activity, and decreased platelet count.

Treatment should be targeted toward the underlying etiology in conjunction with specific therapies for bleeding. Treatment for bleeding in liver failure can be difficult due to the risk of thrombosis and fluid overload. Fresh frozen plasma (FFP) can be used, since it contains all coagulation factors as well as cryoprecipitate to replace fibrinogen (Youssef et al. 2003). Prothrombin complex concentrates (PCCs) are lower in volume than FFP and can help replace factors II, VII, IX, and X. Specific therapies for menorrhagia discussed in the treatment/management section should be used with caution, as with all treatment in liver disease due to the risk of thrombosis.

> Patients with end-stage renal disease have bleeding secondary to platelet dysfunction due to uremia (Escolar et al. 2005).

Uremia can affect platelet granule secretion, which leads to platelet activation and aggregation, as well as affecting platelet adhesion to the vascular endothelial wall with the help of fibrinogen and VWF. Platelet function can temporarily improve after dialysis removes toxins such as urea. Patients can have mucocutaneous bleeding such as HMB, easy bruising, or gum bleeding. Treatment of bleeding in patients with end-stage renal disease includes dialysis, which removes the urea, desmopressin (DDAVP) which releases VWF, and cryoprecipitate (Kaw and Malhotra 2006).

5 Laboratory Evaluation

It is difficult to determine what menstrual symptoms warrant further work-up as patients have difficulty quantifying blood loss. Further, adolescents who have not had many menstrual periods may not have a reference point for normal due to their lack of experience, especially if their mothers, aunts, or siblings also have heavy periods. A few tools have been developed to assess menstrual blood loss with regard to the presence or absence of an underlying bleeding disorder. Bleeding assessment tools (BATs) are excellent at capturing bleeding symptoms but unfortunately are frequently too long to administer in a clinic visit. The pictorial blood assessment chart (PBAC) is a tool that can be employed to assess for HMB (Higham et al. 1990, 2016). A total score of greater than 100 is concerning for an underlying bleeding disorder as a cause for HMB. Further, the Phillip score can be employed to further assess a patient (Philipp et al. 2011). A bleeding disorder should be pursued if one of the following four criteria of the Phillip score is met: duration of menses more than 7 days and either flooding or impairment of daily activities, a history of treatment for anemia, a family history of a bleeding disorder, or a history of bleeding with tooth extraction, delivery or miscarriage, or surgery. These two tools, the PBAC and the Phillips tool, have been validated in the adult population but not in the adolescent population.

For a laboratory evaluation, a few screening labs can be employed by the gynecologist or primary care physician (Table 2). A CBC will allow for assessment of platelet count as well as for the presence of anemia. The secondary hemostatic system should be screened for deficiencies with a PT, aPTT, and fibrinogen. A VWD panel should also be obtained to screen for VWD, including a VWF/antigen, VWF/activity, and factor VIII activity. Abnormally low values or borderline values should be repeated given the variability in laboratory assessments. Screening for platelet dysfunction is difficult due to lack of sensitive and specific platelet disorder screening assays. The platelet function analyzer-100 (PFA-100) was created as a screen for platelet function disorders but unfortunately is not sensitive or specific enough to use as a screening test. If the CBC, PT, aPTT, fibrinogen, and VWD panel are normal and the patient is still experiencing symptoms, then

Table 2 Overview of appropriate laboratory tests and referral recommendations for adolescents with heavy menstrual bleeding

Stage of hemostasis being assessed	Test	Abnormal result suggesting bleeding disorder	Follow-up
Primary	CBC	Thrombocytopenia	Referral to hematology for evaluation of thrombocytopenia, obtain iron studies if not completed for anemia
		Anemia	
Primary	VWD panel (VWF/Ag, VWF/RCo, FVIII act)	VWF/Ag <40%	Repeat VWD panel
		VWF/RCo <40%	Referral to hematology for further evaluation
		FVIII Act <60%	
Secondary	PT	Elevated PT	Mixing study
			Factor VII activity
			Referral to hematology
Secondary	aPTT	Elevated PTT	Mixing study
			Factor VIII, IX, XI, and XII activities
			Referral to hematology
Secondary	Fibrinogen	Low fibrinogen	Thrombin time
			Referral to hematology

CBC complete blood count, *VWD* von Willebrand disease, *VWF/Ag* von Willebrand factor antigen, *VWF/RCo* VWF activity, *FVIII Act* factor VIII activity, *PT* prothrombin time, *aPTT* partial thromboplastin time

referral to a hematologist is warranted for further work up. Because hypothyroidism can affect VWF levels and affect menses, screening for thyroid dysfunction may also be prudent to add in the evaluation.

A CBC can be employed to screen for anemia. However, there are a significant proportion of young women with HMB with iron deficiency without anemia.

Thus, if symptoms of anemia are present such as fatigue, difficulty concentrating, restless legs, or pica, iron studies should be obtained (ferritin, total iron binding capacity, serum iron, and percent transferrin saturation).

6 Treatment/Management

From a gynecologic standpoint, oral contraceptives are often the first line in controlling HMB as they reduce menstrual blood loss. The levonorgestrel-releasing intrauterine device (IUD) is also a very effective intervention and has been shown to result in a significant reduction in PBAC scores as well as an increase in hemoglobin concentration. The NHLBI guidelines state that the first choice of therapy for HMB in patients with bleeding disorders should be combined oral contraceptives followed by the IUD (O'Brien 2012).

Specific treatment options for patients with bleeding disorders include DDAVP (1-desamino-8-D-arginine vasopressin), antifibrinolytic therapies, and factor concentrates. DDAVP stimulates the release of stored VWF from Weibel–Palade bodies in endothelial cells. It is available in both intravenous and intranasal forms, but is only effective for 48–72 h. DDAVP is commonly used to treat bleeding associated with VWF, but it is also effective in treating bleeding in patients with some platelet dysfunction disorders, likely by increasing platelet adhesion due to increased VWF levels. Patient with type 2 VWD have a variable response as the released VWF is likely dysfunctional. DDAVP is not effective in patients with type 3 VWD or the platelet dysfunction diseases, GT or BSS. A DDAVP stimulation test should be performed prior to its use in order to determine an individual's response. DDAVP's primary side effect is increased water retention and secondary hyponatremia, thus fluid guidelines should be provided to patients.

The antifibrinolytic therapies include aminocaproic acid and tranexamic acid. These two agents inhibit fibrinolysis and allow for clot stabilization. They are particularly useful hemostatic agents in the setting of mucocutaneous bleeding (O'Brien 2012). Aminocaproic acid is available in tablet and liquid forms, allowing for use in patients who are unable to swallow pills. Tranexamic acid is generally better tolerated, though, with regard to gastrointestinal upset and headaches. The antifibrinolytics are effective treatments in all bleeding disorder types.

Factor concentrates contain specific clotting factors for VWD or factor deficiencies. While factor concentrates are rarely used to treat HMB, in acute menorrhagia unresponsive to antifibrinolytics or estrogen therapies, factor concentrates may be necessary. These concentrates must be administered intravenously (IV), and the concentrates that are currently available in the United States include VWF, fibrinogen, as well as factors VII, VIII, IX, X, and XIII. Not all hospitals carry factor concentrates so it is encouraged that patients with VWD or factor deficiencies have at least one life-saving dose of factor available to them at home. Patients can also receive fresh frozen plasma (any factor deficiency), cryoprecipitate (fibrinogen, FXIII deficiency), or prothrombin complex concentrates (factors II, VII, IX, and X deficiency) if specific factor replacement is unavailable. Fresh frozen plasma is the only current replacement for factor V and XI deficiency in the USA. For patients with platelet disorders, platelet transfusions or recombinant factor VIIa may be necessary to control bleeding, particularly at times of surgery, childbirth, or dental work (Young et al. 2009).

As indicated above, iron deficiency with and without anemia is common in adolescents with HMB.

If iron deficiency is diagnosed, replacement iron therapy should be initiated. Oral iron with ferrous sulfate 325 mg (65 mg elemental iron) daily is often effective. At least 3 months of therapy are typically required in order to replenish iron stores. However, if HMB is ongoing, it may take longer to replenish iron losses. Continuing iron therapy 3 months beyond improvement of HMB is often an effective strategy. Iron supplements should be taken with vitamin C to increase absorption, and they should not be taken with milk or teas as these decrease absorption. Gastrointestinal side effects such as abdominal pain, nausea, and constipation are common. If oral iron is not tolerated, IV iron should be considered. There are several formulations of IV iron available, with improved side effect profiles compared to previous IV iron preparations. If iron stores do not improve following improvement of menstrual losses, other sources of blood loss should be investigated. Iron deficiency and iron deficiency anemia have been associated with lower academic success and impaired physical activity; thus, it is imperative to address this issue in adolescent females (Rae et al. 2013).

6.1 Medications to Avoid

In patients with bleeding disorders, medications that affect hemostatic function should be avoided.

The nonsteroidal anti-inflammatory medications (NSAIDs) affect platelet function and may exacerbate an underlying bleeding disorder.

NSAIDs are found in a variety of medications, and patients with bleeding disorders should be instructed on reading labels in order to avoid taking one of these medications unintentionally. While NSAIDS are generally not recommended for patients with bleeding disorders, their beneficial effect on dysmenorrhea and menorrhagia requires additional consideration. NSAIDs inhibit cyclo-oxygenase and reduce the production of prostaglandins and thromboxanes. In women with menorrhagia, prostaglandins are elevated and result in vasodilation, which likely results in increased menstrual losses. As NSAIDs block prostaglandin production, they can decrease menstrual blood loss through this mechanism. Thus, NSAIDs may be an effective tool to decrease menstrual losses in adolescents with HMB and bleeding disorders, particularly if their primary symptom is HMB. The risks and benefits of NSAIDs should be discussed with the patient and her parent or guardian, and if instituted, careful monitoring of bleeding symptoms should be undertaken (O'Brien 2012).

The selective serotonin reuptake inhibitors (SSRIs) inhibit the serotonin reuptake transporter 5-HTT and are a common medication employed in the management of depression and anxiety. Serotonin is a platelet agonist, and 5-HTT is present on the platelet surface. Platelets do not make their own serotonin and are dependent upon 5-HTT for their serotonin content. There have been reports of bleeding in patients on SSRIs, including gastrointestinal and perioperative bleeding. The effect appears to be modest and more common in older patients. As SSRIs are a very effective tool in the management of mental health disorders, the bleeding risk should be balanced with the therapeutic benefit (Konkle 2011).

7 Conclusion

Abnormal bleeding in the adolescent can result in severe anemia and inappropriate procedures if not diagnosed and treated in a timely fashion. Causes of bleeding in adolescents range from inherited disorders such as factor deficiencies and platelet dysfunction to acquired problems such as ITP and liver failure.

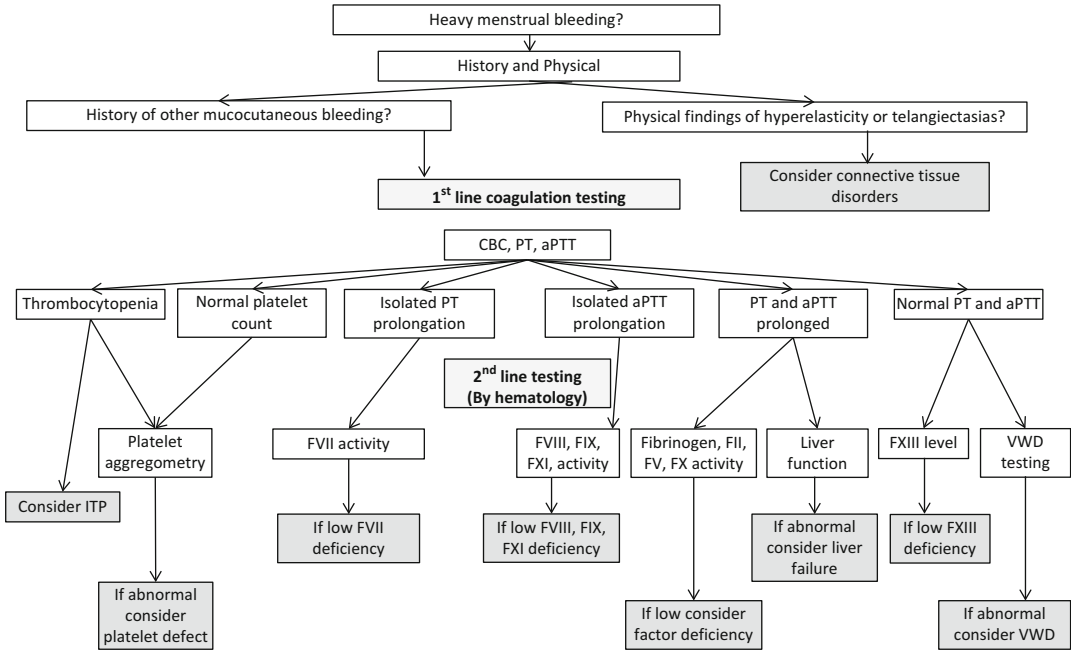

Fig. 2 Coagulation testing algorithm and diagnostic considerations for adolescents with heavy menstrual bleeding and the concern for an underlying bleeding disorder. *CBC=Complete blood count, PT=prothrombin time, aPTT=activated thromboplastin time, FVII=Factor VII, FVIII=Factor VIII, FIX=Factor IX, FXI=Factor XI, FII=Factor II, FV=Factor V, FX=Factor X, FXIII=Factor XIII, VWD=von Willebrand disease, ITP=Immune thrombocytopenia purpura

> Patients with HMB and a history of other mucocutaneous bleeding, such as epistaxis, gum bleeding, easy bruising, or gastrointestinal bleeding, should be evaluated for a bleeding disorder.

Diagnosing a bleeding disorder can be difficult due to issues with procurement of the blood sample and interpretation of the laboratory results. Blood flow into collection tubes must be free-flowing in order for the coagulation system not to be activated. The blood samples are also sensitive to heat inactivation/cold inactivation and delay in centrifugation or processing. Interpretation of coagulation test results is also difficult; thus, any second-tier testing and analysis are best done by a trained hematologist. A framework has been provided to help diagnose and treat adolescents who present with abnormal bleeding (Fig. 2). This algorithm should help primary care physicians and gynecologists begin the work-up for a bleeding disorder as well as guide any emergently needed treatment. Most adolescents with HMB and an undiagnosed bleeding disorder can be treated safely with standard of care measures until a diagnosis has been established. While HMB may be the primary or presenting symptom of many bleeding disorders, it is important that the patient be referred to a hematologist as soon as a bleeding disorder is suspected in order to help manage symptoms as well as to create hemostatic plans for emergencies or invasive procedures.

8 Cross-References

▶ Workup and Management of Polycystic Ovary Syndrome

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