

BRIEF REPORT

Adequate menstrual suppression in adolescents with inherited bleeding disorders often requires multiple treatment changes: Retrospective cohort study of a multidisciplinary clinic

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This work was presented as an abstract under the title "Adequate Menstrual Suppression in Adolescents with Bleeding Disorders Often Requires Multiple Treatment Changes: Five-Year Experience of a Large Multidisciplinary Clinic" at International Society of Thrombosis and Haemostasis Congress 2023.

Abstract

Heavy menstrual bleeding (HMB) is often the presenting symptom for females with inherited bleeding disorders (IBD). Multidisciplinary clinics leverage the expertise of hematologists and women's health specialists. This study characterizes the complexity of HMB management for adolescents with IBDs from a large multidisciplinary clinic. Adolescents often required multiple different menstrual suppression treatments, with only about 20% achieving acceptable suppression with their first treatment. Adolescents switched therapy most often for uncontrolled bleeding, followed by adverse effects, and patient preference. Given the difficulty in achieving adequate menstrual suppression, multidisciplinary clinics offer necessary expertise in accomplishing bleeding control with minimal adverse effects.

KEYWORDS

bleeding disorders, heavy menstrual bleeding, multidisciplinary care, treatment, women's health

1 | INTRODUCTION

Heavy menstrual bleeding (HMB) is a common presentation for females with inherited bleeding disorders (IBD), and is the most common bleeding symptom for females with IBD.^{1–6} The prevalence of bleeding disorders in adolescents referred to a hematologist for HMB was 33% in a prospective multicenter study.⁷ Treatment of HMB in this population can be challenging given the contributions of hemostatic defects and pubertal hormonal changes. To provide optimal care for this population, a model for Centers of Excellence for females with IBD was described, and implementation has been supported by the Foundation for Women and Girls with Blood Disorders.⁸ Centers of Excellence are multidisciplinary clinics consisting of both hematologists and women's health specialists (gynecologists or adolescent medicine physicians); they have increased in numbers throughout

the United States to provide specialized care to this cohort. Initial treatment recommendations do not vary from individuals without IBD; however, achieving HMB suppression can be challenging.^{2,9,10} One cohort study found that about half (46.4%) of adolescents with IBD failed their initial menstrual suppression therapy.¹¹ Another study found that only 17% of women with HMB and IBD were satisfied with their menstrual control on first-line therapy.¹⁰ This study aims to characterize the care at a large multidisciplinary clinic, identifying optimal strategies for menstrual suppression and reasons for treatment failure.

2 | METHODS

For this retrospective cohort study, we reviewed the charts of adolescents with IBD seen in the "Young Women's Bleeding Clinic" at the Hemophilia of Georgia Center for Bleeding and Clotting Disorders at Children's Healthcare of Atlanta from 2018 to 2022. This clinic

Abbreviations: COC, combined oral contraceptive; HMB, heavy menstrual bleeding; IBD, inherited bleeding disorder; IDA, iron deficiency anemia; POP, progesterone only pill; QOL, quality of life.

TABLE 1 Subject demographics.

	Adolescents with HMB and a bleeding disorder N = 71
Age at first visit (years)	16.4 [14.3–17.5]
Race	
Black	26 (36.7%)
White	43 (60.6%)
Declined	2 (2.8%)
Ethnicity	
Hispanic	15 (21.1%)
Menstrual history	
Age at menarche	11 [10–12]
Periods heavy at menarche	48 (67.6%)
Bleeding disorder diagnosis	
Factor VII deficiency	5 (7.0%)
Factor VIII deficiency	1 (1.4%)
Factor XI deficiency	1 (1.4%)
Platelet defect	5 (7.0%)
von Willebrand disease	59 (83.1%)
Clinical findings	
Bleeding 7+ days	61 (85.9%)
Flooding	47 (66.2%)
Change protection every 2 hours or more	46 (64.8%)
History of iron deficiency anemia	38 (53.5%)
Family history of bleeding disorder	6 (8.5%)
Dental bleeding	6 (8.5%)
Adequate menstrual suppression at most recent visit	
Yes	56 (78.9%)
No	6 (8.5%)
Unknown	9 (12.7%)
Number of menstrual suppression treatments	3 [1–4]
Reason for switching menstrual suppression (N = 129)	
Ineffective/bleeding	71 (55%)
Adverse effect	29 (22.5%)
Patient preference	11 (8.5%)
Compliance	8 (6.2%)
Contraindication to current therapy	6 (4.7%)
Unknown	3 (2.3%)
Desire contraception	1 (0.8%)
Anemia treatments	
Oral or intravenous iron therapy	41 (57.7%)
Red blood cell transfusion	9 (12.7%)
Emergency department visit	17 (23.9%)
Hospitalization	10 (14.1%)

(Continues)

TABLE 1 (Continued)

	Adolescents with HMB and a bleeding disorder N = 71
Concurrent diagnoses	
Migraine	7 (9.9%)
Congenital heart disease	3 (4.2%)
Anxiety	5 (7.0%)
Connective tissue disorder	2 (2.8%)
Polycystic ovarian syndrome	5 (7.0%)

Note: Median with IQR or n (%).

serves adolescents with known IBD. Data were extracted through manual chart review, and included demographic information, diagnoses, pertinent laboratory results, medications, and reasons for medication discontinuation. Any reported menstrual suppression was recorded, including therapies prior to comprehensive clinic referral. HMB was defined as bleeding lasting 7 or more days, changing protection every 2 hours or more, flooding, or menstrual bleeding interfering with quality of life (QOL).^{12,13} A subject achieved adequate menstrual suppression when they no longer met the definition of HMB.

3 | RESULTS

During the 4-year study period, the clinic served 71 patients with IBD and HMB. The median age was 16.5 years (interquartile range [IQR]: 15.1–17.5). The majority were Caucasian (60.6%), and 21.1% were of Hispanic ethnicity. Von Willebrand disease was the most common IBD (83%), followed by platelet function defects and factor VII deficiency (7% each). The median age of menarche was 11 years (IQR: 10–12), and 67.6% reported HMB since menarche. Prolonged bleeding (≥ 7 days) was seen in 86% of individuals, 66.2% reported flooding episodes, and 64.8% reported need for frequent changes of menstrual products. A history of iron deficiency anemia (IDA) was reported in 53.5%; most were treated with oral or intravenous iron (57.7%), and nine individuals (12.7%) previously required blood transfusion for severe anemia from HMB. Almost a quarter visited the emergency department for HMB, and 10 were hospitalized. No subjects were admitted from clinic. Almost 30% of the subjects had a concurrent diagnosis that impacted treatment decisions (Table 1).

The median number of menstrual suppression treatments was three (range = 1–8), and only 15 patients (21.1%) achieved acceptable menstrual suppression with their first treatment. Eight were on a progesterone only oral therapy (POP), six were on a combined oral contraceptive (COC), and one was on intramuscular progesterone. The Sankey diagram (Figure 1) depicts treatment changes over time. Most patients were initially started on hormonal therapy with a COC (40%) or POP (35.2%) (Figure 1B). While an intrauterine device (IUD) was not an initial therapy, it was the final solo therapy for 13 individuals, and included in combination therapy for two (21%). The order of therapy

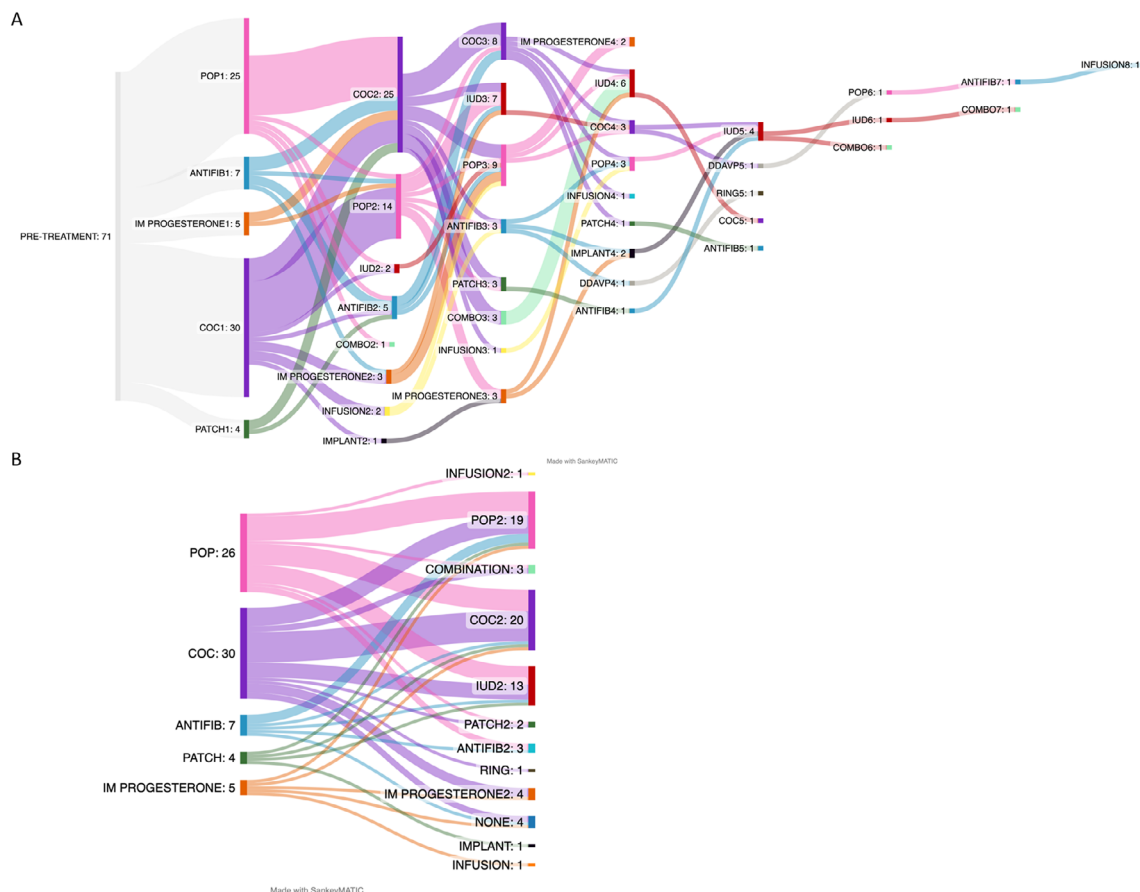


FIGURE 1 Sankey diagrams of menstrual suppression treatments. (A) Menstrual suppression treatments over time. Each node represents a medication change. Node 1 depicts initial strategies for each subject. Bars represent flow of individuals who changed from one treatment to another. (B) Sankey diagram of initial menstrual suppression therapy and final menstrual suppression therapy at the time of data extraction. ANTIFIB, antifibrinolytic; COC, combined oral contraceptive; COMBO, combination of two therapies; DDAVP, desmopressin acetate; IM, intramuscular; IUD, intrauterine device; POP, progesterone only pill.

choices was highly variable (Figure 1A). Adequate menstrual control was obtained by 56 individuals (78.9%). Of those with adequate control, 32% were on a COC, 29% were on a POP, and 18% had an IUD.

There were 129 treatment changes documented. The most frequent reason for switching therapy was uncontrolled or breakthrough bleeding (55%), followed by adverse effects (22.4%) and patient preference 8.5% (Table 1). Adverse effects included weight changes, headache, acne, mood changes, nausea, and abdominal pain, among others. The therapy with the highest percentage of adverse effects was POPs (29.5%), followed by intramuscular progesterone (18.2%). Antifibrinolytic monotherapy was changed most often due to inadequate bleeding control (72%).

4 | DISCUSSION

HMB leads to significant morbidity in adolescents with IBD. HMB leads to IDA, school absenteeism, and decreased health-related QOL.^{14–17} IDA affects cognitive function, energy, and mental health.¹⁸ Adequate

menstrual suppression is important to decrease these negative effects on adolescents. While various treatments are available for HMB in IBD, achieving menstrual control is not simple. This study shows that achieving menstrual suppression often requires attempts of multiple treatment strategies. While the median number of therapies attempted was three, individuals required up to eight therapies or combinations of therapies to suppress their HMB. The need for multiple changes in therapy indicates an unseen and underreported impact of HMB on adolescents with IBD; in our cohort, most therapy changes occurred at an in-person clinic visit, which often requires missed school. Given that 78.9% of subjects required multiple menstrual suppression therapies, there is concern that the negative effects of HMB may persist for months to years as the different therapies are attempted, leading to prolonged impacts on QOL.

This study also identifies the variety of reasons that adolescents choose to change their menstrual suppression strategy. Ineffective bleeding control was the most common reason for a therapy change. However, it is important to recognize that various adverse effects also led to treatment changes. Hormonal therapy is known to be

associated with a variety of side effects including weight changes, mood changes, acne, and nausea.¹⁹ These were among the 16 adverse effects reported by this cohort. These adverse effects likely influenced the next attempted therapy, as these effects can be seen in a variety of hormonal therapies.

There are several relative and absolute contraindications to estrogen-containing therapies. Five individuals were changed from their therapy in the comprehensive clinic due to a contraindication, including migraine with aura and first-degree relative with venous thromboembolism. It is critical that comorbid conditions be considered and evaluated when prescribing menstrual suppression therapies. In this cohort, several individuals had comorbid conditions such as migraine, congenital heart disease, or polycystic ovarian syndrome, which all impact therapeutic choices. Comprehensive care by a reproductive health specialist and a hematologist allows complementary expertise in making these decisions, especially in medically complex populations.

Medical control of HMB in adolescents with IBD requires careful consideration of patient preferences, comorbid conditions, and potential side effects. Offering thoughtful treatment options in the context of a comprehensive multidisciplinary clinic may help to identify individualized treatment plans that limit adverse effects and support patient preferences. These data will provide anticipatory guidance regarding the number of attempts it may take to achieve optimal HMB control. Given the limited data about efficacy of these treatments in adolescents, prospective comparative effectiveness studies would help guide initial treatment decisions, and may decrease the number of treatments needed to achieve adequate menstrual suppression. These studies should include the impact of HMB and menstrual control on QOL outcomes such as school attendance, mood, and extracurricular activity participation.

CONFLICT OF INTEREST STATEMENT

Megan C. Brown participated in advisory boards for Hema Biologics and Genentech and has IIS funding from Vega Therapeutics and Sanguina, and also serves on the Advisory Board for Partners Physician Program. Robert F. Sidonio participated in advisory boards for Takeda, Novo Nordisk, Bayer, Pfizer, Octapharma, Vega Therapeutics, Roche/Genentech, Hema Biologics, and LFB, and has IIS funding from Takeda, Genentech, Octapharma, Hema Biologics, and LFB. Robert F. Sidonio is the medical advisor to HFA and is on the ATHN board. Kalinda Woods's work in the hemophilia treatment center is funded by Hemophilia of Georgia. Kelly Tickle participated in advisory boards for Hema Biologics and Genentech.

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How to cite this article: Brown MC, Tickle K, Woods K, Sidonio RF. Adequate menstrual suppression in adolescents with inherited bleeding disorders often requires multiple treatment changes: Retrospective cohort study of a multidisciplinary clinic. *Pediatr Blood Cancer*. 2024;71:e30944. <https://doi.org/10.1002/pbc.30944>