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Utility of a screening tool for haemostatic defects in a multicentre cohort of adolescents with heavy menstrual bleeding

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Abstract

Introduction: Heavy menstrual bleeding (HMB) may be expected for many adolescents after menarche. Accurate assessment of HMB, a key component in the diagnosis of a haemostatic defect (HD) is a well-recognized challenge.

Aim: Our objective was to determine the diagnostic accuracy of an HMB-specific screening tool for HDs in adolescents with HMB, presenting to a secondary care setting.

Methods: Adolescents with HMB were evaluated for a HD at 4 US centres. A screening tool, the Philipp Tool, developed and validated in adult women with HMB, was administered. We modified the tool by assigning a score based on the number of affirmative responses. Sensitivity, specificity and likelihood ratios (LR) of a positive tool, modified tool, with a pictorial blood assessment chart (PBAC) score >185, and with serum ferritin 20ng/mL were calculated for HDs.

Results: Among 248 adolescents with HMB, 29% were diagnosed with HDs. Sensitivity, specificity and LR of a positive screening tool was HDs was 95% (range 88–99), 14% (9–21) and 1.1 (1–1.2), respectively. A score of 2, addition of a PBAC score >185 and ferritin 20ng/mL changed the sensitivity, specificity and LR of the tool to 72% (61–81), 94% (83–99), 76% (65–

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85); 60% (53–68), 24% (16–34) and 39% (31–47) and 1.8 (1.4–2.2), 1.2 (1.1–1.4) and 1.2 (1–1.4) respectively.

Conclusion: Although sensitive, the discriminative ability of the tool to identify adolescents with HDs from those without, who presented with HMB, was low. Further research is needed to optimize or develop an adolescent specific HMB tool for secondary care settings.

Keywords

Philipp Screening Tool; Heavy Menstrual Bleeding; Bleeding Disorders; Bleeding assessment tool; Haemostatic Disorders

Introduction

Menstrual problems are common in adolescence.[1] Adolescents frequently have irregular and/or painful cycles, but occasionally experience unpredictable, prolonged or excessive menstrual bleeding that can become a medical emergency. [2, 3] Heavy menstrual bleeding (HMB) is often multifactorial. [4] Of the possible causes, anovulation is likely to be the most common reason for HMB in this age group [5] but other aetiologies, such as underlying haemostatic disorders (HDs) are often present. [6] A growing body of literature suggests that 10–62% of adolescents with HMB may have an underlying HD. [7–10]

The reporting and interpretation of HMB is subjective. Wide ranges of reported prevalence, difficulty in discerning normal from excessive bleeding, widespread use of hormones and the mundane nature of the ‘heavy period’ complaint makes identification of HDs in adolescents challenging. [6] Bleeding assessment tools (BATs) can accurately distinguish normal from abnormal bleeding, identify patients with mild bleeding disorders, and can be used to describe bleeding severity. Most validated BATs quantify overall bleeding symptoms, including complaints of HMB. An HMB specific tool with high specificity would be helpful to narrow down the subset of adolescents with HMB who are referred to secondary care settings, when the suspicion of HD is high, and patients may be subjected to extensive laboratory testing.

Philipp et al developed the Philipp tool, as a screening tool to screen for HDs in 146 women (“the development cohort” from here forward), aged 18–50 years with pictorial blood assessment chart (PBAC) score > 100 and a normal pelvic ultrasound [11]. Age differences were observed when the screening tool was evaluated without the addition of PBAC. The overall sensitivity of the tool for HDs was 82%, which increased to 95% with the addition of PBAC >100. The sensitivity was lowest for adolescents (62% for 38 subjects < 19 years), however, when combined with PBAC, the sensitivity increased to 92%. The screening tool was subsequently evaluated in a prospectively recruited US multisite study of 217 women with HMB between 18–50 years (“the validation cohort” from here forward). [11] The screening tool showed a sensitivity of 89% for a HDs overall, 93% with the addition of iron deficiency (defined as serum ferritin < 20 ng/mL), and 95% with an increased PBAC score cut-off > 185. The specificities were 16, 6 and 11% respectively. The adolescent cohort was not separately analysed in the multisite validation cohort, and neither cohort included girls in early to mid-adolescence. The objective of our study, therefore, was to evaluate the

diagnostic utility of the screening tool in adolescents referred to a secondary care setting, (multidisciplinary young women's haematology clinics) for evaluation of HMB. We hypothesized that assigning a scoring system to the Philipp tool, from 1 through 4, compared to just a 'positive' or 'negative' tool, would increase the discriminatory power or specificity for HDs in adolescents with HMB.

Material and methods

Post-menarcheal adolescents through age 18 years, referred for or with complaints of self-perceived HMB without an already established HD or use of anticoagulants were eligible to participate. Subjects were enrolled from the Young Women's Blood Disorders Program at The University of Texas Southwestern Medical Center (UTSW), Dallas, Texas [12], The Young Women's Hematology Program at Nationwide Children's Hospital (NCH) [8], The Hemostasis and Thrombosis Center at The Rainbow Babies and Children's Hospital and Akron Children's Hospital, Ohio after informed consent and/or assent between 2014 and 2016.

Laboratory testing

All participants underwent laboratory testing that included complete blood count and serum ferritin. A systematic approach for testing was undertaken, as previously described [6, 12], except approach to von Willebrand disease (VWD) testing with respect to oral contraceptives (OCs) and qualitative platelet dysfunction. All participants were tested for prothrombin time, activated partial thromboplastin time, fibrinogen and VWD. Participants were also screened for thyroid disorders with thyroid stimulating hormone and free T4 at UTSW.

VWD testing with respect to OCs: Blood samples were obtained irrespective of menstrual cycle phase at all centres. As VWD testing on OCs containing 30–35 µg of oestrogen is unlikely to affect the laboratory diagnosis of VWD [13–15], none of the participants were taken off OCs for testing. For those on OCs, all were tested on standard dose (containing 30–35 µg of oestrogen), monophasic once-a-day pill (vs. on an OC taper). Testing for participants from The Rainbow Babies and Children's Hospital and Akron Children's Hospital was performed either off OCs or during placebo weeks (Supplemental Table 1A).

Qualitative platelet dysfunction: For platelet aggregation testing, all subjects were asked to withhold non-steroidal anti-inflammatory agents, aspirin, other platelet impairing medications, allergy medications and any other over the counter herbal supplements for 7 days or more before testing.

At UTSW, platelet aggregation and ATP release were performed using whole blood impedance and chemiluminescence (Chronolog, Haverton, PA) on all participants as first tier. At Ohio centres, platelet aggregation was done as second tier testing, when suspicion of a bleeding disorder was high and all tests listed under 'laboratory testing' were normal. At NCH, whole blood platelet aggregation and platelet electron microscopy were used to diagnose qualitative platelet dysfunction. At Rainbow Babies and Children's Hospital,

platelet aggregation using platelet rich plasma (PRP) and at Akron Children's Hospital, platelet function analyser (PFA-100; Siemens Healthcare Diagnostics, Deerfield, IL) was used as the screening test for qualitative platelet dysfunction, and platelet aggregation using PRP was used to confirm abnormal findings (Supplemental Table 1B).

Clotting factor deficiencies: Coagulation factors VII, IX, XI clotting assays, measured using factor deficient plasmas, and FXIII, measured by a chromogenic assay were only tested for all participants at UTSW.

Pictorial Blood Assessment Chart (PBAC)

A PBAC score was computed for subjects enrolled at UTSW only, and an average score of three cycles were taken as the final score. All subjects were instructed on how to complete the PBAC score for their next menstrual cycle. For subjects already on hormonal suppression for HMB, this was completed for cycles prior to initiation of hormonal suppression by recall (59% of subjects) or using data from personally maintained menstrual calendars or smartphone apps (41%). The PBAC score is quantified by menstrual blood loss determined by visual assessment of the degree of saturation of sanitary pads and tampons, presence and size of clots and flooding, as previously described. [16]

Screening Tool

All participants completed the screening tool called the Philipp Tool. [17] It contains 8 questions in 4 categories: 1) severity of HMB; 2) history of treatment of anaemia; 3) family history of a diagnosed bleeding disorder and 4) personal history of treatment of excessive bleeding after specific haemostatic challenges (Table 2). The severity of HMB is assessed by three questions encompassing duration of menstrual flow as menstrual bleeding for 7 days and presence of "gushing" *or* "flooding" during every or most periods or bleeding through a tampon or napkin in 2 hours or less during every or most periods. Personal history of bleeding after haemostatic challenges is quantified for specific challenges that include dental extractions or procedures, surgeries and childbirth. The screening tool is considered positive for any affirmative response to any of the four categories. We further modified the screening tool by assigning a score from 1–4, based on the number of affirmative responses received for each of the 4 categories, whereby a positive tool reflected a score of 1.

Haemostatic defects

HDs were defined as low VWF levels, VWD, qualitative platelet dysfunction, isolated thrombocytopenia (familial/inherited) and/or clotting factor deficiencies. Low VWF was defined as VWF:Ag or VWF:RCo between 30–50% on 2 occasions and VWD was diagnosed when VWF:Ag or VWF:RCo was < 30% on 2 occasions, using NHLBI guidelines. [18] Qualitative platelet dysfunction was diagnosed when there was impaired aggregation to one or more agonists (except isolated epinephrine defects) or impaired ATP secretion with reproducible findings on 2 occasions. [19] A cut-off of 2 or fewer dense granules/platelets was used as a diagnostic cut-off to diagnose platelet storage pool disorders.[20] Clotting factor deficiency was defined when a clotting factor level was below the age based reference range. Thrombocytopenia was defined as platelet count < 150/cumm.

Iron deficiency/iron deficiency anaemia

Anaemia was defined as haemoglobin <11 g/dL and iron deficiency or low ferritin levels were defined as serum ferritin levels <20 ng/mL.

Statistical analyses

We planned to enrol and obtain screening tool assessments for at least 200 patients in order to obtain adequate 95% confidence interval estimates for sensitivity and specificity with marginal errors of, at most, $\pm 10\%$. [21] Demographic and clinical characteristics in the study population were summarized with descriptive statistics. To assess ability for the screening tool to predict HDs, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and likelihood ratios (LR) and their corresponding 95% confidence intervals were calculated for the Philipp tool as a stand-alone tool, with a modified scoring system, with PBAC score of >185 and serum ferritin <20 ng/mL. Statistical analysis was performed using the base R statistical package (R Foundation for Statistical Computing, Vienna, Austria).

Results

The study included 248 participants with HMB from four centres: UTSW (140 participants) and NCH (70 participants), Rainbow Babies and Children's Hospital (21 participants), and Akron Children's Hospital, (17 participants). Eighty percent of the cohort was non-Hispanic (199/248). Over half of the participants were anaemic (52.3%; 113/248). The mean Hgb was 10.9 ± 2.8 g/dL (range: 3.3–15.2). The mean serum ferritin in all participants was 13.6 ± 14.2 ng/mL (range: 0.9–72). Serum ferritin <20 ng/mL was found in 66% and 26% were iron deficient without concomitant anaemia. Only one participant at UTSW had an established diagnosis of hypothyroidism, on levothyroxine. The mean PBAC score was 480 (SD: 291; range 100–1500; n= 139) (Table 1).

On testing, 29% (72/248) were diagnosed with a HD. VWD was present in nearly 11% and low VWF in 9% of participants. Qualitative platelet dysfunction was present in 7% and three participants (~1%) turned out to be new haemophilia A carriers.

The response rate for individual and contingency questions on the tool was 100%. Among contingency questions, 13% reported a family history of a bleeding disorder, 6% reported problems after tooth extraction or dental surgery and 7% reported bleeding problems after surgery (Table 2). 25 subjects had a 'negative' screening tool; none of these subjects were diagnosed with a HD (Figure 1).

The screening tool demonstrated 95% sensitivity and 14% specificity for HDs (Table 3). With the scoring system, we found 95 subjects with a score of 2, 26 subjects with a score of 3 and 3 subjects with a score of 4. We calculated the sensitivity of the screening tool with a score of ≥ 2 , thereby including all participants with a score of 2, 3 and 4 and found that the sensitivity decreased to 72% but specificity increased to 60%. The specificity of a positive tool in combination with a PBAC score of > 185 and low serum ferritin (< 20 ng/ml) was 24% and 39% when added to a positive tool (or score of 1) (Table 3). Results of the performance of the tool for UTSW, the only centre where PBAC was completed, and age

group <14 yrs. vs.> 14 yrs. are reported separately in supplemental material (Table 3A and 3B).

Discussion

Our study demonstrated that the Philipp tool, either as a stand-alone instrument or with modifications, when evaluated in specialty haematology clinics, was not diagnostic for HDs. In a referral setting like ours, where the prevalence of HDs is likely to be higher compared to a primary care setting, the intent was to assess its performance as a diagnostic tool – a tool that can clearly demarcate between those with and without HDs, identify those that need subsequent comprehensive coagulation testing, or possibly, inform bleeding phenotype. A high specificity, therefore, was desirable as the suspicion of a HD is already high by the time an adolescent with significant or hard to manage HMB is referred to a secondary care setting.

We believe the reasons for our findings are as follows: The specificity of the tool for HDs is dependent on the proportion of participants without a HD and without HMB, or in other words, the true negatives. Because every participant in our cohort was referred for significant HMB and completed a screening tool weighted towards HMB and its aftermath (anaemia in this case), the specificity decreased at the cost of high sensitivity. The posttest probability (or positive predictive value) of a HD in our cohort was 35%, not very different from the pre-test probability of 29%, rendering it as a tool that does not add additional information regarding better identification of adolescents with HDs. We also calculated LR_s to discern further the diagnostic accuracy of the tool. The positive LR of the tool for a HD was only 1.1 (Table 3). Our findings are also supported by findings of low specificity of the tool in another cohort of women with a similar prevalence (30%) of HDs[22]. The sensitivity and the specificity of the tool in this study was 67% and 24%, and positive LR was 0.87.

Laboratory or imaging tests, signs, and symptoms, irrespective of the prevalence of a disorder, can be combined to improve either the sensitivity or specificity of a survey tool, provided the results are independent of each other. Using this principle, the addition of a PBAC score >185 or iron deficiency improved specificity, though only modestly, and predictably decreased sensitivity. The PBAC is a semi-quantitative method that allows women to track the number of pads or tampons used for a menstrual period, as well the degree of soiling. The sensitivity and specificity of the PBAC for HMB is 86% and 89%, respectively, in adult women. [23, 24] The PBAC cut off chosen during the development phase of the screening tool was 100, traditionally used to define HMB or a blood loss of > 80 millilitre but a cut-off of > 185 was used for the validation cohort. [23, 25] We incorporated the higher PBAC cut-off but speculate that the addition of PBAC scores to the tool likely thwarted the effect, if any, of a subset of adolescents with more severe HMB or a bleeding phenotype (e.g. those with family history of bleeding disorder or with bleeding after haemostatic challenges).

Adolescents have much higher PBAC scores than older women.[26] Dietrich and colleagues evaluated PBAC scores in adolescents, who self-identified as having heavy, normal, or light periods. The mean PBAC score for the entire cohort was 195 but was quite different when

the three groups were analysed separately – 362, 136 and 44 respectively, for subjects in heavy, normal or light periods groups. Twenty percent of subjects in the ‘heavy group’ were diagnosed with a bleeding disorder while there were no patients with bleeding disorders in the other two groups. [26] We also found uniformly elevated PBAC scores across our cohort (median PBAC score of 507; only ~13% had a PBAC <185). Like high PBAC scores in adolescents in HMB, iron deficiency is very common, irrespective of the aetiology of HMB. [27, 28] The mean ferritin of our cohort was ~ 13 ng/mL and 66% were iron deficient. Iron deficiency, like high PBAC values, simply represented heavier periods and did not impact specificity, as each element of the combination was not independent from each other.

Assigning a scoring system to capture elements in the tool independent of each other, also, only modestly improved specificity. The most common scores for our cohort were 1 and 2 (95 subjects in each category, marked for HMB and history of treatment of anaemia). We analysed the specificity of the tool by using the score 2 for heavy bleeding and either a positive family history of bleeding disorders or a history of bleeding after haemostatic challenges. The specificity of the tool improved to 34.6% (CI: 24.3–46). We believe small numbers of subjects – 15 and 17– that bled after dental and surgical procedures respectively, may have contributed to these findings. This is not surprising as paediatric patients with HDs generally have not accumulated many haemostatic challenges, and HMB is often the sole complaint in women with such disorders.

The strengths of our study include the largest cohort of adolescents of HMB studied prospectively and a multicentre population, which increases the validity of our findings. Even though the approach toward diagnosis of HDs had differences across centres, it reflects real-world practices. The PBAC tool was collected only at one centre (See supplementary material for sensitivity, specificity and LR ratios for HDs for UTSW only), which is also a limitation. It is possible that having this information from all centres may have changed results; however, review of the PBAC scores at NCH for other on-going studies show uniformly high PBAC scores for adolescents with HMB (unpublished data). Subjects were not provided or requested to use the same brand of tampons, which may have influenced the PBAC scores. The PBAC score has been validated when used prospectively, therefore, another limitation is that the PBAC was obtained by recall (59% of subjects) or using data from menstrual calendars/apps (41%) for those subjects that had already initiated hormonal suppression (51%) for HMB. To circumvent this issue, caregivers of these subjects, generally mothers were interviewed regarding the subjects’ HMB to assess accuracy of recall; most reported they were ‘quite sure’ or ‘sure’ of the accuracy of their daughters’ responses. In addition, adolescents who reported PBAC scores < 100 or > 1000 were interviewed a second time for under- or over-reporting, and inconsistencies were resolved.

In summary, the findings of this paper highlight the need for future research on adolescent specific HMB tools for a secondary care setting. Philipp tool will detect almost all adolescents with HD but will have a high proportion of high false positive results if used in a secondary care setting. Perhaps the expectation that one bleeding assessment tool can both be highly sensitive and specific is far too ambitious but it challenges us to optimize our tools. Until such a tool is developed, comprehensive haemostatic testing is likely required to rule out a HD in adolescents with significant HMB.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Diagnostic Test Characteristics of the Philipp Tool for a Haemostatic Defect (HD) in Adolescents with Heavy Menses

Table 1.

Demographic Characteristics of Study Participants

	N (%)	Mean± SD (Range)
Age		15 (10–18 yrs.) *
Race		
White	171 (69)	
Black	52 (21)	
Others [#]	25 (10)	
HDs		72 (29)
VWD	27 (11)	
Low VWF	23 (9)	
Qualitative Platelet Dysfunction	18 (7)	
FVIII deficiency	3 (1)	
Familial Thrombocytopenia	1 (0.4)	
Anaemia		113 (52.3)
Haemoglobin		10.9 ± 2.8 (3.3–15.2)
Iron deficiency		164 (66%)
Ferritin		13.6 ± 14.4 (0.9–72)
PBAC (n = 139)		480 ± 291 (100–1500)

* Age is reported as median with range

[#] Others include Asians; HD, haemostatic defects; VWD, von Willebrand Disease; VWF, von Willebrand factor; PBAC, pictorial blood assessment chart

Table 2.

Philipp tool questions and responses

Question	% Response
Q1. How many days did your period usually last, from the time bleeding began until it completely stopped?	
< 7 days	17
7 days	82
I don't know	1
Q2. How often did you experience a sensation of "flooding" or "gushing" during your period?	
Every or most periods	70
Never, rarely, or some periods	26
I don't know	4
Q3. During your period did you ever have bleeding where you would bleed through a tampon or napkin in < 2 hours?	
Yes	67
No	31
Q4. Have you ever been treated for anemia?	
Yes	58
No	42
Q5. Has anyone in your family ever been diagnosed with a bleeding disorder?	
Yes	13
No	85
I don't know	2
Q6. Have you ever had a tooth extracted or had dental surgery?	
Yes	25
No	75
Q6a. Did you have problem with bleeding after tooth extraction or dental surgery?	
Yes	24
No	76
Q7. Have you ever had surgery other than dental surgery?	
Yes	30
No	70
Q7a. Did you have bleeding problem after surgery?	
Yes	7
No	93
Q8. Have you ever been pregnant?	
Yes	0
No	100

Table 3.
Predictive Value of the Screening Tool, Modified Screening Tool and Screening Tool combined with PBAC and Serum Ferritin

Variable	Sensitivity	Specificity	PPV	NPV	+LR	-LR
<u>Screening Tool Only</u>						
Positive	95 (88–99)	14 (9 – 21)	35 (33–37)	86 (68–94)	1.1 (1–1.2)	0.36 (0.1–1)
Tool 2	72 (61–81)	60 (53–68)	47 (41–53)	47 (41–53)	1.8 (1.4–2.2)	0.5 (0.3–0.7)
<u>Screening Tool & PBAC^a</u>						
Positive Tool & PBAC > 185	94 (83–99)	24 (16 – 34)	39 (30 – 49)	88 (70–96)	1.2 (1.1–1.4)	0.2 (0.1–0.6)
Tool 2 & PBAC > 185	73 (59 – 85)	57 (46 – 67)	48 (36 – 60)	80 (68 – 89)	1.7 (1.3–2.1)	0.5 (0.7–0.7)
<u>Screening Tool & Serum Ferritin</u>						
Positive & Ferritin 20	76 (65–85)	39 (31–47)	39 (35 – 43)	76 (66–83)	1.2 (1.0–1.4)	0.6 (0.4–0.9)
Tool 2 & Ferritin 20	59 (47–70)	68 (59–75)	48 (41–56)	76 (70–81)	1.8 (1.4–2.4)	0.6 (0.4–0.8)

^aData available on 139 patients

+LR, positive likelihood ratio;

–LR, negative likelihood ratio;

PBAC, pictorial blood assessment chart.

Values in parentheses are 95 percent confidence intervals