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Abnormal Uterine Bleeding in Young Women with Blood Disorders

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Introduction

Abnormal uterine bleeding (AUB) is common in adolescents¹. Immaturity of the hypothalamic pituitary ovarian (HPO) axis is the most common cause of AUB in this age group². Certain aspects of underlying inherited or acquired blood disorders, as discussed in this chapter, exacerbate the “expected” hormonal imbalance at this age, thereby, increasing the morbidity of the underlying problem^{3,4}. Even though blood disorders may induce AUB, uterine structural and/or endocrine abnormalities tend to be overlooked in the presence of a blood disorder⁵. A multifactorial etiology demands a collaborative approach between hematologists and gynecologists or adolescent medicine physicians^{6,7}. In this chapter, we will discuss management of AUB in adolescents within 4 clinical contexts: AUB while on anticoagulant therapy, and with inherited bleeding disorders, bleeding management with

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cytopenias, specifically, thrombocytopenia, and in sickle cell disease. Throughout, areas of controversy and opportunities for further research are highlighted.

There has been a long-standing confusion concerning terminologies and definitions surrounding female reproductive tract bleeding⁵. ‘Menorrhagia’, a loosely defined term is used for heavy menstrual bleeding (HMB). ‘Dysfunctional uterine bleeding’ is associated with adolescents and often implies anovulatory bleeding. We will use the International Federation of Gynecology and Obstetrics terminologies and classification system throughout this chapter, and strongly recommend them for use in every day practice⁵. These have been published after years of robust international cooperation and consensus forming in 2011⁵. AUB or HMB are the preferred overarching terms, and the work up of HMB or AUB proceeds within the realm of *PALM-COEIN* classification, irrespective of age. PALM indicates *structural causes*: polyp, adenomyosis, leiomyoma, and malignancy, and COEIN indicates *non-structural causes*: coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified⁵. HMB is defined as periods lasting more than seven days, soaking through a pad or tampon under two hours or soaking through bed clothes, passing clots and ferritin below normal limits or anemia⁸. AUB refers to any departure from normal uterine bleeding, either in volume or duration of flow, regularity or frequency, and in theory, encompasses HMB.

I. Abnormal uterine bleeding during treatment of venous thromboembolism (VTE)

The number of adolescents in need of antithrombotic therapy has gradually increased over the past decades⁹. Anticoagulation is associated with AUB in 20–70% of patients¹⁰. One retrospective study of 90 women aged 15–49 years found that frequency of HMB increased from 17.8% before anticoagulation to 29.5% thereafter¹¹.

Another consideration is that heavy periods, often the reason for hormone induced VTE in the first place, are associated with stopping hormonal therapy may be intensified by anticoagulants. Estrogens are known to increase the risk for VTE twofold to fourfold in a dose-dependent way^{12,13}. The risk is also increased with third generation when compared with the first or second-generation progestins¹³. Patients with hormone-induced VTE are instructed to discontinue them, generally at the time of diagnosis. There is controversy regarding whether discontinuation should be immediate upon diagnosis of the VTE or deferred to the time point of discontinuation of anticoagulant therapy. The former recommendation is found in a World Health Organization (WHO) publication from 2010, stating that estrogen-containing oral contraceptives (OCs) should not be used, even on established oral anticoagulation¹⁴. In contrast, the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (ISTH) in a guidance document, suggested, hormonal therapy can be continued in selected patients but anticoagulants should be continued for the duration of hormonal therapy¹⁵. This is based on the premise that the anticoagulant effect trumps the thrombogenic potential of estrogens.

Key implications in this clinical context, therefore, include: a) the risk of recurrence with hormones while on anticoagulation, and b) medication options for AUB control and pregnancy prevention while on anticoagulants.

a. Risk of recurrent VTE with hormonal therapy while on anticoagulant

therapy—The risk of continuing hormonal therapy in women younger than 60 years of age (mean age 41.3 years) with VTE, was investigated in those treated with either lowmolecular-weight heparin followed by vitamin K antagonists (VKA) or with a direct oral anticoagulant (DOAC), Rivaroxaban, in one landmark study; 1888 women were analyzed, evenly distributed between the 2 anticoagulant regimens¹⁶. Of those, 475 women were taking concomitant hormonal treatment, either remaining on it despite the VTE diagnosis (n= 402) or initiated during the study period (n=73). The key finding of this study was the similar incidence rate during the time periods at risk, among those on hormonal therapy (3.7% per year) and those off/without hormonal therapy (4.7% per year), even after adjustment for age, prior hormonal therapy, assigned anticoagulant treatment, and cancer at baseline. In addition, there was no difference in crude incidence densities between women taking estrogen vs. progestin (3.7% per year and 3.8% per year, respectively), suggesting that the patient may continue with the type of hormones of her choice while on anticoagulation. Only 7 VTE events occurred on hormonal therapy (4 on estrogen-containing and 3 on progestin-only therapy)¹⁶. Despite these findings, there is reluctance among physicians to prescribe estrogen-containing OCs to women on anticoagulation. Moreover, there are no data to guide such management decisions in adolescents with AUB on anticoagulation. A recent systematic review highlighted that anticoagulant dose reduction or temporal cessation for controlling AUB while on anticoagulation was associated with a higher risk of recurrent VTE, though this was based on findings from only one study in this systematic review¹⁰.

b. Treatment options for AUB while on anticoagulant therapy—Treatment of AUB/HMB in adolescents taking anticoagulants, like in older women, depends on comorbidities, hormonal imbalance, either due to immaturity of the HPO axis or polycystic ovarian syndrome, need for contraception and rarely, the presence of structural uterine changes. Other general principles, specific to adolescents, are discussed in Table 1. In women of childbearing potential who receive VKAs (e.g. Warfarin), adequate contraception is required because these drugs cross the placenta, potentially leading to bleeding in the fetus and/or severe embryopathy¹⁷. The DOACs, currently in phase III trials in pediatrics, have as yet unknown adverse effects on fetal development.¹⁸ Even without the teratogenic effects, anticoagulants in therapeutic doses increase the length and severity of menstrual bleeding, which often requires medical management. In adolescents with AUB on anticoagulants, options such as non-steroidal anti-inflammatory drugs (NSAIDs) and estrogen containing OCs, as discussed above, are either contraindicated or not used. A recent systematic review shows that insertion of a progestin-releasing intrauterine device seems to decrease the length and severity of menses in most women on anticoagulation. The investigators of this review also acquired the clinical judgement of two panels of key opinion leaders (10 international AUB and 10 thrombosis experts) and compared expert opinion to current practice patterns by surveying ~300 international physicians (hematology, gynecology, internal medicine cardiology, pulmonology etc.). The expert recommendations were divergent and different in several important points from actual clinical practice, which was quite heterogenous. Only the following aspects of combined expert opinion analyses met the predefined threshold of 70% agreement: 1) hormonal contraception was not judged to be a risk factor for recurrent VTE during active/on-going anticoagulation; 2) progestin-only pill and progestin releasing

IUD were suggested to be best options for patients wishing to initiate contraception on anticoagulants; 3) tranexamic acid was suggested to be useful for treatment of anticoagulant associated AUB, and 4) anticoagulant dose reduction and inferior vena cava filter placement were not recommended management options for AUB, especially not in the first month following a VTE.

Invasive approaches such as endometrial ablation are an alternative to hysterectomy in older women with refractory or life-threatening HMB on anticoagulation¹⁹. However, as opposed to the “general” principles of AUB management in older women that conceivably can be applied to young women with AUB on anticoagulants, invasive management approaches require careful consideration given the lack of recent or any data, respectively.

To summarize, key management points include:

- Women of reproductive age may suffer from HMB when treated with anticoagulants. Adequate information regarding this risk should be given to the patient when initiating anticoagulation.
- Women taking oral anticoagulants for VTE *may* use estrogen or progestin hormonal therapy to control menstrual bleeding without increased risk for recurrent VTE.¹⁶
- For women with HMB on anticoagulant therapy, tranexamic acid is an alternative to hormonal therapy to reduce the bleeding. The latter does not provide a contraceptive effect.
- The thrombogenic effect of estrogens does not disappear precipitously upon discontinuation of estrogen containing OCs. The WHO Collaborative Study had noted that the effect disappeared 3 months after stopping OCs¹³. It therefore seems reasonable to recommend discontinuing OCs or oral estrogen substitution at least 1 month before planned discontinuation of anticoagulation rather than at the same time.
- A collaborative, multidisciplinary approach between thrombosis and AUB experts is paramount for effective health care delivery.

During anticoagulation, adequate measures to control AUB and prevent pregnancy, and reproductive toxicity to a fetus are indicated for all women with reproductive potential, including adolescents. Research on this subject is desperately needed to guide clinical practice in young women.

II. Abnormal uterine bleeding in inherited bleeding disorders

Menstruation disrupts blood vessels, restoration of which requires an intact hemostatic system and successful interaction of platelets, clotting factors and fibrinolytic proteins²⁰. Although less likely to present with spontaneous bleeding, inherited bleeding disorders (BDs) can become particularly severe after hemostatic challenges such as surgery, trauma, menses or childbirth. Mounting evidence suggests that 10–62% adolescents with HMB may have an underlying BD (Table 2)⁷. The average age of women identified with an underlying BD, however, is 35 years. In other words, the diagnosis of a BD is a relatively late one. Wide

ranges of reported prevalence, difficulty in discerning normal menstrual bleeding from HMB and the semi-empiric use of hormonal therapy makes BDs in adolescents challenging to identify²¹. There have been awareness efforts by the American College of Obstetricians and Gynecologists (ACOG) in 2001, and in 2006, by the American Academy of Pediatrics (AAP) in collaboration with ACOG advising that hematologic disorders (particularly, von Willebrand disease (VWD)) be considered in HMB, especially at menarche^{22,23}. VWD is reviewed in “Von Willebrand disease: Diagnostic Strategies and Treatment Options” by Drs. Ng and DiPaola in this issue. However, despite awareness efforts, BDs remain under-diagnosed in women⁷.

Historically, clinical questions that discriminate individuals with BDs from those without have been bleeding following hemostatic challenges such as tonsillectomy or dental extraction and the presence of a BD in the family; however, such exposures are often absent in the pediatrics. Generic bleeding assessment tools (BATs) that quantify bleeding symptoms in adults improve diagnostic accuracy and predict bleeding phenotype for a variety of BDs^{24–26}. The ISTH BAT was specifically designed to incorporate pediatric specific bleeding symptoms, including frequency and severity of bleeding²⁷. Even though the ISTH BAT can discriminate between no BD and a possible BD with acceptable accuracy, it has not been tested in adolescents²⁸. The pictorial blood assessment chart (PBAC) is a semi-quantitative method and allows women to track the number of pads or tampons during a menstrual period, and the degree of soiling²⁹. A score is generated based on that information, and PBAC scores of 100 correlate with 80 mL of menstrual blood loss, the classic definition of HMB. The sensitivity and specificity of the PBAC is 86% and 89% respectively in adult women with HMB^{30,31}. PBAC was evaluated in adolescents³². The mean PBAC score for the entire cohort was 195, but notably different when three groups were analyzed separately; 362, 136 and 44 for subjects in heavy, normal or light periods group respectively. Twenty percent of subjects in the ‘heavy group’ were diagnosed with a BD while there were no patients with a BD in the other two groups. Although analysis of diagnostic utility was not performed, this is the first study in adolescents investigating PBAC³². More recently, another HMB specific BAT called the Phillip screening tool was evaluated to screen for BDs in women aged 18–50 years with PBAC score > 100 and a normal pelvic ultrasound³³. This tool has a sensitivity of 89% for a BD. The sensitivity was lower (62%) for the 25 adolescents included in the study. The overall sensitivity improved to 93% by adding iron deficiency, and to 95%, when the PBAC score was increased to > 185³⁴. The utility of this tool is yet to be studied in an exclusive adolescent population.

The initial laboratory evaluation of patients with a suspected BD should start with a complete blood count, review of peripheral blood smear for platelet morphology, prothrombin time, partial thromboplastin time, and optionally either fibrinogen or thrombin time³⁵. The ACOG and AAP recommend testing for VWD in adolescents with HMB, especially at menarche^{23,36}. Ideally testing should be repeated at least twice for those with a high suspicion of a BD, and subnormal results should be confirmed³⁵. Testing on OCs containing 30–35 µg of estrogen does not affect the laboratory diagnosis of VWD^{37,38}. However, testing should not be performed during an OC taper or after high dose estrogen pulses because VWF levels are elevated with OCs containing 50 µg of estrogen³⁹. If these tests are normal, further testing should include screening for qualitative platelet disorders

with a platelet aggregation and secretion study^{40,41}. The authors propose a management algorithm, including laboratory testing (Figure 1) developed in the context of multidisciplinary management of young women with HMB⁶.

Recommended gynecological testing for HMB includes screening for pregnancy, and chlamydia trachomatis and Neisseria gonorrhea in this age group⁴². A history of irregular bleeding prior to the onset of heavy bleeding should prompt hormone testing to screen for polycystic ovarian syndrome (PCOS) and hypothyroidism^{2,43}. The role of pelvic examination is debated but an external genital exam is generally undertaken to detect anatomical abnormalities^{1,44}. Pelvic ultrasonography is generally performed in cases that are refractory to therapy^{45,46}.

A multidisciplinary approach to management, with involvement from a hematologist, an adolescent medicine specialist and/or gynecologist results in optimal treatment outcomes^{47,48}. OCs, the prototype for other combined hormonal contraceptives, offer both contraceptive and non-contraceptive benefits in adolescents with HMB, and include reduction of menstrual flow^{49,50}. The 2008 NHLBI VWD treatment guidelines recommend OCs as the first choice for HMB in an adolescent who does not desire pregnancy but may desire future child bearing⁵¹. Effectiveness of OCs in adolescents with platelet function defects remains to be studied. Extended cycling of OCs to reduce withdrawal bleeding that would otherwise occur every 28 days with conventional OCs is promising⁵². Studies in adult women have demonstrated that menstruating less frequently than monthly is highly acceptable⁵². Use of progesterone-only hormonal therapy, such as progesterone only pills, medroxyprogesterone acetate (MPA) and the progestin implant, also may reduce menstrual flow and are another alternative to OCs in adolescents with HMB but seem less preferable due to weight gain⁴⁹. Increasingly used in adolescents, the levonorgestrel intra-uterine system (LNG-IUS) steadily releases 20 mcg of levonorgestrel per 24 hours for 5 years into the endometrial cavity⁵³. IUDs are safe in nulliparous adolescents but require the expertise of an experienced gynecologist⁵⁴. LNG-IUS was shown to be an effective option in adolescents in a number of BDs with minimal complications, high compliance rate, and improvement in HMB and anemia^{50,55}.

Antifibrinolytics decrease the fibrinolytic activity observed in the endometrial tissue of women with HMB⁵⁶. Two antifibrinolytics, epsilon aminocaproic acid (Amicar) and tranexamaic acid (TA) have a well-established safety profile⁵⁷ and both reduce menstrual flow and improved QOL among females with HMB and abnormal laboratory hemostasis⁵⁸.

Data on the use of NSAIDs for management of HMB in adolescents are non-existent. Expert guidelines suggest they should not be used as first-line therapy for HMB, because they affect platelet function and may further increase menstrual blood loss in patients with undiagnosed BDs⁵⁹. Because menstrual pain is common in adolescents with BDs, the use of NSAIDs in those with severe menstrual cramps with hemostatic therapy deserve further study. In contrast to BDs, such as severe hemophilia reviewed in Evolving Complexity in Hemophilia Management by Dr. Croteau, in this issue, in which prophylaxis is the accepted standard of care, factor replacement such as VWF replacement for VWD, is less frequently used in women with HMB and is another area in need of investigation.

The need for surgery in adolescents with HMB is based on the clinical stability of the patient. Examination under general anesthesia, evacuation of blood clots from the uterine cavity and curettage should be considered, for serious or refractory menstrual bleeding. Endometrial ablation is not considered in adolescents due to concerns for future fertility preservation⁶⁰. Endometrial balloon tamponade using a Foley catheter may provide a temporary measure to control bleeding in a hemodynamically unstable patient⁶¹. Readers are encouraged to refer to other reviews for management protocols for acute HMB on an inpatient and outpatient basis^{6,59}.

III. Abnormal uterine bleeding in cytopenias/thrombocytopenia

There are many conditions in childhood that feature thrombocytopenia, of which those with moderate to severe thrombocytopenia may likely experience AUB. Thrombocytopenia can arise from a production problem, such as that associated with inherited bone marrow failure syndromes (iBMF), idiopathic aplastic anemia (iAA)(which is reviewed in chapter 12 by Savasan), and chemotherapy-induced thrombocytopenia (CIT), or because of platelet destruction such as with immune thrombocytopenia (ITP). The treatment of AUB in patients with thrombocytopenia should always include the treatment of the underlying disorder (Table 3), but there are some unique differences in the approach to those with impaired production vs. increased destruction.

a. Impaired platelet production—The most logical therapy for platelet production disorders may appear to be platelet transfusion, but given the risk of alloimmunization and transfusion-related complications, it may be desirable to pursue adjunctive therapies, especially in disorders that may require future hematopoietic stem cell transplant (HSCT) or in which one might choose to reserve platelet transfusion for life-threatening bleeding. Other therapeutic modalities include hormonal and hemostatic agents. There is little to no evidence in iBMF and iAA for the use of antifibrinolytics such as amicar and TA⁶². Induction of amenorrhea with hormone based therapies or leutenizing-hormone releasing hormone agonist (GnRH-a) or MPA may be useful. In conditions in which it is not expected for the production to improve or when the thrombocytopenia is moderate, one could consider the use of an intrauterine device (IUD) for induction of amenorrhea⁶³. Desmopressin Acetate (DDAVP) can also increase the release of VWF making what few platelets are in circulation more effective, but given the limited literature in these disorders, this should be considered when other methods are not effective⁶⁴.

Chemotherapy induced thrombocytopenia often leads to a transient window of risk of AUB. Platelet transfusion is recommended prophylactically when platelet count falls below 10,000/mm³⁶⁵. The incidence of moderate to severe HMB is 40% in patients receiving ablative chemotherapy for HSCT⁶³. Induction of amenorrhea is commonly pursued in oncology and HSCT patients as the severity and duration of thrombocytopenia is expected to be quite long and the impact of chemotherapy on ovaries may additionally lead to AUB due to HPO-axis disruption. Scarce evidence exists for Amicar and TA in patients undergoing chemotherapy in conjunction with platelet transfusion for the treatment of abnormal bleeding, but this is not specific to menstrual bleeding⁶². GnRH-a and MPA are commonly employed in advance of conditioning chemotherapy +/- radiation^{63,66}, with the

recommendation that GnRH-a is more effective than MPA for menstrual suppression and reduction of HMB^{63,67}. Due to the risk of VTE in cancer patients, providers may choose to avoid estrogen-based hormonal therapy. Additionally, whether a foreign body such as an IUD serves as a nidus of infection in patients with prolonged immunosuppression is controversial and no studies have been done to determine the exact risk.

b. Increased platelet destruction—In ITP, platelet transfusion should be reserved for life threatening bleeding when all the mainstays of ITP therapy have been exhausted. In persistent or chronic ITP, it is important to consider the use of hormonal suppression of menses or slowing of menstrual flow with the use of antifibrinolytic agents⁶². For history of HMB prior to the diagnosis of ITP, it is important to exclude VWD and qualitative platelet dysfunction with a thorough hemostatic evaluation⁶⁸.

IV. Abnormal uterine bleeding in sickle cell disease

The gynecological issues in adolescents with SCD include a later onset of menarche, AUB and vaso-occlusive pain associated with menstrual cycles⁶⁹. Menstrual patterns are reported to be normal⁷⁰. An important feature, exclusive to women, is the association of SCD related pain with menstrual cycles⁷⁰. Readers should refer to chapter 2 focused on current therapies for women with SCD. While hormonal fluctuations seem to underlie the painful SCD episodes associated with menses⁷⁰, there is a paucity of data investigating HMB in this group of adolescents. Conceivably, etiological factors underlying HMB in non-SCD patients should also be present in SCD patients. It is possible that mild BDs are mitigated by the SCD related hypercoagulability but a more pronounced bleeding phenotype is present in those who experience HMB and manifests with the monthly challenge of menstruation.

Adolescents with SCD and HMB are also at higher risk of iron deficiency anemia that may be masked in the presence of the underlying chronic anemia. This is especially true for the patients on hydroxycarbamide whose higher mean corpuscular volume (MCV)⁷¹ masks the microcytosis characteristic of iron deficiency. Low ferritin levels, the hallmark of iron deficiency anemia⁷², are not present in SCD due to the underlying inflammatory state, making diagnosis difficult.

AUB in adolescents with SCD, like other blood disorders, requires a systematic approach that begins with a thorough menstrual history. A careful consideration of other blood disorders, such as underlying VWD, systemic medical illnesses like hypothyroidism, PCOS or structural uterine abnormalities is paramount. Iron deficiency should be screened with ferritin level; though, caution should be exercised with interpretation. A better marker of iron deficiency in SCD may be percent transferrin saturation of less than 25%⁷³. There is reluctance to use estrogen containing OCs for hormonal suppression in an already hypercoagulable state, however, WHO guidelines on contraceptives in SCD, also endorsed by ACOG, state that the benefits of combined injectable contraceptives, low-dose OCs, and IUDs outweigh the risks associated with the increased morbidity and mortality associated with pregnancy⁷⁴. Additionally, progesterone-only pills can be used without restriction¹⁴. It should be noted that data are based on the high unplanned pregnancy risk rather than the safety profile of these pills⁷⁵. Longitudinal, prospective studies on etiology of AUB, uses

and complications of contraception, risk of unplanned pregnancy and prevalence of other reproductive issues are urgently needed for adolescents with SCD.

Summary/Discussion

Several issues for adolescents with AUB remain to be studied. A correct appreciation of the importance of AUB and its management are skills that all pediatricians should strive to achieve. It is quite clear that failure to do so could result in suffering and risk of serious bleeding. Despite advances in the clinical investigation and management of adult women with AUB and blood disorders, several areas need to be studied in adolescents as covered in the previous sections. These gaps urgently require future research and should be filled in the next years by multicenter collaborative studies.

References

1. Gray SH, Emans SJ. Abnormal vaginal bleeding in adolescents. *Pediatrics in review / American Academy of Pediatrics*. 2007; 28(5):175–182.
2. Benjamins LJ. Practice guideline: evaluation and management of abnormal vaginal bleeding in adolescents. *Journal of pediatric health care : official publication of National Association of Pediatric Nurse Associates & Practitioners*. 2009; 23(3):189–193.
3. Claessens EA, Cowell CA. Acute adolescent menorrhagia. *American journal of obstetrics and gynecology*. 1981; 139(3):277–280. [PubMed: 6970521]
4. Khosla AH, Devi L, Goel P, Saha PK. Puberty menorrhagia requiring inpatient admission. *JNMA; journal of the Nepal Medical Association*. 2010; 49(178):112–116. [PubMed: 21485595]
5. Munro MG, Critchley HO, Broder MS, Fraser IS. Disorders FWOm. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics*. 2011; 113(1):3–13.
6. Zia A, Lau M, Journeycake J, et al. Developing a multidisciplinary Young Women's Blood Disorders Program: a single-centre approach with guidance for other centres. *Haemophilia : the official journal of the World Federation of Hemophilia*. 2016
7. Zia A, Rajpurkar M. Challenges of diagnosing and managing the adolescent with heavy menstrual bleeding. *Thrombosis research*. 2016; 143:91–100. [PubMed: 27208978]
8. Warner PE, Critchley HO, Lumsden MA, Campbell-Brown M, Douglas A, Murray GD. Menorrhagia I: measured blood loss, clinical features, and outcome in women with heavy periods: a survey with follow-up data. *American journal of obstetrics and gynecology*. 2004; 190(5):1216–1223. [PubMed: 15167821]
9. Raffini L, Huang YS, Witmer C, Feudtner C. Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001 to 2007. *Pediatrics*. 2009; 124(4):1001–1008. [PubMed: 19736261]
10. Klok FA, Schreiber K, Stach K, et al. Oral contraception and menstrual bleeding during treatment of venous thromboembolism: Expert opinion versus current practice: Combined results of a systematic review, expert panel opinion and an international survey. *Thrombosis research*. 2017; 153:101–107. [PubMed: 28376343]
11. Sjalander A, Friberg B, Svensson P, Stigendal L, Lethagen S. Menorrhagia and minor bleeding symptoms in women on oral anticoagulation. *Journal of thrombosis and thrombolysis*. 2007; 24(1): 39–41. [PubMed: 17260163]
12. Lidegaard O, Lokkegaard E, Svendsen AL, Agger C. Hormonal contraception and risk of venous thromboembolism: national follow-up study. *Bmj*. 2009; 339:b2890. [PubMed: 19679613]
13. World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Venous thromboembolic disease and combined oral contraceptives: results of

- international multicentre case-control study. *Lancet*. 1995; 346(8990):1575–1582. [PubMed: 7500748]
14. Centers for Disease C, Prevention. U S. Medical Eligibility Criteria for Contraceptive Use, 2010. *MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports / Centers for Disease Control*. 2010; 59(RR-4):1–86.
 15. Baglin T, Bauer K, Douketis J, et al. Duration of anticoagulant therapy after a first episode of an unprovoked pulmonary embolus or deep vein thrombosis: guidance from the SSC of the ISTH. *Journal of thrombosis and haemostasis : JTH*. 2012; 10(4):698–702. [PubMed: 22332937]
 16. Martinelli I, Lensing AW, Middeldorp S, et al. Recurrent venous thromboembolism and abnormal uterine bleeding with anticoagulant and hormone therapy use. *Blood*. 2016; 127(11):1417–1425. [PubMed: 26696010]
 17. Bates SM, Greer IA, Hirsh J, Ginsberg JS. Use of antithrombotic agents during pregnancy: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004; 126(3 Suppl):627S–644S. [PubMed: 15383488]
 18. Ginsberg JS, Hirsh J, Turner DC, Levine MN, Burrows R. Risks to the fetus of anticoagulant therapy during pregnancy. *Thrombosis and haemostasis*. 1989; 61(2):197–203. [PubMed: 2665171]
 19. Farley TM, Rosenberg MJ, Rowe PJ, Chen JH, Meirik O. Intrauterine devices and pelvic inflammatory disease: an international perspective. *Lancet*. 1992; 339(8796):785–788. [PubMed: 1347812]
 20. Kulkarni R. Improving care and treatment options for women and girls with bleeding disorders. *European journal of haematology*. 2015; 95(Suppl 81):2–10. [PubMed: 26679392]
 21. Sramek A, Eikenboom JC, Briet E, Vandenbroucke JP, Rosendaal FR. Usefulness of patient interview in bleeding disorders. *Archives of internal medicine*. 1995; 155(13):1409–1415. [PubMed: 7794090]
 22. ACOG Committee Opinion No. 349. Menstruation in girls and adolescents: using the menstrual cycle as a vital sign. *Obstetrics and gynecology*. Nov; 2006 108(5):1323–1328. [PubMed: 17077267]
 23. Committee Opinion: number 263. von Willebrand's disease in gynecologic practice. *Obstetrics and gynecology*. Dec; 2001 98(6):1185–1186. [PubMed: 11755584]
 24. Marcus PD, Nire KG, Grooms L, Klima J, O'Brien SH. The power of a standardized bleeding score in diagnosing paediatric type 1 von Willebrand's disease and platelet function defects. *Haemophilia : the official journal of the World Federation of Hemophilia*. 2011; 17(2):223–227. [PubMed: 20860605]
 25. Rodeghiero F, Castaman G, Tosetto A, et al. The discriminant power of bleeding history for the diagnosis of type 1 von Willebrand disease: an international, multicenter study. *Journal of thrombosis and haemostasis : JTH*. 2005; 3(12):2619–2626. [PubMed: 16359502]
 26. Biss TT, Blanchette VS, Clark DS, et al. Quantitation of bleeding symptoms in children with von Willebrand disease: use of a standardized pediatric bleeding questionnaire. *Journal of thrombosis and haemostasis : JTH*. 2010; 8(5):950–956. [PubMed: 20136710]
 27. Bidlingmaier C, Grote V, Budde U, Olivieri M, Kurnik K. Prospective evaluation of a pediatric bleeding questionnaire and the ISTH bleeding assessment tool in children and parents in routine clinical practice. *Journal of thrombosis and haemostasis : JTH*. 2012; 10(7):1335–1341. [PubMed: 22578063]
 28. Elbatarny M, Mollah S, Grabell J, et al. Normal range of bleeding scores for the ISTH-BAT: adult and pediatric data from the merging project. *Haemophilia : the official journal of the World Federation of Hemophilia*. 2014; 20(6):831–835. [PubMed: 25196510]
 29. Higham JM, O'Brien PM, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. *British journal of obstetrics and gynaecology*. 1990; 97(8):734–739. [PubMed: 2400752]
 30. Zakherah MS, Sayed GH, El-Nashar SA, Shaaban MM. Pictorial blood loss assessment chart in the evaluation of heavy menstrual bleeding: diagnostic accuracy compared to alkaline hematin. *Gynecologic and obstetric investigation*. 2011; 71(4):281–284. [PubMed: 21228538]

31. Janssen CA, Scholten PC, Heintz AP. A simple visual assessment technique to discriminate between menorrhagia and normal menstrual blood loss. *Obstetrics and gynecology*. 1995; 85(6): 977–982. [PubMed: 7770270]
32. Sanchez J, Andrabi S, Bercaw JL, Dietrich JE. Quantifying the PBAC in a pediatric and adolescent gynecology population. *Pediatric hematology and oncology*. 2012; 29(5):479–484. [PubMed: 22866673]
33. Philipp CS, Faiz A, Dowling NF, et al. Development of a screening tool for identifying women with menorrhagia for hemostatic evaluation. *American journal of obstetrics and gynecology*. 2008; 198(2):163e161–168. [PubMed: 18226613]
34. Philipp CS, Faiz A, Heit JA, et al. Evaluation of a screening tool for bleeding disorders in a US multisite cohort of women with menorrhagia. *American journal of obstetrics and gynecology*. 2011; 204(3):209e201–207. [PubMed: 21247551]
35. James AH, Kouides PA, Abdul-Kadir R, et al. Von Willebrand disease and other bleeding disorders in women: consensus on diagnosis and management from an international expert panel. *American journal of obstetrics and gynecology*. 2009; 201(1):12e11–18. [PubMed: 19481722]
36. ACOG Committee Opinion No. 451. Von Willebrand disease in women. *Obstetrics and gynecology*. 2009; 114(6):1439–1443. [PubMed: 20134302]
37. Kadir RA, Economides DL, Sabin CA, Owens D, Lee CA. Variations in coagulation factors in women: effects of age, ethnicity, menstrual cycle and combined oral contraceptive. *Thrombosis and haemostasis*. 1999; 82(5):1456–1461. [PubMed: 10595638]
38. Zia A, Callaghan MU, Callaghan JH, et al. Hypercoagulability in Adolescent Girls on Oral Contraceptives- Global Coagulation Profile and Estrogen Receptor Polymorphisms. *American journal of hematology*. 2015
39. Alperin JB. Estrogens and surgery in women with von Willebrand's disease. *The American journal of medicine*. 1982; 73(3):367–371. [PubMed: 6981997]
40. Mikhail S, Varadarajan R, Kouides P. The prevalence of disorders of haemostasis in adolescents with menorrhagia referred to a haemophilia treatment centre. *Haemophilia : the official journal of the World Federation of Hemophilia*. 2007; 13(5):627–632. [PubMed: 17880454]
41. Diaz R, Dietrich JE, Mahoney D Jr, Yee DL, Srivaths LV. Hemostatic abnormalities in young females with heavy menstrual bleeding. *Journal of pediatric and adolescent gynecology*. 2014; 27(6):324–329. [PubMed: 25256871]
42. Practice bulletin no. 128: diagnosis of abnormal uterine bleeding in reproductive-aged women. *Obstetrics and gynecology*. 2012; 120(1):197–206. [PubMed: 22914421]
43. Azziz R, Carmina E, Dewailly D, et al. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. *Fertility and sterility*. 2009; 91(2):456–488. [PubMed: 18950759]
44. Westhoff CL, Jones HE, Guiahi M. Do new guidelines and technology make the routine pelvic examination obsolete? *Journal of women's health (2002)*. 2011; 20(1):5–10.
45. Snook ML, Nayak S, Lara-Torre E, Sanfilippo JS. Adolescent gynecology: special considerations for special patients. *Clinical obstetrics and gynecology*. 2012; 55(3):651–661. [PubMed: 22828097]
46. Tayal VS, Crean CA, Norton HJ, Schulz CJ, Bacalis KN, Bliss S. Prospective comparative trial of endovaginal sonographic bimanual examination versus traditional digital bimanual examination in nonpregnant women with lower abdominal pain with regard to body mass index classification. *Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine*. 2008; 27(8):1171–1177. [PubMed: 18645075]
47. Lee CA, Chi C, Shiltagh N, et al. Review of a multidisciplinary clinic for women with inherited bleeding disorders. *Haemophilia : the official journal of the World Federation of Hemophilia*. 2009; 15(1):359–360. [PubMed: 18691371]
48. Winikoff R, Amesse C, James A, Lee C, Pollard D. The role of haemophilia treatment centres in providing services to women with bleeding disorders. *Haemophilia : the official journal of the World Federation of Hemophilia*. 2004; 10(Suppl 4):196–204. [PubMed: 15479398]
49. Ott MA, Sucato GS. Committee on A. Contraception for adolescents. *Pediatrics*. 2014; 134(4):e1257–1281. [PubMed: 25266435]

50. Chi C, Pollard D, Tuddenham EG, Kadir RA. Menorrhagia in adolescents with inherited bleeding disorders. *Journal of pediatric and adolescent gynecology*. 2010; 23(4):215–222. [PubMed: 20471874]
51. Nichols WL, Hultin MB, James AH, et al. von Willebrand disease (VWD): evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel report (USA). *Haemophilia : the official journal of the World Federation of Hemophilia*. 2008; 14(2):171–232. [PubMed: 18315614]
52. Miller L, Notter KM. Menstrual reduction with extended use of combination oral contraceptive pills: randomized controlled trial. *Obstetrics and gynecology*. 2001; 98(5 Pt 1):771–778. [PubMed: 11704167]
53. Sivin I, Stern J, Coutinho E, et al. Prolonged intrauterine contraception: a seven-year randomized study of the levonorgestrel 20 mcg/day (LNg 20) and the Copper T380 Ag IUDs. *Contraception*. 1991; 44(5):473–480. [PubMed: 1797462]
54. Finer LB, Jerman J, Kavanaugh ML. Changes in use of long-acting contraceptive methods in the United States, 2007–2009. *Fertility and sterility*. 2012; 98(4):893–897. [PubMed: 22795639]
55. Adeyemi-Fowode OA, Santos XM, Dietrich JE, Srivaths L. Levonorgestrel-Releasing Intrauterine Device Use in Female Adolescents with Heavy Menstrual Bleeding and Bleeding Disorders: Single Institution Review. *Journal of pediatric and adolescent gynecology*. 2017; 30(4):479–483. [PubMed: 27108228]
56. Dockeray CJ, Sheppard BL, Daly L, Bonnar J. The fibrinolytic enzyme system in normal menstruation and excessive uterine bleeding and the effect of tranexamic acid. *European journal of obstetrics, gynecology, and reproductive biology*. 1987; 24(4):309–318.
57. Lethaby A, Farquhar C, Cooke I. Antifibrinolytics for heavy menstrual bleeding. *The Cochrane database of systematic reviews*. 2000; (4):CD000249.
58. Srivaths LV, Dietrich JE, Yee DL, Sangi-Haghpeykar H, Mahoney D Jr. Oral Tranexamic Acid versus Combined Oral Contraceptives for Adolescent Heavy Menstrual Bleeding: A Pilot Study. *Journal of pediatric and adolescent gynecology*. 2015; 28(4):254–257. [PubMed: 26024940]
59. James AH, Kouides PA, Abdul-Kadir R, et al. Von Willebrand disease and other bleeding disorders in women: consensus on diagnosis and management from an international expert panel. *American journal of obstetrics and gynecology*. 2009; 201(1):12e11–18. [PubMed: 19481722]
60. Rubin G, Wortman M, Kouides PA. Endometrial ablation for von Willebrand disease-related menorrhagia—experience with seven cases. *Haemophilia : the official journal of the World Federation of Hemophilia*. 2004; 10(5):477–482. [PubMed: 15357774]
61. Hamani Y, Ben-Shachar I, Kalish Y, Porat S. Intrauterine balloon tamponade as a treatment for immune thrombocytopenic purpura-induced severe uterine bleeding. *Fertility and sterility*. 2010; 94(7):2769e2713–2765.
62. Estcourt LJ, Desborough M, Brunskill SJ, et al. Antifibrinolytics (lysine analogues) for the prevention of bleeding in people with haematological disorders. *The Cochrane database of systematic reviews*. 2016; 3:CD009733. [PubMed: 26978005]
63. Kirkham YA, Ornstein MP, Aggarwal A, McQuillan S, Canpago C. Menstrual suppression in special circumstances. *Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC*. 2014; 36(10):915–924.
64. Kobrinsky NL, Tulloch H. Treatment of refractory thrombocytopenic bleeding with 1-desamino-8-D-arginine vasopressin (desmopressin). *The Journal of pediatrics*. 1988; 112(6):993–996. [PubMed: 3373409]
65. Barkhan P. Blood and neoplastic diseases. Thrombocytopenia. *Br Med J*. 1974; 2(5914):324–325. [PubMed: 4857083]
66. Ghalie R, Porter C, Radwanska E, Fitzsimmons W, Richman C, Kaizer H. Prevention of hypermenorrhea with leuprolide in premenopausal women undergoing bone marrow transplantation. *American journal of hematology*. 1993; 42(4):350–353. [PubMed: 8493984]
67. Quaas AM, Ginsburg ES. Prevention and treatment of uterine bleeding in hematologic malignancy. *European journal of obstetrics, gynecology, and reproductive biology*. 2007; 134(1):3–8.

68. Bevan JA, Maloney KW, Hillery CA, Gill JC, Montgomery RR, Scott JP. Bleeding disorders: A common cause of menorrhagia in adolescents. *The Journal of pediatrics*. 2001; 138(6):856–861. [PubMed: 11391329]
69. Stimpson SJ, Rebele EC, DeBaun MR. Common gynecological challenges in adolescents with sickle cell disease. *Expert Rev Hematol*. 2016; 9(2):187–196. [PubMed: 26613137]
70. Smith-Whitley K. Reproductive issues in sickle cell disease. *Hematology / the Education Program of the American Society of Hematology American Society of Hematology Education Program*. 2014; 2014(1):418–424.
71. Kattamis A, Lagona E, Orfanou I, et al. Clinical response and adverse events in young patients with sickle cell disease treated with hydroxyurea. *Pediatric hematology and oncology*. 2004; 21(4): 335–342. [PubMed: 15205096]
72. Powers JM, Buchanan GR. Potential for Improved Screening, Diagnosis, and Treatment for Iron Deficiency and Iron Deficiency Anemia in Young Children. *The Journal of pediatrics*. 2017; 188:8–10. [PubMed: 28549635]
73. Killip S, Bennett JM, Chambers MD. Iron deficiency anemia. *Am Fam Physician*. 2007; 75(5): 671–678. [PubMed: 17375513]
74. Bulletins-Gynecology ACoP. ACOG practice bulletin. No. 73: Use of hormonal contraception in women with coexisting medical conditions. *Obstetrics and gynecology*. 2006; 107(6):1453–1472. [PubMed: 16738183]
75. O'Brien SH, Klima J, Reed S, Chisolm D, Schwarz EB, Kelleher KJ. Hormonal contraception use and pregnancy in adolescents with sickle cell disease: analysis of Michigan Medicaid claims. *Contraception*. 2011; 83(2):134–137. [PubMed: 21237338]

KEY POINTS

- Abnormal uterine bleeding is common in adolescents with blood disorders but remains under recognized.
- Most data on management approaches is extrapolated from adult guidelines.
- A multidisciplinary approach is needed to address gynecologic morbidity associated with blood disorders in young women for optimal outcomes.

SYNOPSIS

Abnormal uterine bleeding (AUB) is common in adolescents and is thought to affect 9–14% of women in their reproductive years. Certain unique aspects of underlying inherited or acquired blood disorders, as discussed in this chapter, exacerbate the “expected” hormonal imbalance at this age, thereby, increasing the morbidity of the underlying problem. A multifactorial etiology demands a collaborative approach between hematologists and gynecologists or adolescent medicine physicians to effectively manage AUB in young women with blood disorders.

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Figure 1. Testing and Management Algorithm for Young Women with Heavy Menstrual Bleeding (HMB)

The current management protocol is being tested prospectively in the setting of a research study. Asterisks (*) denote research assessments.

HMB, heavy menstrual bleeding; PBAC, pictorial blood assessment tool; ISTH, International Society of Thrombosis and Haemostasis, BAT, bleeding assessment tool; CBC, complete blood count; FT4, free T4; TSH, thyroid stimulating hormone; PFA, platelet function analyser; TT, thrombin time; VWD, von Willebrand disease; VWF, von Willebrand factor; RCo, ristocetin cofactor activity; CB, collagen binding assay; PT, prothrombin time; aPTT, activated partial thromboplastin time; FSH, follicle stimulating hormone; LH, luteinizing hormone; DHEAS, dehydroepiandrosterone; PCOS, polycystic ovarian syndrome; ALT, alanine transaminase; RIPA, ristocetin induced platelet aggregation; PAI-1, plasminogen activator inhibitor-1

\$ Beighton Score is a nine-point evaluation to assess joint hypermobility, with attribution of one point in the presence of any of the following: (a) Passive apposition of the thumb to the flexor aspect of the forearm (one point for each hand), (b) passive dorsiflexion of the V finger beyond 90 (one point for each hand), (c) hyperextension of the elbow beyond 10 degrees (one point for each arm), (d) hyperextension of the knees beyond 10 degrees (one point for each leg), (e) forward flexion of the trunk with the knees extended and the palms resting flat on the floor (Reference # 126).

@ A psychosocial assessment using the HEEADSSS (Home environment, Education, Eating, peer-related Activities, Drugs, Sexuality, Suicide/depression, and Safety from injury and violence) format is recommended for adolescents during preventive health screening to

identify depression and other high-risk behaviour, which may need to be addressed given that these may be underlying causes of HMB. Similarly, a PHQ (patient health questionnaire) screen is performed to screen, diagnose and measure the severity of depression.

Whole bleed aggregation is suggested as part of this algorithm because of the availability at our institution. Light transmission aggregometry remains the gold standard method for measurement of platelet function at this time.

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Table 1

General principles for AUB management on anticoagulation

<ul style="list-style-type: none">• Assess pregnancy status before initiating anticoagulation, especially, if there are plans to transition to VKAs or DOACs (either in the setting of a clinical trial or in anticipation of meeting FDA approved age criteria for DOAC use during therapy duration)• Assess and document menstrual bleeding pattern (frequency, duration, flow and volume) before initiating anticoagulation• Consider hormonal suppression or regulation at the time of VTE diagnosis, if there is a history of AUB or HMB prior to VTE, irrespective of whether VTE was hormone induced or not• Assess anticoagulation (LMWH Anti-Xa or INR) and hematology parameters (hemoglobin and ferritin) at the time AUB or HMB is reported• Determine if current anticoagulant needs to be changed in view of AUB or HMB (e.g. fluctuating INRs with Warfarin, or a different DOAC)• Initiate treatment for AUB based on personal preference and needs• Consider a multidisciplinary, collaborative management approach, with inclusion of gynecology or adolescent medicine for improved patient outcomes

AUB, abnormal uterine bleeding; VKA, vitamin K antagonist; DOAC, direct oral anticoagulant; HMB, heavy menstrual bleeding; VTE, venous thromboembolism; LMWH, low molecular weight heparin; INR, international normalized ratio

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Table 2
Overview of published prevalence studies of bleeding disorders in adolescents with heavy menstrual bleeding (HMB)

Lead authors	Study design/ Study setting	Study population	Year (Study Period)	n	Age	BD frequency (%)	VW D (n)	PFD (n)	Clotting factor deficiency (n)	Fibrinolytic disorders (n)	Definition of BD	Limitations
Gursel and Albayrak	Cross sectional/ University students selected by survey	Adolescents with PBAC scores >100	2014	76	17–25	14.5	5	4	2 (FXI and FVII deficiencies)	NT	-VWF:Ag and/or VWF: RCo <45 for O and <50 for non-O blood types -Decreased platelet aggregation to ADP and/or collagen	-Platelet aggregation performed without release
Diaz and Srivaths	Retrospectiv e/Young Women’s BD clinic	Adolescents referred for HMB	2014 (20092011)	131	10–14	21	–7–32 with low VW F	11	2	1* (PAI-1 deficiency)	-VWF:Ag and/or VWF:RCo <30 -2 abnormalities in platelet aggregation and/or secretion	-Clotting factors and fibrinolytic protein testing when deemed necessary
Rodriguez and Simmons	Retrospectiv e/primary care, hematology clinics; inpatient or outpatient	Adolescents referred for HMB	2013	160	10–19	16	12	10	Not described	NA	Not provided	
Seravalli and Bruni	Retrospectiv e/Pediatric and Adolescent Gynecology Clinic	Adolescents referred for HMB	2013 (20072011)	113	11–20	48	15	20	14	NA	Not provided	Platelet aggregation performed without release
Vo and O’Brien	Retrospective/Young Women’s BD clinic	Adolescents referred for HMB	2012 (20092011)	105	8–18	62	9	-36 PSPD -8 other PFDs	NT	NT	-VWF:Ag and/or VWF:RCo <40 -PSPD: 3.68 granules per platelet -Other PFD: not clearly defined	-Platelet aggregation was not performed uniformly -Diagnosis of PFD based mainly on platelet EM
Mikhail and Kouides	Retrospectiv e/ Hemophilia Treatment Center or Hematology outpatient clinic	Adolescents referred for HMB	2007 (20012004)	61	11–19	41	36	7	NT	NT	-VWF: RCo < 40% and/or VWF: Ag <50% PFD: dec in agg to one or more agonists < 2SD of local lab range and /or abnormal PFA	-Platelet aggregation was not performed uniformly -Platelet aggregation performed without release
Jayasinghe and Grover	Retrospectiv e/ Inpatient outpatient gynecology clinic	Adolescents referred for HMB	2005 (2001–2003)	10	9–19	10.4	5	8	NT	NT	-VWF: RCo < and/or VWF: Ag below local lab reference range. -PFD: Abnormalities to ADP, collagen, ristocetin, or epinephrine	
Philipp and Saidi	Prospective/ Outpatient primary care clinic	Adolescents referred for HMB	2005 (1999–2004)	25	19	56	4	44	8	NT	Clear definitions of BD not provided	
Bevan and Scott	Retrospective/ED, urgent care, inpatient	Adolescents referred for HMB	2001 (1990–1998)	71	10–19	11	2	6	NT	NT	-VWF: RCo or VWF: Ag <45% -Platelet agg. < 50% with ADP, collagen, TRAP, ristocetin and AA	-9 cases had ITP -Only 14 girls in this series had hemostatic evaluation performed.
Oral and Ocer	Retrospective/Inpatient	Adolescents hospitalized for HMB	2001 (1988–1995)	25	11–17	8	2	NT	NT	NT	Clear definitions of BD not provided	An additional 4 cases were diagnosed with ITP

Lead authors	Study design/ Study setting	Study population	Year (Study Period)	n	Age	BD frequency (%)	VWD (n)	PFD (n)	Clotting factor deficiency (n)	Fibrinolytic disorders (n)	Definition of BD	Limitations
Smith and Hertzberg	Retrospective/Inpatient	Adolescents hospitalized for HMB	1998 (1979–1995)	37	10–20	13	5	NT	NT	NT	Clear definitions of BD not provided	
Claessens and Cowell	Retrospective/Inpatient	Adolescents hospitalized for HMB	1981 (1971–1981)	59		19	3	2	NT	NT	Clear definitions of BD not provided	

BD, bleeding disorder; NT, not tested; PBAC, pictorial blood assessment chart; VWF, von Willebrand factor; Ag, antigen; RCo, ristocetin co factor activity; ADP, adenosine diphosphate; PAI-1, plasminogen activator-1 activity; PSPD, platelet storage pool disorder; PFD, platelet functional disorders; EM, electron microscopy; TRAP, thrombin receptor activation peptide; AA, arachidonic acid; ITP, immune thrombocytopenia.

Table 3

General principles for AUB management in the setting of thrombocytopenia

-
- Assess pregnancy status before initiating therapy, especially, if there is clinical concern that thrombocytopenia is possibly secondary to SLE or that the use of possible anti-biologics such as Rituximab may be needed.
 - Assess and document menstrual bleeding pattern (frequency, duration, flow, and volume) prior to presumed onset of thrombocytopenia. Determine if AUB or HMB predates thrombocytopenia.
 - Consider hormonal suppression or regulation at the time of thrombocytopenia diagnosis, especially if there is a history of AUB or HMB prior to thrombocytopenia.
 - Assess severity of thrombocytopenia and hematology parameters (hemoglobin and ferritin) at the time AUB or HMB is reported.
 - Determine underlying cause of thrombocytopenia and if current severity of thrombocytopenia would be improved by/responsive to platelet transfusion.
 - Treat underlying cause of thrombocytopenia as indicated by standard of care for each underlying entity.
 - Initiate treatment for AUB based on personal preference and needs.
 - Consider a multidisciplinary, collaborative management approach, with inclusion of gynecology or adolescent medicine for improved patient outcomes AUB, abnormal uterine bleeding; SLE, systemic lupus erythematosus; HMB, heavy menstrual bleeding
-