Original Study

Bleeding Disorders in Adolescents with Heavy Menstrual Bleeding: The Queensland Statewide Paediatric and Adolescent Gynaecology Service

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A B S T R A C T

Study Objective: Heavy menstrual bleeding (HMB) is a common gynecological complaint among young women with up to 40% having experienced HMB. Bleeding disorders are increasingly being recognized in adolescents and young adults with HMB. The aim of this study was to determine the prevalence of bleeding disorders in adolescents with HMB, among patients who presented to the Queensland Statewide Paediatric and Adolescent Gynaecology Service between July 2007 and July 2017.
Design, Setting, Participants, Interventions, and Main Outcome Measures: The study was a retrospective review of 124 female adolescents aged 8 to 18 years with HMB who presented to the Queensland Paediatric and Adolescent Gynaecology Service, Brisbane, Australia. The primary outcome measure was diagnosis of a bleeding disorder, with secondary outcomes including iron deficiency and/or anemia and treatment modalities.
Results: Screening for bleeding disorders was performed in 77/124 (62.1%) of patients with HMB. Twenty-seven adolescents were diagnosed with a bleeding disorder, giving a prevalence of 27/124 (21.7%) in those with HMB, and 27/77 (35%) with HMB who were screened. Of these 35%, von Willebrand disease was the most common bleeding disorder, found in 14/27 (51.6%), followed by inherited platelet function disorders diagnosed in 9/27 (33.3%), thrombocytopenia (inherited or acquired) in 3/27 (11.1%), and Factor IX deficiency in 1/27 (3.7%). Iron deficiency and/or anemia was diagnosed in 53/107 (49.5%) of patients with HMB who were screened for this, and 19/27 (70.3%) of those diagnosed with a bleeding disorder.
Conclusion: Adolescents with HMB who present to a tertiary pediatric and adolescent gynecology service should be screened for bleeding disorders, because of the considerably high prevalence in this at-risk population.
Key Words: Heavy menstrual bleeding, Adolescents, Bleeding disorders, Pediatric and adolescent gynecology, von Willebrand disease

Introduction

Heavy menstrual bleeding (HMB) is a common gynecological complaint among adolescents with up to 40% having experienced HMB.[1] In many cases, immaturity of the hypothalamic-pituitary-ovarian axis, leading to anovulatory cycles, is thought to be the underlying cause for heavy menses. However, in young women with HMB, particularly in those who present with anemia and those not responding to the usual hormonal attempts to manage HMB, it is prudent to consider the presence of an underlying bleeding disorder.

Bleeding disorders are increasingly being recognized in women with HMB, and several studies have shown that 10%-62% of adolescents with HMB have an underlying bleeding disorder.[2–4] These studies show the prevalence of von Willebrand disease (VWD) to be 5%-36%, platelet function disorders to be 2%-44%, thrombocytopenia to be 13%-20%, and clotting factor deficiencies to be 8%-9%.[5,6]

The aim of this study was to determine the prevalence of bleeding disorders in adolescents with HMB who presented to a tertiary hospital pediatric and adolescent gynecology (PAG) service.

Materials and Methods

This study was a retrospective review of all patients with HMB who presented to the Queensland Paediatric and Adolescent Gynaecology Service from July 2007 to July 2017. Ethics approval was obtained from the Royal Brisbane and Women's Hospital Human Research Ethics Committee (HREC/17/QRBW/488). All patients coded in our database who presented with menstrual disorders were identified, and the medical records of those with HMB were reviewed. Data were collected on patient demographic characteristics, clinical history and symptoms, pathology results, therapeutic regimens, outcomes, and follow-up. SPSS version 22 (IBM Corp) was used for all analysis.

Clinical and laboratory findings from patients with bleeding disorders were independently reviewed by a specialist pediatric hematologist to ensure that patients were classified in accordance with recognized international

The authors indicate no conflicts of interest.

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criteria. The difficulty in accurately diagnosing mild type 1 VWD has been well described, presenting classification challenges in the clinical and research spheres.[6,7] For the purposes of this study, and in keeping with recent British guidelines, type 1 VWD was classified as a positive bleeding and/or family history with reduced von Willebrand factor antigen (VWF:Ag) and ristocetin cofactor (VWF:RCo), where either VWF:Ag or VWF:RCo was less than 0.3 U/mL^{-1} with an RCo:Ag ratio of greater than 0.6. "Low VWF" was classified as a positive bleeding history and/or family history with VWF:Ag and VWF:RCo levels of 0.30-0.49 U/mL^{-1}. Criteria for classification of subtypes of type 2 VWD and type 3 VWD were in keeping with recent published guidelines.[8] Platelet function disorders were classified by the hematologist in keeping with recognized diagnostic criteria according to blood film findings, platelet aggregation studies (light transmission aggregometry), and platelet electron microscopy findings.[9] Dense body (granule) deficiency was specifically defined as a dense granule count of 2.5 or less according to electron microscopy,[9] replicated on 2 occasions (according to locally established protocols). Where there was a clearly abnormal bleeding history and abnormally prolonged automated platelet function testing (PFA-100 test) without other cause, but definitive platelet function testing had not been performed, the temporary designation was "possible platelet function disorder." Hemophilia A or B was classified according to factor VIII or factor IX levels of less than 1% to 40% with severe less than 1%, moderate 1%-5% and mild 5%-40%. Known carriers of hemophilia A or B who had a factor VIII or IX level of 40%-60%, and a bleeding history, were designated as symptomatic carriers of hemophilia A or B.[10]

Results

One hundred twenty-four adolescents presented with HMB from a total cohort of 635 adolescents referred to the PAG service over the study time for a multitude of gynecological conditions (Fig. 1). The median age of adolescents with HMB was 14 years and 3 months (range, 10 years and 9 months to 18 years and 5 months). Screening for bleeding disorders was performed in 77/124 (62.1%) of all patients who presented with HMB. Overall, 27/124 (21.7%) of all patients with HMB, and 27/77 (35%) of those screened had a bleeding disorder. VWD was the most common bleeding disorder and diagnosed in 14/27 (51.6%; Fig. 2). Of these, 6 adolescents were classified as low VWF and 8 adolescents were classified as type 1 VWD. There were no patients in this

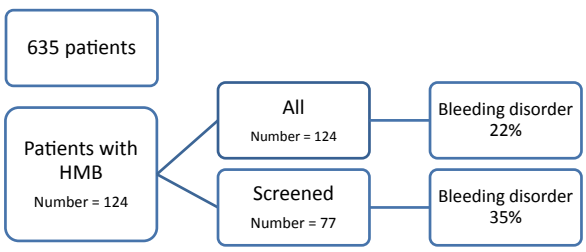

Fig. 1. Prevalence of bleeding disorders in patients with heavy menstrual bleeding (HMB) who presented to Queensland Paediatric and Adolescent Gynaecology Service.

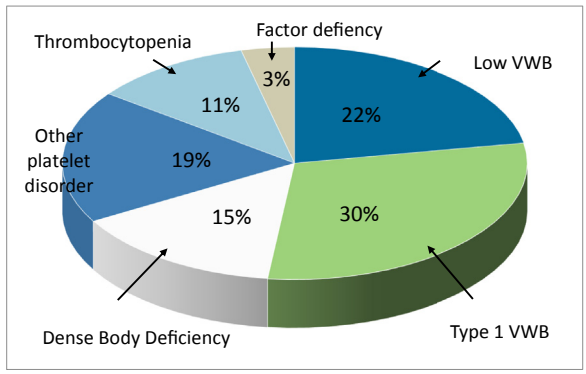

Fig. 2. Classification of bleeding disorders in adolescents with heavy menstrual bleeding. VWD, von Willebrand disease.

study with rarer, more severe forms of VWD, such as type 2 or type 3 VWD. Platelet function disorders were detected (or strongly suspected) in 9/27 (33.3%), of which dense body deficiency was the most common form confirmed, found in 4 adolescents. Thrombocytopenia was diagnosed in 3/27 (11.1%), of which 2 were acquired (immune thrombocytopenia) and 1 inherited. Factor IX deficiency (symptomatic carrier of hemophilia B) was diagnosed in 1/27 (3.7%).

Iron deficiency and/or anemia was screened for in 107/124 (86.3%) and diagnosed in 53/107 (49.5%) of those screened. In the 27 patients who had been diagnosed with a bleeding disorder, 19/27 (70.3%) were iron deficient and/or anemic, and 2/27 (7.4%) patients required a blood transfusion for anemia.

In patients with bleeding disorders, hormonal therapies were prescribed in 26/27 (96%) of patients. Several patients were treated with more than 1 treatment modality, simultaneously or consecutively. The combined oral hormonal pill was used in 17/27 (62%), Medroxyprogesterone, either orally or in Depot form in 7/27 (26%), and levonorgestrel intrauterine system (Mirena, Bayer) in 8/27 (30%). Tranexamic acid (TEXA), an antifibrinolytic agent, was used in 87% of all patients with a bleeding disorder. Iron replacement was required in 19/27 (70%) of patients. It was uncommon for targeted hemostatic therapies such as desmopressin and factor concentrates to be required for HMB, and these were prescribed under the supervision of the treating hematologist. Acute surgical management for HMB was not required in any case, because all cases could be medically managed.

Discussion

The findings of this study would suggest that adolescents who present with HMB and/or anemia to a tertiary center should be further evaluated for a bleeding disorder, including a thorough bleeding and family history and laboratory hemostatic investigation. Adolescents referred to the PAG are likely to be a higher-risk population for bleeding disorders. They are more likely to have had a previous review in the primary care or general gynecology setting, and might have been nonresponsive to usual first line management for HMB. The adolescent with heavy menses and iron deficiency anemia might be affected by fatigue, be spending less time on enjoyable activities such as sport, more time absent from

school, and be having difficulty concentrating and performing schoolwork.[11] Early diagnosis of a bleeding disorder might assist in reducing morbidity and suffering from HMB in the adolescent period, but importantly it will identify those at increased risk for long-term complications such as surgical or obstetric hemorrhage. Published data show that 8%-18% of women with a bleeding disorder will proceed to have surgery for HMB, including for management of hemorrhagic ovarian cysts or hysterectomy. An undiagnosed bleeding disorder might pose a greater risk of complications in these women.[12]

Screening

A systematic and stepwise hemostatic evaluation in young women who present with HMB should be undertaken. A comprehensive bleeding history is critical and should include detailed questioning regarding the presence of abnormal bruising, mucosal bleeding (epistaxis and oral bleeding), post-surgical and post-dental procedure bleeding, and bleeding after minor trauma. There is a wide spectrum of minor bleeding reported by healthy individuals and it can be difficult to be definitive around what constitutes a history of "abnormal bleeding." Screening tools, such as the Pictorial Blood Assessment Chart, might be of assistance in quantifying the amount of bleeding the adolescent is experiencing.[13] The use of validated bleeding assessment tools (BATs) are increasingly being used in clinical hematology practice to assist in identifying individuals with a bleeding history that is abnormal and predictive of an underlying bleeding disorder. Although there are pediatric-specific BATs (the Pediatric Bleeding Questionnaire[14,15] and International Society for Thrombosis and Haemostasis BAT[16]), these BATs still lack sensitivity, efficiency, and flexibility in the pediatric and adolescent setting.[17] It should be noted that these younger patients are less likely to have had significant surgical challenges compared with their adult counterparts and therefore (apart from menstruation) have had fewer opportunities for a bleeding disorder to become manifest. The limitations of currently available pediatric BATs are recognized and newer BATs are in development that will hopefully address these deficiencies.[18]

Investigation

Initial laboratory testing as outlined in Figure 3 should reasonably include a full blood count and examination of the blood film, prothrombin time (PT), activated patient thromboplastic time, clottable (Clauss) fibrinogen, and von Willebrand screen (including a factor VIII level, VWF:Ag, VWF:RCo activity and VWF:collagen binding assay. An automated platelet function analysis test (PFA-100) might also be considered as part of the general screen. When a family history of a clotting factor deficiency is present or when the initial screening coagulation profile is abnormal then additional factor levels will be required in consultation with the hematologist. It should be noted that despite hemophilia A and B being X-linked recessive disorders, that approximately 20% of female carriers do have reduced

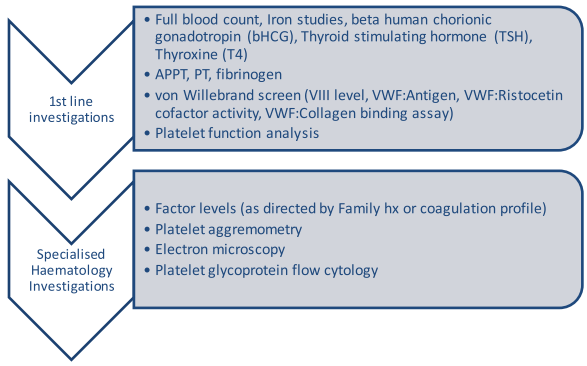

Fig. 3. Tiered approach to the laboratory investigation of adolescents with heavy menstrual bleeding. APPT, activated patient thromboplastic time; hx, history; PT, prothrombin time; VWF, von Willebrand factor.

factor VIII or IX levels (because of skewed lyonization) and that this can lead to problematic menstrual bleeding.[19]

When initial testing results are normal but the clinical history is suggestive of a bleeding disorder or when HMB is persistent (without other gynecological or endocrine cause) then more detailed hemostatic investigation is warranted in consultation with the hematologist. Disorders of platelet function requires specialized platelet aggregometry (with or without electron microscopy and platelet glycoprotein flow cytometry) testing and such investigations can usually only be performed in a tertiary hemostatic laboratory. It is important to note that automated platelet function testing (for example the PFA-100) is not considered diagnostic of a platelet function disorder because it is subject to considerable preanalytical variables, and abnormal results might be encountered simply because of transport artifact or medication use, particularly nonsteroidal anti-inflammatory drugs. The PFA-100 test is also not sensitive to mild disorders of platelet function.[20]

Because of the many preanalytical variables that can affect the hemostatic system investigations (particularly VWF levels and platelet aggregometry) it is not uncommon for repeat investigations to be required before a diagnosis can be confirmed. Accurate subclassification of type 2 VWD will also require further specialized testing including a ristocetin-induced platelet aggregation test.[21] The repeated testing to establish a formal diagnosis might prove frustrating for children and their families in some situations.

Diagnosis

The challenge of making an accurate diagnosis of mild type 1 VWD also exists in this group, because mildly reduced VWF levels of 40%-50% are a relatively common finding that might well improve with age and are not themselves diagnostic of type 1 VWD. We had incomplete blood group data for our cohort, however, it is well described that individuals who are blood group 0 often have VWF levels that are less than 0.5 U/mL and this laboratory finding might not clearly segregate with a bleeding or family history.[22] There is some controversy in the literature regarding the testing for VWD in patients already receiving the combined hormonal oral pill. From the best available

evidence, it is not necessary to discontinue these to investigate for VWD, because VWF Ag, factor III, and RCo parameters are not affected by combined hormonal pills.[23]

Because of the propensity for borderline levels to resolve with age, for patients with borderline low VWF levels it might be more appropriate to use the term "low VWF" levels rather than labeling a young adolescent with a disease. Patients with low VWF levels can be considered to have a risk factor for bleeding, rather than a disorder and their bleeding history and VWF levels can be followed-up over time and many will never meet the criteria for formal diagnosis of VWD.[24]

We did not diagnose any rarer forms of VWD (type 2 or type 3) in our cohort, likely reflective of their comparatively lower prevalence and the higher likelihood that these (more severe) disorders would have already become apparent before onset of menstruation because of the manifestation of other bleeding symptoms.

Rare factor deficiencies are occasionally found in girls who present with refractory HMB. Factor II, V, and X deficiency would be suspected because of prolongation of the activated thromboplastin time (APTT) and prothrombin time (PT) (see diagram), and factor VII deficiency by prolongation of the PT. It should be noted that mild intrinsic pathway deficiencies (factor VIII, IX, XI) might not always prolong the APTT, and if suspected from the family or clinical history these should be specifically requested. Factor XIII deficiency does not alter the coagulation profile, however, it is extremely rare and should only be tested when HMB is occurring in conjunction with other unexplained significant bleeding symptoms.[25]

Management

Institution of appropriate long-term management of menses in adolescents with bleeding disorders will be of considerable benefit in preventing morbidity. With mild bleeding disorders causing chronic HMB, the combined oral hormonal pill, progesterone-only hormonal options, and antifibrinolytics are considered first-line treatment.[26–28] In our institution, it would be routine to present all of the hormonal and nonhormonal options, screen for contraindications, and then allow the adolescent and parent/caregiver to make an informed choice after counseling.

Estrogen-containing oral contraceptive medications are effective in reducing the frequency and duration of menstrual periods. Administration of a combined pill containing 30 μg ethinyl estradiol diminishes the secretion of luteinizing hormone and follicle-stimulating hormone from the pituitary, thereby inhibiting ovulation and leading to stabilization of the endometrial surface of the uterus.[29] Alternative routes of administration of combined estrogen and progesterone preparations are transdermal preparations and vaginal rings, however, these are not in widespread use in Australia in the adolescent population, and have not been investigated in the adolescent bleeding disorder population.

If there are contraindications to the use of estrogen-containing preparations, or patient preference is for a progesterone-only method, we commonly offer either cyclical medroxyprogesterone acetate 20- to 40-mg oral once daily for 21 days each month, or if the goal is menstrual suppression, depot medroxyprogesterone acetate 150 mg every 12 weeks. We have found the levonorgestrel intrauterine system to be highly effective at achieving menstrual suppression in adolescents with bleeding disorders, with 30% of our cohort proceeding to insertion of Mirena intrauterine system. At our institution we would routinely offer this as a treatment modality for all adolescents with HMB, with insertion using general anesthesia, because the safety in the adolescent population has been well established.[30]

TEXA is an antifibrinolytic agent that may be used alone or in conjunction with hormones, and is highly effective at reducing menstrual bleeding in patients with bleeding disorders. TEXA was used in up to 87% of adolescents with bleeding disorders in this cohort. It competitively inhibits the activation of plasminogen to plasmin, and at higher concentrations, is a noncompetitive inhibitor of plasmin.[31] Typically, TEXA is dosed intermittently for HMB, with our usual protocol being a 15- to 25-mg/kg dose (maximum 1.5 g) given orally 3 times a day, for days 1 to 4 of the menstrual cycle. Aminocaproic acid (Amicar, Xanodyne Pharmaceuticals Inc) is an alternative antifibrinolytic, however, it is not currently marketed in Australia. We typically prescribe TEXA in conjunction with progesterone-only preparations, such as medroxyprogesterone or norethisterone, rather than estrogen-containing combined pills, because the use of estrogen in addition TEXA might pose a greater risk of venous thromboembolism.

Acute Hemorrhage

In cases involving acute hemorrhage, hospitalization and/or blood transfusions might be required. It is interesting to note that blood transfusion was required very rarely in our cohort of adolescents with HMB and an underlying bleeding disorder. This might reflect the prompt recognition of iron deficiency and early aggressive management with appropriate iron therapy in our cohort while

Table 1
Medical and Hormonal Therapies for Acute Heavy Menstrual Bleeding

Therapy	Dose	Route	Initial Frequency
Conjugated estrogen	25 mg	IV	Every 4-6 hours
50 μg ethinyl estradiol combined pill	1 Tablet	Oral	Every 6 hours
30 μg ethinyl oestradiol combined pill	1 Tablet	Oral	Every 6 hours
Medroxyprogesterone	10-20 mg	Oral	Every 6 to 8 hours
Norethisterone	5-10 mg	Oral	Every 8 hours
Tranexamic acid	1 g	Intravenous	One dose over 10 minutes
Tranexamic acid	15-25 mg/kg per dose (maximum 1.5 g)	Oral	Every 8 hours

working to control underlying HMB with hormonal and antifibrinolytic therapy. The well established "restrictive transfusion policy" at our center might have also contributed to the low blood transfusion rate observed.

There are various hormonal regimens that can be used (Table 1), however, the data in the literature specifically comparing the effectiveness of various modalities specifically in adolescents with bleeding disorders with acute heavy bleeding are limited. Estrogen might be given intravenously, 25 mg intravenously every 4-6 hours, or alternatively in the form of a 30- to 50-μg ethinyl estradiol combined pill, 1 tablet every 6 hours, until bleeding ceases, which in most cases occurs within 24 hours of treatment. Alternatively, progesterone-only treatments are available and have been shown to be effective. At our institution, for heavy acute bleeding we would commence medroxyprogesterone acetate 10-20 mg every 6-8 hours, or norethisterone 5-10 mg every 8 hours. When bleeding has settled, tapering of the hormonal therapies will be required, and there are various protocols for weaning to a maintenance dose of hormonal therapies that exist.[28] Additionally, in the setting of acute heavy bleeding, TEXA may be given at a dose of 1 g by intravenous injection over 10 minutes, followed by oral administration as per the protocol described previously. Surgical interventions such as dilatation and curettage, and or insertion of a 30-cc Foley catheter balloon is only very rarely required when prompt medical management is instituted.

Targeted Therapy

Accurate and early recognition of bleeding disorders in the adolescent is critical for management of future severe bleeding episodes that might benefit from directed therapies, preoperative prophylaxis, and treatment of surgical hemorrhage, including future preparation for obstetric-related bleeding. For patients with mild to moderate VWD type 1, mild hemophilia A, some patients with type 2A and type 2M VWD and some mild platelet function disorders, desmopressin (a synthetic vasopressin analogue) can be used. In Australia this is available in subcutaneous and intravenous preparations, and in some countries, in nasal preparations. Desmopressin stimulates the release of endothelial VWF, thereby increasing the levels of VWF, and enhancing platelet adhesion to the vessel wall.[32] Desmopressin is generally reserved for refractory HMB that has not responded to antifibrinolytic and multiple hormonal approaches. Caution with fluid restriction to two-thirds maintenance for 24 hours after each dose is imperative to prevent hyponatremia.[33] Severe forms of VWD require clotting factor concentrates containing VWF for treatment (or rarely prevention) of hemorrhages.

Iron Replacement

Iron deficiency and/or anemia contributes to morbidity seen in this population, and this study has shown a high prevalence of iron deficiency and/or anemia. Adolescents with HMB should therefore be screened for iron deficiency anemia, and appropriate treatment instituted. It is very important to be very specific when prescribing oral iron replacement because there exist many over the counter supplements that have very low content of iron and provide little benefit (Table 2). We routinely recommend a combined iron formulation such as Ferrograd C (Mylan Health) containing ferrous sulfate 325 mg (equivalent to 105 mg of elemental iron) and sodium ascorbate (equivalent to 500 mg of ascorbic acid or Vitamin C) for improved absorption, at a dose of 1 tablet daily. The availability of newer, safer, more cost effective intravenous iron preparations (iron carboxymaltose, Ferinject, Mylan Health) and generally unfavorable side effect profile of oral preparations might lower the threshold for replacing iron intravenously. Ferinject is given at a maximum single dose of up to 1000 mg as an intravenous infusion over 15 minutes, which might be repeated a week later, according to the Ganzoni formula.[34]

Limitations and Strengths

The retrospective nature of this cohort study meant that HMB was not able to be objectively measured, which is a limitation encountered by other groups investigating HMB and reflects the challenges in trying to design and carry out prospective studies in adolescent menstruation. The research was carried out in a tertiary care center and by virtue of a referral pattern reflecting more refractory cases of HMB, it is almost certain that the prevalence of bleeding disorders in the population has been overestimated compared with that seen in studies from a primary care setting. A strength of this study is that all patients were reviewed and classified according to standardized criteria by a specialist pediatric hematologist.

Conclusion

Our data are consistent with international published literature that shows that a large proportion of adolescent girls with HMB referred to a tertiary PAG clinic will have an underlying bleeding disorder. It is likely that a high proportion of adolescents with HMB who present in the primary setting might also be under-recognized and untreated, and thus there should be a low threshold to recognize, screen, and treat.

These findings support comprehensive and systematic hemostatic evaluation in adolescents with HMB. A higher level of awareness of bleeding disorders as a cause for HMB

Table 2
Commonly Available Oral Iron Preparations

Brand name	Formulation	Elemental iron Content
Ferro-gradumet (AFT Pharmaceuticals)	Ferrous sulfate 325 mg controlled-release tablets	105 mg
Ferrograd C (Mylan Health)	Ferrous sulfate 325 mg Vitamin C 500 mg Controlled-release tablets	105 mg
Ferro-tab (AFT Pharmaceuticals)	Ferrous fumarate 200 mg	65.7 mg
Ferro-liquid (AFT Pharmaceuticals)	Ferrous sulfate 30 mg/mL	6 mg/mL

in adolescence, especially VWD and platelet function disorders, is needed and close multidisciplinary collaboration between the pediatric and adolescent gynecologist and hematologist in a specialized tertiary center should be established in the management of these patients. Effective management can be accomplished with either hormonal medications alone or in conjunction with antifibrinolytic agents in most patients. In adolescents who are already known to have a bleeding disorder, consultation with a pediatric gynecologist and/or hematologist before menarche might be helpful to outline abnormal patterns of menstrual bleeding and to discuss options of treatment in the event of HMB.

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