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Bleeding disorders in adolescents with heavy menstrual bleeding in a multicenter prospective US cohort

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ABSTRACT

Heavy menstrual bleeding is common in adolescents. The frequency and predictors of bleeding disorders in adolescents, especially with anovulatory bleeding, are unknown. Adolescents referred for heavy menstrual bleeding underwent an evaluation of menstrual bleeding patterns, and bleeding disorders determined *a priori*. The primary outcome was the diagnosis of a bleeding disorder. Two groups were compared: anovulatory and ovulatory bleeding. Multivariable logistic regression analysis of baseline characteristics and predictors was performed. Kaplan Meier curves were constructed for the time from the first bleed to bleeding disorder diagnosis. In 200 adolescents, a bleeding disorder was diagnosed in 33% (n=67): low von Willebrand factor levels in 16%, von Willebrand disease in 11%, and qualitative platelet dysfunction in 4.5%. The prevalence of bleeding disorder was similar between ovulatory and anovulatory groups (31% *vs.* 36%; *P*=0.45). Predictors of bleeding disorder included: younger age at first bleed (OR: 0.83; 95%CI: 0.73, 0.96), Hispanic ethnicity (OR: 2.48; 95%CI: 1.13, 5.05), non-presentation to emergency department for heavy bleeding (OR: 0.14; 95%CI: 0.05, 0.38), and International Society on Thrombosis and Haemostasis (ISTH) Bleeding Assessment Tool score ≥4 (OR: 8.27; 95%CI: 2.60, 26.44). Time from onset of the first bleed to diagnosis was two years in the anovulatory, and six years in the ovulatory cohort (log-rank test, *P*<0.001). There is a high prevalence of bleeding disorders in adolescents with heavy periods, irrespective of the bleeding pattern. Among bleeding disorders, the prevalence of qualitative platelet dysfunction is lower than previously reported.

Introduction

Heavy menstrual bleeding (HMB) is common in adolescents after menarche.[1] Anovulation is the most common etiology of HMB and is expected to persist for up to five years.[2] Underlying bleeding disorders (BD) are another important etiology of HMB affecting up to 20% of adults and 13-60% of adolescents.[3] A large body of research has focused on the prevalence of BD in adult women and its predictors. In contrast, pediatric literature on BD frequency has only been recently accrued. Most data are retrospective and prevalence studies by and large excluded women with anovulatory bleeding.[4-6] Data on predictors of BD in adolescents with HMB, when anovulation is most prevalent, are scant and it is difficult to determine whom to screen for BD.[3]

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Our study aimed to describe the frequency, predictors, and time from bleeding onset to BD diagnosis in a prospective cohort of adolescents with HMB, using a well-defined and rigorous protocol of hemostasis testing and platelet function analysis. We hypothesized that the frequency of undiagnosed BD in adolescents with HMB would be similar to adults, and that the menstrual bleeding pattern will not predict a BD.

Methods

Postmenarchal adolescents up to 18 years of age referred for HMB without a diagnosis of BD were eligible to participate (Figure 1). Participants were enrolled prospectively from the Young Women's Blood Disorders Program at The University of Texas Southwestern (UTSW), Dallas, TX (primary site), USA, and the Children's Hospital of Buffalo (CHOB), NY, USA (external site) between July 2014 and December 2017, after informed consent and/or assent.[7] The institutional review board at both UTSW and CHOB (Institutional Review Board numbers: STU 102014-001 and 00003126, respectively) approved the study. Participants were excluded if they did not complete: 1) a minimum of two visits and 2) the minimum BD evaluation, decided *a priori.*

Definitions

Heavy menstrual bleeding was defined by menstrual duration ≥7 days with a sensation of "gushing" or "flooding" or bleeding through a pad or tampon for ≤2 hours.[8,9] Based on the pattern of HMB in the entire cohort, participants were classified and compared among two groups: the anovulatory HMB group was defined as having menstrual duration <21 or >45 days; the ovulatory HMB group was defined when this menstrual pattern was not present.[10]

Laboratory testing

All participants underwent testing that included complete blood count, serum ferritin, prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, von Willebrand Factor (vWF) analysis (repeated at least twice for every participant), platelet aggregation (repeated if abnormal), Factor (F) XI, FXIII factor assays and systemic hyperfibrinolysis assessment using rotational thromboelastometry (ROTEM).[11] This comprised the minimum BD evaluation for retention into the final analysis.

Iron deficiency/iron deficiency anemia

We defined anemia as hemoglobin <110 g/L and iron deficiency as serum ferritin levels ≤ 20 μg/L.

Bleeding assessment tools

Pictorial Blood Assessment Chart (PBAC) - a PBAC score was computed for all participants, and an average score of three cycles was taken as the final score.[12] Standardized pads and tampons were not provided.

Outcomes

The primary outcome of the study was the diagnosis of BD defined as low von Willebrand disease (vWD), qualitative platelet dysfunction (QPD), clotting factor deficiencies or hyperfibrinolysis.

Statistical analysis

Sample size - based on adult data,[4,5] we assumed that 20% of adolescents with HMB, irrespective of menstrual bleeding pattern, will be diagnosed with BD within six months from study entry; with a total of 180 patients, we estimated the rate of BD in this group with such precision that the 95% confidence interval has a half-length smaller than 8%.[14]

Main outcome

The frequency of BD was compared among groups using χ^2 test.

A multivariable logistic regression model was built following the technique described by Hosmer, Lemeshow, and Sturdivant.[15] Variable selection was performed using the stepwise procedure.

Kaplan-Meier curves were constructed from the first bleed to BD diagnosis for the entire cohort and the main two groups and compared using the log-rank test.

Further information on the methods used is available in the *Online Supplementary Appendix.*

Results

Demographic and clinical characteristics

Two hundred and thirty-five consecutive adolescents were enrolled during the study period, of which 200 participants met eligibility criteria, and had complete outcome data: 185 from UTSW and 15 from CHOB. The median age of participants was 15 years (y) (Table 1), and 28% were Hispanic. Fifty-five percent had normal body mass index (BMI) as determined by Center for Disease Control (CDC) growth charts. The median age at menarche was 12 years, and BD evaluation occurred at a median of three years from menarche. Thirty-three percent presented to the Emergency Department (ED) for evaluation and management of HMB; 25% needed to be hospitalized, of which 19% received packed red blood cells (pRBC). The mean PBAC score was 386 [standard deviation (SD), 243] and the ISTH score was 3.5 (SD 1.3). A

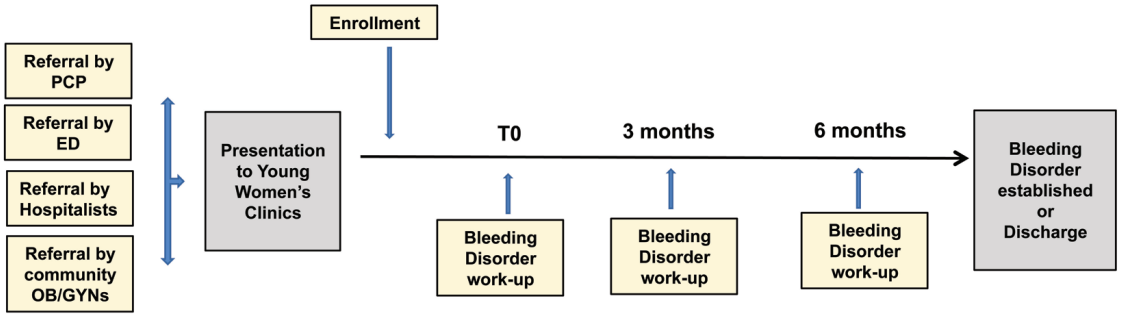

Figure 1. Study design. Prospective, multicenter, observational study of adolescents presenting with heavy menstrual bleeding.

family history of bleeding symptoms or established BD was present in 21% and 6.5%, respectively. Family history of gynecologic or obstetric bleeding was present in 60%: 57% (n=114) with HMB alone; 1.5% (n=3) with HMB and post-partum hemorrhage (PPH) (n=3), and 1.5% (n=3) had only PPH. Of the first-degree relatives with HMB, 38% underwent hysterectomy for HMB (n=44) and 2% underwent endometrial ablation (n=2) to control HMB. Thirty-six percent (n=72) had iron deficiency anemia, 29% (n=57) had iron deficiency alone, and overall iron deficiency was documented in 65% (n=129). Participants with anovulatory HMB had a higher BMI (66.7% *vs.* 36%) and increased frequency of refractory HMB (34% *vs.* 19%), ED visits (42 % *vs.* 25%), hospitalizations (28% *vs.* 17%), and pRBC (24% *vs.* 14%) administration for HMB compared to those with ovulatory pattern bleeding.

Frequency and types of bleeding disorders and additional bleeding symptoms

Overall, 33% (n=67) of adolescents were diagnosed with a BD. Among those with BD, there were no differences in the frequency of BD in the anovulatory and the ovulatory HMB groups (31% *vs.* 36%; *P*=0.45). Low vWF levels were detected in 57% (n=38 of 67); 25% (n=17 of 67) were diagnosed with vWD (type 1=13, type 2=4), 13.5% (n=9 of 67) with QPD, and two participants were found to have coagulation factor deficiencies (one with mild FVIII deficiency (FVIII:C= 29%) and mild FXIII deficiency (FXIII: 40%). One participant, referred for HMB

Table 1. Baseline characteristics of the entire study cohort and according to menstrual bleeding pattern.

	All patients (N=200) n (%)	Anovulatory HMB (N=100) n (%)	Ovulatory HMB (N=100) n (%)
Age, y	15 (10-19)	14 (10-18)	15 (11-19)
Ethnicity			
Hispanic	56 (28)	33 (33)	23 (23)
Non-Hispanic	144 (72)	67 (67)	77(77)
Race			
White	131 (65)	70 (70)	61(61)
Black	41 (20·5)	13 (13)	28 (28)
Other	28 (14)	17 (17)	11 (11)
BMI, kg/m^2	23·3 (14·5-55)	24·4 (17-55)	22·9 (14·5-44)
Normal weight	110 (55)	45 (45)	65 (65)
Overweight/Obese	90 (45)	55 (55)	35 (35)
Age at menarche, y	12 (9-15)	12 (9-15)	12 (9-15)
Years since menarche	3 (1-4)	3 (1-4)	3 (1-4)
Time to HMB, y	0·5 (0-5)	0·5 (0-5)	0·4 (0-5)
Age at first bleed	12 (2-17)	12 (2-16)	12 (2-17)
Refractory HMB$^{\$}$	53 (26·5)	34 (34)	19 (19)
Presentation to ED for HMB$^{@}$	67 (33.5)	42 (42)	25 (25)
≤ 1 visit	47 (23.5)	26 (26)	21 (21)
≥ 2 visits	19 (9·5)	15 (15)	4 (4)
Hospitalizations for HMB	45 (22·5)	28 (28)	17 (17)
pRBC	38 (84)	24 (86)	14 (82)
Parenteral Iron	76 (38)	36 (36)	40 (40)
PBAC at study entry*$^{\#}$	386 (243)	427 (274)	345 (201)
ISTH-BAT*	3.5 (1·3)	3.4 (1·3)	3.5 (1·3)
FMH of bleeding or BD	55 (27·5)	28 (28)	27 (27)
FMH of gynecologic or obstetric bleeding	120 (60)	55 (55)	65 (65)
Hypermobility	20(20)	9(23)	11(17)
Hemoglobin, g/L	11·8 (3·4-16·4)	11·7 (3·9-15)	11·8 (3·4-16·4)
Ferritin, ng/mL	8 (0·9-78)	10·2 (0·9 – 70)	7·2 (1-98)
TSH, mIU/L	1·5 (1·2-8·4)	1·7 (0·5-8·4)	1·4 (1·2-5·1)
BD diagnosis	67(33)	31(31)	36(36)

Values are medians with interquartile ranges except normally distributed variables marked with an asterisk; mean and standard deviations are reported. BMI: body mass index; ED: emergency department; HMB: heavy menstrual bleeding; ISTH-BAT: International Society of Thrombosis Haemostasis-Bleeding Assessment Tool; pRBC: packed red blood cells; PBAC: pictorial blood assessment chart; TSH: thyroid-stimulating hormone; y: years. Statistically significant differences between the anovulatory and ovulatory groups were found for refractory HMB, presentation to ED and PBAC @ # $*P*=0.01.

Table 2. Types of bleeding disorders in the whole group and according to menstrual bleeding pattern.

	All patients (N=200) n (%)	Anovulatory HMB (N=100) n (%)	Ovulatory HMB (N=100) n (%)
Low	38 (19)	14 (14)	24 (24)
vWF	17 (8.5)	12 (12)	5 (5)
Type 1	13 (6.5)	5(5)	8(8)
Type 2	4 (2)	3(3)	1(1)
Qualitative platelet dysfunction	9 (2)	5 (5)	4(4)
Clotting factor deficiencies	2 (1.5)	2(2)	–
Symptomatic hemophilia carrier	1 (0.5)	1(1)	–

vWF: von Willebrand factor; vWD: von Willebrand disease.

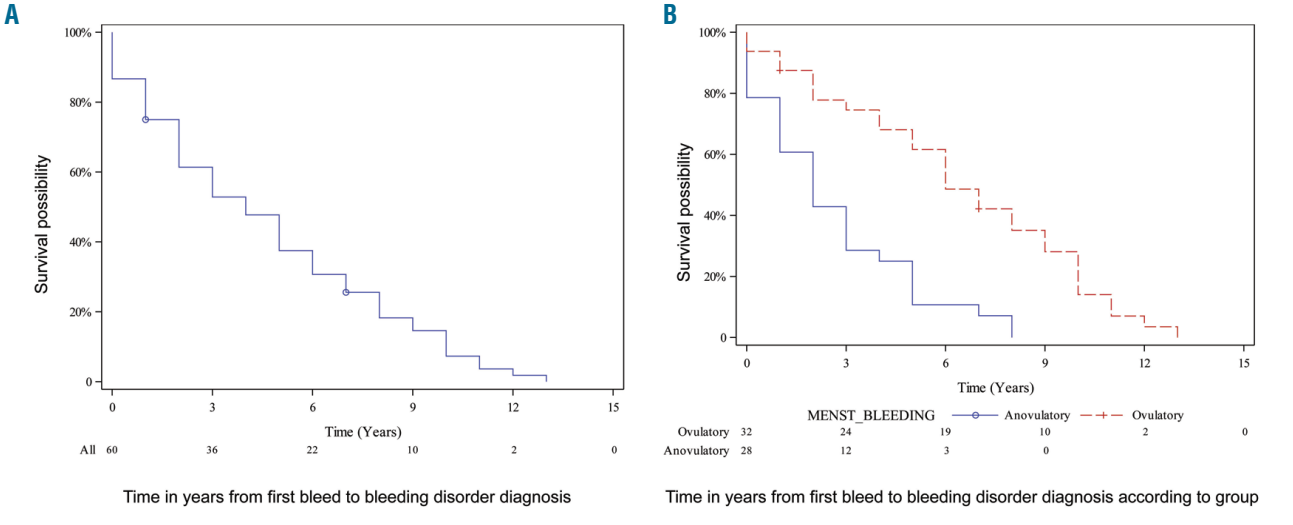

Figure 2. Kaplan-Meier curves showing time from the first bleeding event to bleeding disorder diagnosis. (A) Time until diagnosis for the entire group. (B) Time according to the menstrual bleeding group. The number of patients diagnosed according to the group is shown at the bottom of the graphic, on the x-axis.

four years after menarche because of a brother with FVIII deficiency, was diagnosed to be a symptomatic hemophilia carrier (FVIII: 124%; positive for a pathogenic type 1 intron 22 inversion mutation (F8 c.6429+?_6430-? inv.). None of the participants showed evidence of systemic hyperfibrinolysis based on our testing protocol, though specific testing for plasminogen activator inhibitor or antiplasmin deficiency were not performed (Table 2 and *Online Supplementary Tables S3 and S4*). Of those diagnosed with BD, 29 (43%) had HMB as the sole complaint, 21 (31%) had one additional, 12 (18%) had two, four (6%) had three, and one participant had five additional bleeding symptoms. Of those without BD, 118 (88%) had HMB as the sole complaint; 12 (9%) had one, and 3 (2%) had two additional bleeding symptoms in addition to HMB (*Online Supplementary Table S5*).

Predictors of bleeding disorders

The results of the univariable logistic regression of potential predictors of BD are shown in Table 3. The final model (multivariable, stepwise logistic regression) included four predictors: younger age at first bleeding event, Hispanic ethnicity, non-presentation to ED, and ISTH BAT score of ≥4.

Time to diagnosis

Kaplan-Meier curves showed that the median time from the first bleed to BD diagnosis was four years (range 2-5) in the entire cohort, two years (range 1-3) in the anovulatory group, and six years (range 4-9) in the ovulatory group. There was a significant difference in time to diagnosis across groups (log-rank test, $P<0.0001$) (Figure 2).

Concomitant non-hemostatic disorders

Twenty-three participants with BD were diagnosed with additional disorders: three (1.5%) with polycystic ovarian syndrome, and four with uterine structural abnormalities (three with endometriosis and one with uterine polyps). Four participants without BD were diagnosed with vWF exon 28 polymorphism p.D1472H (suspected based on isolated decreased vWF:RCo) (Table 4). Only 100 participants underwent a joint exam for benign joint hypermobility (BJH); of those, 20 met criteria for BJH.

Discussion

Our study systematically investigated adolescents with HMB and showed that 33% had a BD. Almost 80% of

Table 3. Univariate and multivariate analyses of the association between baseline patient characteristics and bleeding disorder in the entire cohort.

Parameter	OR for BD	95% CI	*P*
		UNIVARIATE ANALYSIS	
Intercept			
Age, y	0·98	0.84, 1.14	0.802
Ethnicity			
Hispanic	1.95	1.03, 3.70	0.038
Non-Hispanic			
Race			
White	1·74	0.45, 6.65	0.416
Black	1·38	0.32, 5.90	0.665
Other			
Age at menarche, y	1.02	0.84, 1.25	0.789
Time to HMB, y	0·84	0.65, 1.09	0.199
Age at first bleed, y	0·74	0.66, 0.84	<0.0001
Refractory HMB			
Yes	1·72	0.90, 3.30	0.099
No			
Surgical bleeding			
Yes	4·57	1.28, 16.31	0.019
No			
Dental bleeding			
Yes	5·42	1.02, 28.78	0.047
No			
Presentation to ED for HMB			
Yes	0·50	0.26, 0.97	0.042
No			
Hospitalization for HMB			
No	2.03	0.93, 4.42	0.072
Yes			
pRBC			
Yes	0·55	0.24, 1.24	0.151
No			
Need for IV iron			
Yes	1·39	0.76, 2.54	0.275
No			
PBAC	1·001	1.0001, 1.002	0.036
ISTH BAT score			
≥3	1·83	0.70, 4.7	0.217
≥4	4·51	1.91, 10.64	0.0006
≤2			
FMH of bleeding or BD			
Positive	3.09	1.61, 6.42	0.0007
Negative			
FMH of GYN/OB bleeding			
Positive	2·23	1.16, 4.29	0.015
Negative			
Hemoglobin, g/L	0.99	0.97, 1.01	0.752
Ferritin, pmol/L	1.00	0.97, 1.02	0.980
		MULTIVARIATE ANALYSIS	
Intercept			
Age at first bleed, y	0·83	0.73, 0.96	0.011
Ethnicity			

Hispanic	2·48	1.13, 5.05	0.021
Non-Hispanic			
ED evaluation for HMB			
Yes	0·14	0.05, 0.38	<0.0001
No			
ISTH BAT score			
≥3	1·57	0.54, 4.13	0.435
≥4	8.27	2.60, 26.44	0.0004
≤2			
	C-statistic:	**0.78**	

BMI: body mass index; ED: emergency department; HMB: heavy menstrual bleeding; ISTH-BAT: International Society of Thrombosis Haemostasis-Bleeding Assessment Tool; pRBC: packed red blood cells; PBAC: pictorial blood assessment chart; TSH: thyroid-stimulating hormone; y: years.

those with BD had a diagnosis of either low vWF or vWD. Our findings suggest that BD are equally prevalent in the anovulatory or ovulatory pattern of menstrual bleeding. Identification of adolescents with BD is the first step in preventing delays in diagnosis and, by extension, long-term untoward complications of BD. HMB soon after menarche is traditionally deemed as "hormonal," and anovulation is the default etiology. These findings have implications for clinicians who routinely manage adolescents with HMB: screening or referral for screening for BD is appropriate, irrespective of the pattern of menstrual bleeding.

Seravalli *et al*. investigated the frequency of BD in adolescents, dividing participants into two groups based on whether abnormal uterine bleeding started in the first two years from menarche or later. Overall, 48% of adolescents were diagnosed with a hemostatic defect (18% with QPD, 14% with vWD, 13% with clotting factor deficiencies, and 7% with an increase in bleeding time), but there were no differences in the prevalence of BD between the groups (44% *vs.* 59%; *P*=0.17).[16] Philipp *et al*. also reported that adolescents and peri-menopausal women were just as likely to have hemostatic defects as were women aged 20-44 years;[17] the former age brackets representing periods of anovulatory menstrual bleeding. Furthermore, Vo *et al*. reported that adolescents with BD were more likely to perceive and report their menstrual cycles as irregular.[18] These studies had certain limitations, such as retrospective data collection, and a lack of uniform and comprehensive laboratory investigation.

In our cohort, younger age at first bleeding event, Hispanic ethnicity, non-presentation to the ED for HMB, and ISTH BAT score of ≥4 were identified as predictors of BD. Younger age at first bleeding event is known to be associated with hemostatic evaluation and BD diagnosis, representing those with an earlier phenotypic expression or more severe bleeding phenotype. Hispanic girls in our cohort were more likely to have a BD, even though non-Hispanics made up the majority. Previous studies have included mostly non-Hispanics; more specifically, women of eastern European ancestry and a lower prevalence of vWD and higher levels of VWF antigen, vWF activity, and FVIII have been reported in black women,[19,20] which can explain these findings. Adolescents who presented to ED for evaluation and management of HMB in our cohort were less likely to have a BD, which is similar to results from another multicenter analysis.[21] This may be further explained by: a) negative family history of HMB (60% of adolescents did not have a first-degree relative with HMB and the caregivers of these adolescents were likely unprepared to manage HMB at home); and b) 55% presenting to the ED had anovulatory bleeding (generally deemed difficult to manage with conventional route and doses of hormones).[22] Moreover, 67% of those with anovulatory bleeding were overweight or obese, the latter being associated with gonadal steroid hormone changes that result in disruption of ovulation and menstrual irregularities including HMB.[23,24] Previous studies show that adolescents who present acute symptoms and require hospitalization are more likely to have an underlying BD that was reported only in descriptive analyses, showing 19% and 33% of patients with abnormal uterine bleeding and coagulation disorders when compared with 74% and 67% without, respectively.[25-27]

When objectively assessing bleeding in patients with BD, consensus guidelines recommend the use of BAT.[28] The ISTH BAT has been shown to optimally identify BD in both adults and children; the pediatric cut-off able to optimally discriminate between no BD and a possible BD is a score of ≥3.[13] Instead, we identified a score of ≥4 to be predictive of BD. Recently, using identical data, ISTH-BAT was shown to be more sensitive for assessment of HMB in women with low vWF levels compared with other BAT, supporting a need to investigate and validate a higher "adolescent" specific cut-off.[29] The ISTH BAT score of ≥4 in those with BD was driven mostly by the presence of additional bleeding symptoms with HMB; 57% of adolescents with BD had other bleeding symptoms compared to 12% in those without BD. Previous data clearly show that the number of hemorrhagic symptoms is higher in the young when a more severe bleeding phenotype or disorder is present.[30,31] The presence of at least three bleeding symptoms, irrespective of severity, result in 99.5% specificity for the most common bleeding disorder, vWD, a finding that has been confirmed in the pediatric age group.[32]

The median time from onset of the first bleeding symptom to BD diagnosis was four years in the entire cohort, two years in the anovulatory, and six years in the ovulatory group. Adolescents with anovulatory HMB had heavier (mean PBAC score 427 *vs.* 345) or difficult to manage menses, resulting in an earlier referral and diagnosis, accounting for an earlier diagnosis. Lavin *et al*., on the other hand, have reported no differences in age at diagnosis for women with low vWF levels who reported HMB to physicians compared to those who did not go to the doctor (age 34.2 *vs.* 33.4 years; *P*=0.7).[29] Even though the time to diagnosis in our cohort is a significant improvement

Table 4. Prevalence of non-hemostatic disorders and concomitant disorders.

	Anovulatory HMB		Ovulatory HMB	
	BD (n=31)	No BD (n=69)	BD (n=36)	No BD (n=64)
PCOS	3	3	0	0
BJH**	3	7	6	4
Uterine structural ab.	1[@]	1[^]	3[@@]	0
Systemic disorders	6*	10[!]	1[#]	4[&]
Exon 28 polym.	0	1	0	3

ab: abnormalities; BD: bleeding disorder; PCOS: polycystic ovarian syndrome; BJH: benign joint hypermobility; polym: polymorphism. **BJH assessment was performed only on 100 participants. Systemic or medical disorders: *depression (n=4), remote history of cancer (n=1), and hypothyroidism (n=1); [!]depression (n=3), asthma requiring medications (n=3), remote history of cancer (n=3), hypothyroidism (n=1); #one had juvenile rheumatoid arthritis; [&]depression (n=1), diabetes mellitus (n=2); celiac disease (n=1). Uterine structural abnormalities; [@]one had endometriosis; [^]one had erosive vaginitis from tampon use; [@@]two were diagnosed with endometriosis, and one was diagnosed with uterine polyps.

from the average delay of 16 years previously reported in women with BD,[33] it highlights the importance of hematologists in the care of adolescents with HMB. For primary care practitioners, the relatively high prevalence of vWD in adolescent HMB is a reminder to test for vWD. A recent retrospective analysis of a large national claims database of 23,888 post-pubertal girls and adolescents with HMB observed a very low rate of screening for vWD of only 8% in those with HMB and 16% in those with severe HMB.[34]

The strengths of our study include the largest powered adolescent cohort ever prospectively examined. Participants underwent a uniform, protocolized evaluation for BD compared to "tiered" testing based on suspicion of a BD. Another finding of interest is an overall lower prevalence of QPD than that previously reported in the literature, where initial abnormal platelet aggregation was not repeated for confirmation. We diagnosed QPD based on reproducible findings, an approach that had been not undertaken in previous studies, leading to the overestimation of QPD (*Online Supplementary Table S4 and Online Supplementary Figure S1*).

Our study has some limitations. Although we consecutively enrolled unselected adolescents with HMB, they had, in effect, already been selected by their referring providers. This referral bias probably led to a higher frequency of BD in our center compared to primary care settings. This bias, however, is inherent to all studies carried out in tertiary care centers. The overall frequency of BD in our cohort is lower than that in previously reported data from other multidisciplinary clinics (33% *vs.* <60%) and is reflective of the stringent criteria used to diagnose BD. We also excluded patients referred for abnormal coagulation profiles, including initial abnormal vWF analysis, which may have under-estimated the prevalence of BD in our cohort.

We did not exclude participants on hormonal suppression for HMB. Even though PBAC scores were calculated for pre-hormonal cycles, it may have impacted PBAC scores and its predictive ability due to recall bias. Moreover, PBAC has not been validated for retrospective use or without using standardized brand pads and tampons. Because our study was conducted in large academic centers with dedicated Young Women's Blood Disorders clinics, our results are unlikely to apply to settings with a low prevalence of BD. Our time to diagnosis is subject to length bias; adolescents with severe bleeding phenotypes were likely referred earlier, leading to differences in time to diagnosis.

Our study will stimulate further research; the pediatric cut-off for an abnormal ISTH BAT score needs to be revisited for the adolescent age group. Even though we showed no difference in the frequency of BD according to HMB pattern, follow-up studies are in order on whether the efficacy of hemostatic-based therapies are equivalent. Finally, future studies are needed to assess the cost-effectiveness of selective testing in multidisciplinary clinics compared with universal screening across the population where the sole bleeding complaint could be HMB. Our predictive model also needs to be validated internally and externally in a larger population.

In summary, a high awareness, irrespective of the type of menstrual bleeding, is paramount to identify adolescents with BD.

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