1 Evaluation of the Adolescent with Heavy Menstrual Bleeding

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Introduction

Adolescence is a time of change, and this change is often reflected in their menstrual bleeding. Heavy menstrual bleeding (HMB) is common in adolescents [1]. In a large insurance claims database of more than 200,000 females aged 10–17 years in the United States, 27% had an outpatient diagnostic code consistent with HMB at least once during the study period [2]. The complaint of HMB is subjective. Beliefs derived from personal experience and cultural, social, and educational influences give rise to a sense of what constitutes "normal" blood loss during menses. HMB is qualitatively defined as blood loss that interferes with a woman's physical, social, emotional, and/or material quality of life, irrespective of the volume lost [3]. School absenteeism and interruption in sports or social activities frequently occur in adolescents with HMB [4]. Given the consequences of HMB, physicians and other healthcare providers should be able to evaluate an adolescent presenting with HMB competently.

Normal Menstruation and Terminologies

The median age of menarche is 12 years old, with a range of 10–15 years [5]. Typically menstrual cycles should occur every 21–45 days and last ≤7 days [6, 7]. Average blood loss during menses for an adolescent female is approximately 30–40 ml, which translates to six menstrual pads/tampons on the heaviest day of bleeding [8]. Many terms have been used to describe abnormal uterine bleeding. The International Federation of Gynecology and Obstetrics (FIGO) recommends against using terms such as menorrhagia, dysfunctional uterine bleeding, or hypermenorrhea [9]. Abnormal uterine bleeding is the umbrella term to describe menstrual bleeding that is abnormal with regard to frequency, volume, duration, and cycle regularity [9]. While blood loss of >80 mL is broadly used in clinical studies and trials to define HMB, this measurement (involving

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L. V. Srivaths (ed.), *Hematology in the Adolescent Female*,
https://doi.org/10.1007/978-3-030-48446-0_1

extracting hemoglobin from sanitary wear) is impractical outside of research settings; therefore, a requirement to change sanitary pads or tampons more often than hourly, clots at least 1 inch in diameter, and a low ferritin level are clinical predictors of heavy periods [10]. FIGO recommends that HMB in women be classified according to the PALM–COEIN system: polyp, adenomyosis, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not otherwise classified [11].

The Association of HMB and Bleeding Disorders

The frequency of bleeding disorders in the general population is approximately 1–2%, but bleeding disorders are found in about ~30% of adolescent girls who are referred for evaluation of HMB to a specialty [12]. Low von Willebrand factor (VWF) levels or von Willebrand disease (VWD) and platelet functional disorders (PFD) are the most common type of bleeding disorders encountered in adolescents [12]. Importantly, bleeding disorders coexist with anovulation and non-hemostatic disorders (Table 1.1). HMB confers a significantly lower perceived quality of life in terms of the ability to fully participate in school, work, and athletic and social activities [13]. It is, therefore, imperative that bleeding disorders resulting in HMB are diagnosed without delay. Additional key points in history taking and screening tools for HMB in adolescents that point toward an underlying bleeding disorder are discussed in Chap. 2.

Table 1.1 Frequency of non-hemostatic and concomitant disorders in adolescents with heavy menstrual bleeding

	Anovulatory HMB		Ovulatory HMB	
	BD (n = 31)	No BD (n = 69)	BD (n = 36)	No BD (n = 64)
PCOS	3	3	0	0
BJH[a]	3	7	6	4
Uterine structural ab.	1[f]	1[g]	3[h]	0
Systemic disorders	6[b]	10[c]	1[d]	4[e]
VWF exon 28 polym.	0	1	0	3

Table adapted from Zia et al. [12]
Ab. abnormalities, *BD* bleeding disorder, *PCOS* polycystic ovarian syndrome, *BJH* benign joint hypermobility, *polym.* polymorphism. [a]BJH assessment was performed only on 100 participants
No differences in the prevalence of bleeding disorders according to menstrual bleeding pattern (31% in anovulatory pattern bleeding vs. 36% ovulatory pattern bleeding; $p = 0.45$)
Systemic or medical disorders = [b]depression (n = 4), remote history of cancer (n = 1) and hypothyroidism (n = 1); [c]depression (n = 3), asthma requiring medications (n = 3), remote history of cancer (n = 3), hypothyroidism (n = 1); [d]one had juvenile rheumatoid arthritis; [e]depression (n = 1), diabetes mellitus (n = 2); celiac disease (n = 1)
Uterine structural abnormalities: [f]One had endometriosis; [g]one had erosive vaginitis from tampon use; [h]two were diagnosed with endometriosis, and one was diagnosed with uterine polyps

Laboratory Evaluation of the Adolescent with HMB: The Hematology Perspective

General Perspectives on Laboratory Evaluation of Bleeding Disorders The laboratory evaluation of an underlying bleeding disorder in an adolescent with HMB does not differ from the assessment in any patient presenting with unusual bruising or bleeding. Table 1.2 reviews the estimated sensitivity and specificity of various hemostasis assays in the evaluation of a bleeding phenotype. There are certain caveats specific to the testing approach in adolescents due to acute HMB and concomitant hormonal use that we will highlight below. There is no simple diagnostic strategy or testing algorithm that can adequately cover all possible bleeding disorders when the presenting complaint is HMB, but a proposed algorithm that the authors have used prospectively to diagnose bleeding disorders in HMB is covered elsewhere [14, 15]. As an educational book chapter, this work does not reflect a systematic review methodology but instead serves as an overview of laboratory evaluation of bleeding disorders in adolescents with HMB. While efforts

Table 1.2 Estimated sensitivities and specificities of hemostasis assays used to evaluate bleeding problems

	Estimated sensitivity (%)	Estimated specificity (%)
PTT	2.1	98
PT	1.0	>99
TT	1.0	86
Clauss fibrinogen	1.0	>99
VWD screen	6.7	>98
Light transmission aggregometry	26	96
Factor assays	Not reported	Not reported

Table adapted from Hayward and Moffat [37]. The estimated sensitivities and specificities reported in this table for a bleeding problem have not been tested specifically in the setting of HMB. PTT indicates partial thromboplastin time; *PT* prothrombin time, *TT* thrombin time, *VWD* von Willebrand disease

were taken to highlight pertinent evidence without bias, the interested reader is encouraged to conduct an additional review of the literature.

The initial laboratory evaluation of patients with a suspected bleeding disorder should include a complete blood count, a review of peripheral blood smear for platelet morphology, prothrombin time, partial thromboplastin time (PTT), and either fibrinogen or thrombin time [16]. These routine coagulation studies can suggest whether a severe coagulation factor deficiency or thrombocytopenia might be the reason for clinical bleeding but will neither rule in nor rule out VWD or PFD, the most common bleeding disorders encountered in adolescents with HMB. When using the PTT in the diagnosis of VWD, the results of this test are abnormal only if the coagulation factor (F) VIII is sufficiently reduced [17]. Some centers add a platelet function analyzer (PFA-100) assay to their initial laboratory screening tests to "loosely" screen for either VWD or PFD. A clinician, faced with an individual with a personal and family history of bleeding, should not use the results of a normal PFA-100 to influence his/her decision to undertake more specific laboratory testing. Thus, irrespective of an abnormal or normal PFA-100 result, VWF and platelet function testing are still warranted to assess the possibility of these disorders in patients with HMB; so in this context, the PFA-100 has a limited utility [18].

VWD Testing in HMB The laboratory diagnosis of VWD can be complicated. The initial tests commonly used to detect VWD or low VWF are determinations of plasma levels of (i) VWF:Antigen (Ag); (ii) VWF:Ristocetin Co-factor activity (RCo); and (iii) FVIII [17]. These three tests, readily available in most larger hospitals, measure the amount of VWF protein present in plasma (VWF:Ag), the function of the VWF protein that is present as VWF:RCo, and the ability of the VWF to serve as the carrier protein to maintain normal FVIII survival. New options for laboratory assessment of VWF activity include a new platelet-binding assay, the VWF:GPIbM, which is subject to less variability than VWF:RCo assay, and collagen-binding (CB) assays that provide insight into a different function of VWF. Because the VWF:RCo uses the nonphysiologic agonist ristocetin to bridge VWF and platelet glycoprotein (GP) Ibα, there is the potential for false results due to defects in VWF's ability to bind ristocetin. The most common of these is the p.D1472H variant, which affects ristocetin binding but not VWF function [19]. The VWF:GPIbM assay introduces gain-of-function mutations into GPIbα, allowing it to bind VWF spontaneously in vitro without the requirement for ristocetin [20]. The VWF:GPIbM allows higher precision, with a reported lower limit of detection of 2 IU/dL and a coefficient of variation of 5.6% [21]. There is a reasonable correlation between VWF:RCo and VWF:GPIbM results [20].

VWF also binds to exposed collagen at sites of injury, which requires specific testing. Collagen binding is dependent on the presence of high-molecular-weight VWF multimers [22]. There may be a dual role for collagen-binding assays in VWD diagnosis, to evaluate multimer status and to screen for a possible collagen-binding defect. Assays using either type I, type III, or a combination of the two will suffice to detect specific A3 domain collagen-binding variants [23]. Specific A1 binding defects are more common, although binding to types IV and VI collagen is rarely assessed in clinical practice [24]. Research from the Zimmerman Program, a large multicenter

US study on patients with all types of VWD, has shown a relatively high incidence of type IV and VI collagen-binding defects in patients with both type 1 (5%) and type 2 M VWD (27%) [24]. The presence of a collagen-binding variant was associated with an increased bleeding score compared with similar subjects without a collagen-binding defect in this cohort. Adolescents with HMB and other unexplained bleeding symptoms or a strong family history of HMB may benefit from collagen-binding testing to explore the possibility of an undiagnosed collagen-binding defect in VWF.

The increased availability and lower cost of genetic testing enable increased use in the diagnosis of VWD. An impediment to the routine use of genetic analysis for VWD is the weak correlation between VWF sequence variants and type 1 VWD, the most common VWD type. A large study of VWD subjects in the United States showed a relatively low rate of probably causative VWF variants in those subjects with VWF:Ag >30 IU/dL [25]. Genetic analysis is most useful in type 2 VWD. Genetic analysis either specifically for the p.D1472H variant or of VWF exon 28 is helpful when the VWF:RCo/VWF:Ag ratio is decreased in the setting of a normal multimer distribution. Sequencing can either verify that the low ratio is caused by p.D1472H or, in patients with suspected type 2 M VWD, reveal a causative variant [26].

VWF levels will increase in the setting of stress, inflammation, and illness and are often found to be quite elevated when measured in adolescents hospitalized for severe HMB [17]. Recent data suggest that VWF levels >100 IU/dL in the pediatric population may not need repeat testing to rule out the diagnosis of VWD [27]; however, a relatively small proportion (18%) of the included patient population in this study tested for VWD had HMB. Patients with blood group type O have VWF levels that are approximately 25% lower than non-O blood group individuals [28]; however, current guidelines recommend against using blood-type-specific reference values and suggest instead using either absolute cutoffs or population-based reference ranges in conjunction with personal and family history of bleeding in making a diagnosis of VWD [17, 29]. High-dose estrogen therapy also elevates VWF levels, but the influence of standard dose (30–35 mcg) estrogen is less clear and unlikely to affect the laboratory diagnosis of VWD. The majority of studies in healthy women who use standard dose combined hormonal contraceptives have shown no significant increase in VWF [30, 31]; however, there have been no studies in women with VWD or low VWF levels at baseline. Patients on a taper of combined hormonal contraceptives or a high-dose pill (estrogen dose >50 mcg) should not undergo testing for VWD until the patient has been tapered down to standard dose for ~3 months [32]. To avoid continued or recurrent HMB, treatment with combined hormonal contraceptives should not be delayed or withheld to complete testing for VWD [32].

PFD Testing in HMB PFD are clinically important bleeding disorders that are particularly challenging for clinical laboratories to diagnose. Many PFD are associated with increased bleeding scores and increased risks for bleeding. Often, laboratory testing for PFD is done after VWD is excluded [33], although testing for PFD and VWD at the same time may improve the evaluation of suspected bleeding disorders. Most PFD tests require rapid processing and testing of freshly collected, hand-delivered blood samples, using assays with validated reference intervals, derived from an adequate number of female and male healthy control samples [34]. The performance characteristics of PFD tests, and the control of pre-analytical, analytical, and post-analytical factors (including ingestion of drugs that inhibit platelet function) and procedures, influence their overall diagnostic usefulness [34].

Beyond complete blood count to assess disorders of platelet numbers and peripheral smear for platelet morphology for platelet storage pool and membrane deficiencies, platelet aggregation is the gold-standard platelet func-

tion testing method. It began with light transmittance aggregometry in 1965 and continues to be used extensively [35]. In light transmittance aggregometry, the operator prepares platelet-rich plasma, adds a platelet agonist to the platelet-rich plasma, and records the rise in light transmission as platelets aggregate and the suspension clears [34, 36]. Whole blood impedance lumiaggregometry represents an updated methodology and is technically more straightforward, wherein the operator prepares a whole blood suspension, adds an agonist, and records the rise in impedance as platelets coat electrodes suspended in the blood. Both whole blood and light transmission aggregation may be enhanced with a luminescence channel to measure and detect platelet-dense granule ATP secretion after in vitro platelet activation [34, 36].

Inherited PFD include platelet membrane receptor abnormalities, secretion disorders related to internal enzyme deficiencies, and storage pool defects, whereas acquired defects are seen with medications and liver and renal disease [36]. Abnormalities on platelet aggregation should be repeated to help rule out false positives, particularly if the findings suggest a drug-induced defect, and should be reproducible. Single agonist abnormalities are usually a false positive and are much less predictive of a bleeding disorder than multiple agonist abnormalities. Many PFD encountered in practice are uncharacterized inherited disorders with abnormal aggregation responses to multiple agonists that do not fit a well-described pattern of abnormal findings [37]. A lack of standardized reference ranges for delta granules/platelets in children and adolescents limits the upfront utilization of platelet electron microscopy in the workup of HMB at this time. Recent strides, however, have been made to establish references and ranges and validate the methodology [38]. Newer technologies such as high-throughput DNA sequencing are low yield unless the clinical picture suggests a probable etiology [33]. The most recent guidance, from the SSC of the ISTH, recommends many tests for the diagnosis of inherited PFD, including assays validated for diagnostic purposes and assays predominantly used for research investigations [33].

Coagulation Factor Deficiencies in HMB Coagulation factor assays may be considered in the presence of a significant bleeding phenotype if the tests mentioned above are normal, but a suspicion of a bleeding disorder remains high. Evidence of abnormal bleeding in factor XI deficiency not confined to severely deficient patients and a previously reported 26% prevalence of HMB in FXIII-deficient women with FXIII levels <70 IU dL justify testing FXI and FXIII levels in select patients [39, 40].

Laboratory Evaluation for "Bleeding Tendencies" It is not infrequent for hematologists to care for adolescents with HMB and other bleeding tendencies such as easy bruising but for whom available hemostatic testing does not reveal a diagnosis [41]. For such patients, it is important to consider a bleeding tendency that may result from a benign joint hypermobility syndrome and to assess for hypermobility [42]. Joint hypermobility is more common in females, and patients with joint hypermobility syndromes (Ehlers-Danlos syndrome being the most common) may bleed because of increased capillary fragility, alterations in collagen protein interactions in platelet function, or changes in the interaction between exposed collagen in endothelial walls and platelet receptors or VWF [43]. Prolonged menses, irregular menses, and dysmenorrhea are all commonly reported by women with Ehlers-Danlos syndrome [44]. Although many of these patients will have prolonged bleeding times [45], results from hemostatic tests are typically normal [46].

Identifying and Managing Iron Deficiency in HMB Hematologists play a key role in diagnosing and managing concomitant iron deficiency or iron deficiency anemia in adolescents with HMB. A CBC and iron panel should be part of the diagnostic evaluation of adolescents with

HMB. This aspect of assessment in HMB is discussed in Chap. 17.

Laboratory Evaluation of the Adolescent with Heavy Menstrual Bleeding: The Adolescent Medicine and Gynecology Perspective

The most frequent cause of HMB in an adolescent medicine or gynecology practitioner's office is anovulatory bleeding. This is a diagnosis of exclusion. Two years post-menarche, over half of menstrual cycles are anovulatory, whereas by 5 years, about one-tenth of menstrual cycles are anovulatory [47]. Anovulation cannot be based on cycle frequency, given that despite irregularity in their cycle frequency, most adolescent females are ovulating [48]. Polycystic ovarian syndrome (PCOS) is an important diagnosis to consider when anovulatory cycles are present. It occurs when hyperandrogenism results in anovulatory cycles. Approximately 1/3 of adolescent female patients admitted for HMB and anemia were diagnosed with PCOS in one study [49]. It is important to remember that either hypothyroid or hyperthyroid states can cause HMB [50].

An often-overlooked reason for HMB is combined hormonal contraceptives due to medication adherence issues, prolonged menstrual suppression, inadequate estrogen dose [51, 52], or the inability of progesterone to regulate shedding of the endometrium [53, 54]. Trauma and foreign bodies are additional causes of HMB [55]. There are a few essential non-hematological tests to evaluate for HMB [56]. These include urine pregnancy test to rule out any pregnancy-related causes, urine for sexually transmitted diseases such as gonorrhea and chlamydia, thyroid studies including thyroid-stimulating hormone and free T4 to evaluate for thyroid disease, and free testosterone to assess for PCOS.

Speculum and pelvic examinations depend on the age of the patient, diagnostic suspicion, and the clinician's judgment [57]. Papanicolau test, endometrial biopsy, or endocervical/vaginal swab for *Chlamydia* and gonorrhea depends on the age of the patient and other features in history. In a virginal adolescent, an abdominal ultrasound may be substituted for the pelvic examination. The transabdominal approach is the procedure of choice for any nonsexually active female, and the transvaginal approach is the procedure of choice for those females who are emotionally mature and sexually active [58]. Intrauterine saline instillation at the time of transvaginal ultrasound (sonohysterography) increases the sensitivity for abnormalities of the uterine cavity but is usually reserved for the evaluation of acquired uterine abnormalities in perimenopausal bleeding [59].

A systematic review examined the use of ultrasound, sonohysteroscopy, and hyteroscopy in the setting of HMB [60]. This review found a wide variation in published results on the accuracy of the various imaging modalities. Ultrasound is an accurate method for identifying uterine pathology with sensitivity ranging from 48% to 100% and specificity 12% to 100% in the setting of HMB. Furthermore, ultrasound is better at identifying fibroids than hysteroscopy but is less accurate for identifying polyps or endometrial disease when compared with hysteroscopy. Saline infusion sonography accurately identifies uterine pathology, with a sensitivity of 85–100% and a specificity of 50–100%. For hysteroscopy, the sensitivity was 90–97% and the specificity was 62–93%. MRI has no advantage over ultrasound as the firstline investigation for HMB but may be reserved for problem-solving where ultrasound provides indeterminate results.

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