Original Study

Hematologic Considerations and Management of Adolescent Girls with Heavy Menstrual Bleeding and Anemia in US Children's Hospitals

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A B S T R A C T

Study Objective: To assess the frequency, severity, and inpatient management of girls admitted with heavy menstrual bleeding and iron deficiency anemia at US children's hospitals, with a focus on hematologic considerations.
Design: Retrospective multicenter cohort study from October 2012 through September 2015.
Setting: Children's hospitals submitting data to the Pediatric Health Information System.
Participants: Female patients, age 8-18 years, admitted with heavy menstrual bleeding and anemia as either a primary or secondary diagnosis. Patients with cancer, immune thrombocytopenic purpura, aplastic anemia, and pregnancy were excluded.
Interventions and Main Outcome Measures: Hemostatic evaluation; provision of iron therapy.
Results: We identified 1183 admissions (1134 unique patients). Patients' median (interquartile range) age was 14 (11-17) years. Forty-one percent were Caucasian (n = 480), 31% African American (n = 371), and 26% Hispanic ethnicity (n = 310). Intensive care use occurred in 5% of admissions (n = 56). Hemostatic assessment was inconsistent; 15% (n = 182) had no such evaluation. Two-thirds (n = 797; 67%) involved transfusions, 37% (n = 433) received no inpatient iron therapy, and 17% (n = 197) received no hormonal or antifibrinolytic therapy. Hemostatic evaluation was associated with intensive care use: odds ratio (OR), 4.80 (95% confidence interval [CI], 1.16-19.86; $P = .03$); emergency department visit: OR, 2.60 (95% CI, 1.86-3.65; $P < .01$); private insurance: OR, 1.62 (95% CI, 1.12-2.35; $P = .01$); and younger age: OR, 0.84 (95% CI, 0.77-0.92; $P < .01$).
Conclusion: Hundreds of girls with heavy menstrual bleeding and anemia are hospitalized at US children's hospitals each year with variable inpatient hematologic evaluation and management. Future guidelines should emphasize early identification of at-risk patients and promote effective implementation strategies to reduce the burden of this preventable complication.
Key Words: Bleeding disorder, Hemostatic evaluation, Transfusion, Hormonal therapy

Introduction

Heavy menstrual bleeding (HMB), defined as bleeding for longer than 7 days or blood loss that exceeds 80 mL per cycle, is common among young women. Up to 40% of women might experience HMB and, of those, up to 20% might have an underlying bleeding disorder.[1–3] In nonpregnant women, HMB is the most common cause for iron deficiency and iron deficiency anemia (IDA). Globally among children and adolescents, IDA was the leading cause of years lived with disability in 2013, affecting 619 million.[4] In the United States, it affects an estimated 9%-16% of young women.[5] In adolescent girls, iron deficiency is associated with poor concentration,[6] fatigue,[7] restless legs,[8] and decreased school performance.[9] When unrecognized, HMB can progress to severe anemia leading to emergent medical care and hospitalization. Young women who require admission for symptomatic anemia or transfusion support have a 20%-30% higher likelihood of having a primary bleeding disorder.[10]

Since 2006, the American Academy of Pediatrics and American College of Obstetricians and Gynecologists have recommended considering menstruation as a "vital sign" in girls and adolescents to promote identification of atypical bleeding and allow for early evaluation and treatment of menstrual and/or bleeding disorders.[11,12] Although symptomatic anemia is considered suggestive of an underlying bleeding disorder,[13] screening recommendations for iron deficiency in adolescent girls are inconsistent. Guidelines on the management of HMB in adolescents from the North American Society of Pediatric and Adolescent Gynecology, published in 2017, recommend a tiered approach to the initial laboratory evaluation of such patients. The guidelines suggest all adolescents with HMB have assessment of a complete blood count, type and screen, and undergo

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screening for IDA or iron deficiency via a serum ferritin measurement.[1] Identification of iron deficiency would allow for early interventions such as hormonal and iron therapies, before the onset of anemia, in at least a subset of at-risk girls. The guidelines additionally include an initial minimum hemostatic evaluation with a prothrombin time (PT), partial thromboplastin time (PTT), and fibrinogen. Further workup may be tailored on the basis of a patient's individual and family history, particularly an evaluation for von Willebrand disease, the most common inherited bleeding disorder, and platelet function defects.[14]

Ideally, all patients with HMB would be identified early to prevent the development of IDA. However, for those who require hospitalization because of severe anemia, acute management might include packed red blood cell transfusion, iron therapy, and intravenous estrogens and/or high dose oral hormonal medications.[1] Limited data exist regarding the scope of young women affected with HMB and IDA as well as hematologic management considerations in such patients.[15,16] Thus, our aim was to assess the frequency, clinical severity, and management of girls and adolescents with IDA and HMB who require inpatient hospitalization at US children's hospitals.

Materials and Methods

In this retrospective multicenter cohort study we used the Pediatric Health Information System (PHIS) administrative database. The PHIS database contains comprehensive inpatient data from 48 not-for-profit tertiary care pediatric hospitals, or approximately 25% of US pediatric centers. Participating institutions represent diverse geographic locations, bed number, and average daily census and are affiliated with the Children's Hospital Association (Overland Park, KS). The data warehouse is managed by Truven Health Analytics (Ann Arbor, MI), and assurance of data quality and reliability is a joint effort between the Children's Hospital Association and participating hospitals. Research using the PHIS database, a deidentified data set, was not considered human subjects research in accordance with the Common Rule (45 CFR 46.102(f)) and was exempt from institutional review board review.

Participants were female and 8-18 years of age admitted to a PHIS hospital between October 1, 2012 and September 30, 2015 with HMB and anemia as either a primary or secondary diagnosis code. International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes confirmed the presence of both conditions during admission and were used to identify comorbid conditions (Supplemental Table 1). Hospitals with incomplete billing data during the study period were excluded. Patients with cancer, immune thrombocytopenic purpura, aplastic anemia, and pregnancy were excluded. ICD-9-CM codes for sexually transmitted infections, polycystic ovarian syndrome (PCOS), and obesity were collected but not considered exclusion criteria (Supplemental Table 1). Procedure codes were assessed for receipt of transfusion, and pharmaceutical billing codes were assessed for iron (intravenous and oral preparations), all hormone therapies, and all coagulants. Patients receiving anticoagulant therapy were not excluded. Evaluation for an underlying bleeding disorder was defined as assessment of any of the following laboratory tests: PT, PTT, fibrinogen, coagulation factor levels, von Willebrand factor activity (ristocetin), or antigen testing, and platelet function studies (platelet function analyzer-100 or platelet aggregation). Data regarding admitting team, consulting physicians, intensive care unit stays, and hospital charges were also collected.

Study variables were summarized using frequencies and percentages for categorical variables. For continuous variables, data were summarized with median and interquartile range (IQR). To assess predictors of laboratory screening for bleeding disorders or receipt of iron, logistic regression models were used and results presented with odds ratios (ORs) and corresponding 95% confidence intervals (CIs). χ^2 or Fisher exact tests were used to compare percentages among groups. *P* values less than .05 were considered statistically significant. All statistical analyses were completed using SAS software, version 9.3 (SAS Institute, Cary, NC).

Results

During the 3-year study period, a total of 1183 admissions (1134 unique patients) from 45 PHIS hospitals met inclusion criteria; 3 hospitals were excluded for incomplete billing data. Patients' median age was 14 (IQR, 11-17) years (Table 1). Median length of hospital admission was 2 (IQR, 1-2) days. Intensive care use occurred in 5% of admissions (n = 56). Thirteen percent (n = 150) had an ICD-9-CM code for obesity, 2% (n = 27) had a code for PCOS, and approximately 1% (n = 12) had a code for sexually transmitted infections. Diverse racial groups were represented, and 96% (n = 1135) of those admitted were insured. African American women, Hispanic women, and those with a form of public insurance (Medicaid, Children's Health Insurance Program) were over-represented compared with national averages at 31% (n = 371), 26% (n = 310), and 61% (n = 724) of admissions, respectively.[17] The median total adjusted charges per admission was $15,676 (IQR, $11,041-$22,847)

Table 1
Clinical Characteristics of Admissions for HMB and Anemia in US Children's Hospitals, 2012-2015 (N = 1183)

Variable	n	%
Age		
8-10 years	34	3
11-14 years	674	57
15-18 years	475	40
Race		
White/Caucasian	480	41
Black/African American	371	31
Asian/Pacific Islander	53	4
Native American	4	<1
Other	198	17
Missing	77	7
Ethnicity		
Hispanic	310	26
Not Hispanic	781	66
Missing	92	8
Insurance Type		
Public (CHIP, Medicaid)	724	61
Private	411	35
Other (charity, self-pay)	48	4

CHIP, Children's Health Insurance Program; HMB, heavy menstrual bleeding.