High prevalence of heavy menstrual bleeding in women with rare bleeding disorders in the Netherlands: retrospective data from the RBiN study

Maas, D.P.M.S.M.; Saes, J.L.; Blijlevens, N.M.A.; Cnossen, M.H.; Exter, P.L. den; Heijden, O.W.H. van der; ... ; RBiN Study Grp

Received: 24 February 2023 | Revised: 22 June 2023 | Accepted: 5 July 2023

https://doi.org/10.1016/j.jtha.2023.07.014

ORIGINAL ARTICLE

High prevalence of heavy menstrual bleeding in women with rare bleeding disorders in the Netherlands: retrospective data from the RBiN study

Dominique P. M. S. M. Maas[1,2] | Joline L. Saes[1,2] | Nicole M. A. Blijlevens[1] | Marjon H. Cnossen[3] | Paul L. den Exter[4] | Olivier W. H. van der Heijden[5] | Ilmar C. Kruis[6] | Karina Meijer[7] | Marjolein Peters[8] | Roger E. G. Schutgens[9] | Waander L. van Heerde[1,2,10] | Laurens Nieuwenhuizen[2,11] | Saskia E. M. Schols[1,2] | for the RBiN study group

[1]Department of Hematology, Radboud University Medical Center, Nijmegen, the Netherlands

[2]Hemophilia Treatment Center Nijmegen–Eindhoven–Maastricht, the Netherlands

[3]Department of Pediatric Hematology and Oncology, Erasmus MC Sophia Children's Hospital, University Medical Center Rotterdam, Rotterdam, the Netherlands

[4]Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, the Netherlands

[5]Department of Obstetrics and Gynecology, Radboud University Medical Center, Nijmegen, the Netherlands

[6]Netherlands Hemophilia Society, Nijkerk, the Netherlands

[7]Department of Hematology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands

[8]Department of Pediatric Hematology, Amsterdam University Medical Centers, location Emma Children's Hospital, Amsterdam, the Netherlands

[9]Center for Benign Hematology, Thrombosis and Hemostasis, Van Creveldkliniek, University Medical Center Utrecht and University Utrecht, Utrecht, The Netherlands

Abstract

Background: Heavy menstrual bleeding (HMB) is associated with a reduced quality of life and limitations in social and physical functioning. Data on HMB in women with rare bleeding disorders (RBDs), including coagulation factor deficiencies and fibrinolytic disorders, are scarce.

Objectives: To analyze the prevalence, severity, and treatment of HMB in Dutch women with an RBD.

Methods: The *Rare Bleeding Disorders in the Netherlands* (RBiN) study included 263 patients with an RBD from all 6 hemophilia treatment centers (October 2017-November 2019). In this analysis, data of 111 women aged ≥16 years were studied. According to the *International Society on Thrombosis and Haemostasis bleeding assessment tool*, HMB symptoms were scored from 0 (no/trivial) to 4 (severe symptoms requiring medical intervention). HMB was defined as a score ≥1. Age at RBD diagnosis was extracted from patient files.

Results: HMB was reported by 80% of women (89/111) and was more prevalent in women with a fibrinolytic disorder (33/35; 94%) than in women with a coagulation factor deficiency (56/76; 74%) (P = .011). Of the 89 women with HMB, 82% (n = 73) ever required treatment. Multiple treatment modalities were frequently used, both in severe and mild deficiencies. Hormonal treatment was mostly used (n = 64; 88%), while antifibrinolytics were prescribed less frequently (n = 18; 25%). In women with HMB since menarche (n = 61; 69%), median age at RBD diagnosis was 28 years (IQR, 14-41).

Manuscript handled by: David Lillicrap

Final decision: David Lillicrap, 5 July 2023

[10]Enzyre BV, Novio Tech Campus, Nijmegen, The Netherlands

[11]Department of Hematology, Maxima Medical Center, Eindhoven, The Netherlands

Correspondence
Saskia E.M. Schols, Department of Hematology, Radboud University Medical Center, PO Box 9101, 6500 HB Nijmegen, the Netherlands.
Email: Saskia.Schols@radboudumc.nl

Conclusion: HMB is common in women with RBDs. Women with mild deficiencies also frequently reported HMB. Only a minority of women were treated with hemostatic agents. A significant diagnostic delay was observed after the onset of HMB symptoms.

KEYWORDS
blood coagulation disorders, inherited, fibrinolysis, menorrhagia, menstruation, uterine hemorrhage

1 | INTRODUCTION

Rare bleeding disorders (RBDs) are a heterogeneous group of inherited bleeding disorders including coagulation factor deficiencies and fibrinolytic disorders. Rare coagulation factor deficiencies refer to deficiencies of fibrinogen, factor (F) II (FII), FV, combined FV and FVIII, FVII, FX, FXI, and FXIII. Fibrinolytic disorders comprise hyperfibrinolysis and deficiencies of plasminogen activator inhibitor type 1 (PAI-1) or α2-antiplasmin.

The clinical bleeding phenotype of patients with RBDs is diverse. In general, spontaneous major bleeding only occurs in the few patients with severe deficiencies. Patients with mild deficiencies most frequently demonstrate mucosal bleeding and excessive bleeding after invasive procedures but exhibit a wide variety in bleeding severity grades [1–3]. This heterogeneity in clinical presentation is also found in patients with the same RBD and similar residual coagulation factor activity levels. In contrast to hemophilia A and B, previous studies demonstrated a poor or only moderate correlation between the deficient coagulation factor activity level and clinical bleeding severity in the majority of RBDs [3,4].

In recent years, awareness of the impact of gender-specific bleeding in patients with inherited bleeding disorders has increased. For women, child delivery and menstruation are physiological hemostatic challenges. Recent data from the Rare Bleeding Disorders in the Netherlands (RBiN) study showed a high prevalence of postpartum hemorrhage in women with both mild and severe rare coagulation factor deficiencies and fibrinolytic disorders (66%) [5].

In contrast to child delivery, menstruation represents a monthly recurring hemostatic challenge. A recent survey conducted by the European Haemophilia Consortium among 709 women with inherited bleeding disorders demonstrated that heavy menstrual bleeding (HMB) is the bleeding symptom with the largest negative impact on women's everyday lives [6]. HMB is associated with a lower health-related quality of life, impairment in social and physical activities, and absence from work or school [7–10]. Furthermore, women with HMB are more prone to iron deficiency anemia resulting in symptoms as weakness, concentration difficulties, and fatigue [6,8,9].

Data on the prevalence of HMB in women with RBDs are scarce and only limited to case series or small observational studies.

Essentials

- Heavy menstrual bleeding (HMB) is common in women with rare bleeding disorders (RBDs).
- Women with only mildly reduced coagulation factor activity levels also often have HMB.
- Only a minority of women with an RBD and HMB received treatment with antifibrinolytics.
- A significant delay in RBD diagnosis was observed after onset of HMB symptoms.

Accurate information about HMB prevalence in RBDs is, however, essential to improve early recognition of an RBD and to provide women with an effective and individualized treatment plan including adequate supportive care for iron deficiency anemia due to HMB. The aim of this RBiN sub-study is to describe the prevalence, severity, and treatment of HMB in a cohort of Dutch women with an RBD.

2 | METHODS

2.1 | Study design

The RBiN study is a nationwide, cross-sectional study among patients with a congenital rare coagulation factor deficiency or fibrinolytic disorder. All patients were diagnosed after hemostatic analysis because of a bleeding tendency, positive family history, or abnormalities in screening laboratory tests. Patients were included in all 6 Dutch hemophilia treatment centers between October 1, 2017, and November 30, 2019. The study was approved by the Medical Research Ethics Committee Oost-Nederland, and is registered at www.clinicaltrials.gov as #NCT03347591. Informed consent was obtained from all patients and/or their parents in case of minors. The study design and patient inclusion have been described in detail previously [1,3]. For the current analysis, we only included women aged 16 years and older.

2.2 | Clinical assessment

For all participants, the same investigator assessed the clinical bleeding phenotype during the study visit. The bleeding assessment tool of the International Society on Thrombosis and Haemostasis (ISTH BAT) was used. This bleeding assessment tool contains a domain with questions on the occurrence, age at first symptoms, severity, and treatment of HMB. The score for this HMB-specific domain ranges from 0 (no or trivial symptoms) to 4 (severe symptoms requiring medical intervention) (Supplementary Table S1) [11]. HMB was defined as an ISTH BAT score ≥1 in this domain [12,13]. Medical treatment was defined as any type of treatment included in the ISTH BAT: antifibrinolytics, hormonal therapy, iron therapy, red blood cell transfusion, plasma, factor concentrate, desmopressin, dilation and curettage, endometrial ablation, hysterectomy, and hospital admission and emergency treatment.

The pictorial blood loss assessment chart (PBAC) was performed for a semiquantitative assessment of the volume of menstrual blood loss in women who had HMB and still had a menstrual cycle. Women who fulfilled all of the following 3 criteria at time of inclusion in the study were considered to still have a menstrual cycle: 1) age <50 years, 2) no actual use of hormonal therapy, and 3) no hysterectomy in the medical history. The use of hormonal therapy was extracted from electronic patient files. A PBAC score ≥185 was used as a cutoff level for this semi-objectively assessed HMB [14].

Finally, all participants completed an extensive questionnaire about several medical and social aspects of their RBD. For the current analysis, reason for referral to a hemophilia treatment center was extracted from this questionnaire. The age at RBD diagnosis was extracted from electronic patient files.

2.3 | Laboratory phenotype

Blood samples for laboratory tests were drawn during the study visit. All coagulation factor activity levels were measured centrally in the *Radboud University Medical Center*. In patients with a PAI-1 deficiency, the lowest PAI-1 activity and antigen levels ever recorded were extracted from electronic patient files because of diurnal variations. In patients with hyperfibrinolysis, we used the euglobulin clot lysis time ratio which was measured during the regular diagnostic work-up. The samples for the measurement of PAI-1 activity and antigen levels and euglobulin clot lysis time ratios were all obtained between 9:00 and 9:30 AM in a fasting state [15].

2.4 | Statistical analysis

Statistical analyses were performed with IBM SPSS Statistics, version 27. Continuous variables were presented as medians with interquartile range (IQR) or range. Mann–Whitney U-tests were used to compare median values. Categorical variables were reported as counts and percentages. Fisher's exact tests were used to compare the following parameters between coagulation factor deficiencies and fibrinolytic disorders: prevalence of HMB and the proportion of women with an HMB-specific ISTH BAT score ≥ 2. All *P* values are two-sided. *P* values < .05 were considered statistically significant.

3 | RESULTS

A total of 263 patients were included in the RBiN study of whom 136 were women aged 16 years and older (Figure 1). ISTH BAT data were available for 111 of these women. Seventy-six women were diagnosed with a rare coagulation factor deficiency and 35 women with a fibrinolytic disorder. Patient characteristics are presented in Table 1. Overall, the median age was 43 years (IQR, 32-57; range, 16-87), and median ISTH BAT score was 11 (IQR, 7-16; range, 1-30). Six patients used anticoagulation or antiplatelet therapy at time of study inclusion (vitamin K antagonist [*n* = 2], clopidogrel [*n* = 2], acetylsalicylic acid [*n* = 1], combination therapy with clopidogrel and acetylsalicylic acid [*n* = 1]).

3.1 | Prevalence and severity of heavy menstrual bleeding

A history of HMB or current HMB was reported by 89 of 111 women (80%) (Table 2). Most women had an HMB-specific ISTH BAT score of 2 (38%). HMB-specific ISTH BAT scores ≥3 were found in 32 women (29%). Almost all women with HMB had to change pads or tampons more frequently than every 2 hours (91%) or experienced flooding or the passage of blood clots during their period (93%). Bleeding >7 days was reported by 60% of women. Daily activities (work, housework, exercise, social activities) were impaired during most menses in 26% of women with HMB. Furthermore, 29% of women reported that they were more than twice a year absent from work or school because of HMB.

Of the 89 women with HMB, 34 were aged <50 years, did not use hormonal therapy at time of inclusion, and did not have a hysterectomy in their medical history (Figure 1). The PBAC score was ≥ 185 in 33 of these women (97%).

3.2 | Coagulation factor deficiencies versus fibrinolytic disorders

Figure 2 provides an overview of the prevalence of HMB in each RBD. HMB was common in all RBDs but was experienced more frequently by women with a fibrinolytic disorder (33/35 women; 94%) than by women with a coagulation factor deficiency (56/76 women; 74%) (*P* = .011, Table 2). Fifty-eight percent of the women with a coagulation factor deficiency had an HMB-specific ISTH BAT score ≥ 2 (*n* = 44) compared to 86% of the women with a fibrinolytic disorder (*n* = 30) (*P* = .005; Figure 3). The proportion of women who had to change pads or tampons more frequently than every 2 hours, experienced flooding

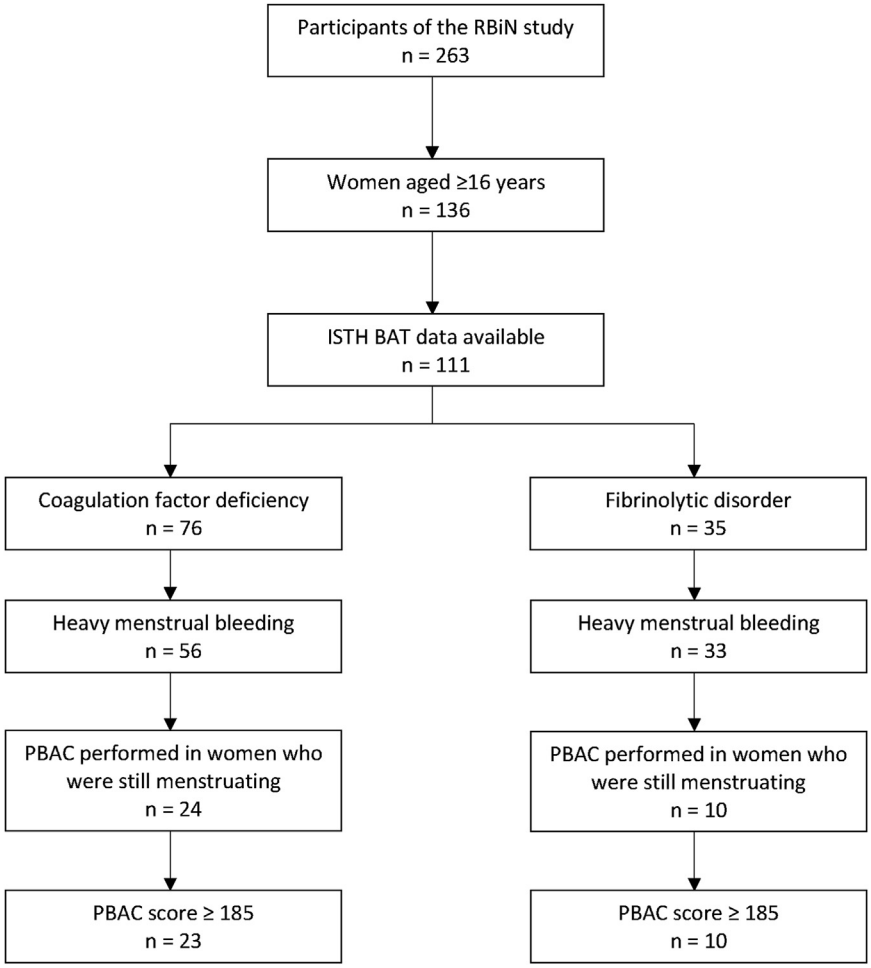

FIGURE 1 Study flowchart. ISTH BAT, International Society on Thrombosis and Haemostasis Bleeding Assessment Tool; PBAC, pictorial blood loss assessment chart; RBiN, Rare Bleeding Disorders in the Netherlands. Women were considered still menstruating if they fulfilled 3 criteria at time of inclusion: 1. Age < 50 years, 2. No current use of hormonal therapy, and 3. No hysterectomy in the medical history.

or passage of blood clots or suffered from bleeding >7 days was comparable between coagulation factor deficiencies and fibrinolytic disorders (Table 2).

3.3 | Treatment of heavy menstrual bleeding

The majority of women with HMB were treated for their menstrual blood loss (*n* = 73; 82%). The exact types of treatment that these 73 women received are shown in Figure 4. Most common therapies were hormonal treatment (64/73; 88%), iron supplementation (47/73; 64%), and antifibrinolytics (18/73; 25%). Factor concentrates or plasma were used in 3 and 2 women, respectively. None of the women used desmopressin. Seventeen women required a surgical intervention for HMB: hysterectomy was performed in 8 women of whom 2 were previously treated with endometrial ablation or dilation and curettage, and a surgical intervention with endometrial ablation or dilation and curettage alone was performed in an additional 9 women. Only 4 of these 17 women also used antifibrinolytics (24%).

An overview of the different treatment types per RBD is provided in Supplementary Table S2. For each RBD, most women were prescribed several different treatment modalities for HMB during their lives. Twenty-four women were prescribed ≥3 different types of treatment (33%). This group includes not only women with severe coagulation factor deficiencies but also women with relatively mildly reduced coagulation factor activity levels.

Hospital admission and emergency treatment were required for HMB in 3 women: 5 times in a woman with a severe FVII deficiency (FVII activity level 2%), once in another woman with a severe FVII deficiency (FVII activity level 2%), and once in a woman with a combination of a mild FXIII and FVII deficiency (FXIII activity level 63%, FVII activity level 52%).

3.4 | Diagnostic delay in RBDs

The age at onset of HMB was available in 80 of 89 women with HMB. In the majority, HMB was present since menarche (*n* = 61; 76%). Eleven women had HMB since the age of 14 to 25 years (14%), and 8 women were over 25 years when they first experienced HMB (10%). In women with HMB since menarche, median age at RBD diagnosis was 28 years (IQR, 14-41; range, 0-71) (Figure 5). In this patient group, fibrinolytic disorders were diagnosed at an older age compared with coagulation factor deficiencies (median age, 32 years; IQR, 24-50,

TABLE 1 Patient characteristics.

Rare bleeding disorder	Patients	Age, y	Coagulation factor activity level		ISTH BAT score
	N	Median (range)	Median (range)	Reference values	Median (range)
Fibrinogen disorder	19	43 (23-87)	1090 mg/L (200-2730)	1800-4200 mg/L	11 (2-21)
FII deficiency	7	39 (32-77)	58% (47-68)	79%-131%	5 (1-13)
FV deficiency	11	39 (23-69)	39% (3-54)	62%-139%	17 (2-30)
FV Amsterdam	1	64	344%	N.A.	16
Combined FV and FVIII deficiency	1	32	FV 93%, FVIII 88%	FV 62%-139% FVIII 72%-225%	6
FVII deficiency	17	34 (16-61)	33% (1-78)	50%-129%	11 (2-24)
FX deficiency	3	45 (29-58)	27% (17-50)	77%-131%	9 (2-16)
FXI deficiency	15	42 (22-76)	45% (2-57)	60%-150%	9 (1-17)
FXIII deficiency	2	16-18	37%-63%	76%-172%	13-24
A2AP deficiency	10	61 (31-76)	72% (23-76)	98%-122%	10 (1-22)
PAI-1 deficiency	14	45 (20-60)	Act: <1.0 (<1.0-<1.0) Ag: <2.5 (<2.5-3.2)	Ag: 3.4-39 ng/mL	12 (6-21)
Hyperfibrinolysis	11	52 (23-75)	8.1 (5.8-11.9)	1.2–5.7	12 (8-24)
Total	111	43 (16-87)	N.A.	N.A.	11 (1-30)

For FV Amsterdam, the reported value in the column for coagulation factor activity level is the tissue factor pathway inhibitor (TFPI) level (anti-K1, percentage compared to normal pooled plasma). For patients with hyperfibrinolysis, the reported value in the column for coagulation factor activity level is the euglobulin clot lysis time ratio. A2AP, alpha 2-antiplasmin; Act, activity; Ag, antigen; ISTH BAT, International Society on Thrombosis and Haemostasis Bleeding Assessment Tool; *N*, number; N.A., not applicable; PAI-1, plasminogen activator inhibitor type 1.

versus median age, 24 years; IQR, 11-33; P = .008). Median age at RBD diagnosis was 39 years (IQR, 11-51; range, 1-68) and 30 years (IQR, 16-41; range, 5-56) in women who first experienced HMB at an age of 14 to 25 years or over 25 years, respectively.

The reason for referral to a hemophilia treatment center for further hemostatic analysis was available in 72 of 89 women with HMB. Of these 72 women, 30 were referred because of bleeding symptoms (42%). The remaining 42 women (58%) were referred because of a positive family history (n = 32, 44%) or an abnormal laboratory screening test result (n = 10, 14%), despite the existence of HMB symptoms.

Screening laboratory tests were frequently normal in women with HMB. Of the 89 women with HMB, 51 had a rare coagulation factor deficiency hypothetically associated with a prolonged activated partial thromboplastin time (APTT) and/or prothrombin time (PT). In 20 of these 51 women (39%), both APTT and PT were normal.

4 | DISCUSSION

In this large nationwide study of patients with RBDs, we found a high prevalence of HMB (80%). Most women with HMB were treated with hormonal therapy (88%), while only a minority was treated with antifibrinolytics (25%). Although HMB was mostly present since menarche, median age at RBD diagnosis was 28 years, suggesting a significant diagnostic delay.

The prevalence of HMB in our RBD study population was significantly higher than that reported in the Dutch general female population (10%-35%) [17] and comparable to that in women with other inherited bleeding disorders, such as von Willebrand disease (74%-92%; [18,19]) and congenital platelet function defects (61%-87%; [20,21]). In our cohort, HMB was more prevalent in women with a fibrinolytic disorder than in women with a rare coagulation factor deficiency. This may be explained by the fact that the fibrinolytic activity in the endometrium is generally high [22]. Women with a fibrinolytic disorder also demonstrated higher HMB-specific ISTH BAT scores. Although fibrinolytic disorders are typically associated with delayed bleeding symptoms, the proportion of women suffering from bleeding >7 days was not different between coagulation factor deficiencies and fibrinolytic disorders.

HMB is not only common in women who are diagnosed with an inherited bleeding disorder but is also frequently a presenting symptom [12]. An underlying bleeding disorder is found in a considerable proportion of women who were referred to the gynecologist because of HMB [23–25]. Nevertheless, previous research demonstrated a significant delay in the diagnosis of a bleeding disorder. A large Dutch study combining data from 1092 patients with von Willebrand disease, congenital platelet function defects and RBDs showed that the delay between age at first bleeding and age at diagnosis was on average 6 years longer in women than in men [12]. A diagnostic delay was also observed in our RBD cohort in which 71% of women who had HMB since menarche were ≥20 years old at diagnosis. Moreover, bleeding symptoms were the reason for referral in only a minority of

TABLE 2 Specifications on heavy menstrual bleeding.

	Total (n = 111)	Coagulation factor deficiencies (n = 76)	Fibrinolytic disorders (n = 35)
Prevalence, n (%)	89 (80%)	56 (74%)	33 (94%)
HMB-specific ISTH BAT score, median (IQR)	2 (1-3)	2 (0-3)	2 (2-3)
0, n (%)	22 (20%)	20 (26%)	2 (6%)
1, n (%)	15 (14%)	12 (16%)	3 (9%)
2, n (%)	42 (38%)	24 (32%)	18 (51%)
3, n (%)	10 (9%)	5 (7%)	5 (14%)
4, n (%)	22 (20%)	15 (20%)	7 (20%)
Descriptions of severity, n (%)			
Changing pads/tampons more frequently than every 2 h	81 (91%)	51 (91%)	30 (91%)
Flooding or clots	83 (93%)	51 (91%)	32 (97%)
Bleeding >7 d	53 (60%)	35 (63%)	18 (55%)
Impairment of daily activities during most menses	23 (26%)	15 (27%)	8 (24%)
>2/y absent from work or school	26 (29%)	17 (30%)	9 (27%)
Ever required medical treatment, n (%)	73 (82%)	44 (79%)	29 (88%)

ISTH BAT, International Society on Thrombosis and Haemostasis Bleeding Assessment Tool; HMB, heavy menstrual bleeding.

these women. These results illustrate that important steps have to be taken to improve the physicians' awareness of a possible underlying RBD or other congenital bleeding disorder in women with HMB. In addition, the education of girls and women and their relatives about a normal menstrual cycle should be improved as many patients do not consider their menstrual blood loss abnormal because many of their female relatives have HMB.

Furthermore, a part of the diagnostic delay may be explained by the fact that normal coagulation screening tests do not rule out the presence of a (mild) rare coagulation factor deficiency. In our cohort, a significant number of women with a rare coagulation factor deficiency had a normal APTT and/or PT. The longest diagnostic delay was observed in women with a fibrinolytic disorder. This may be explained by the lack of abnormalities in coagulation screening assays, and the lack of standardization and high complexity of the diagnostic tests needed to evaluate the fibrinolytic pathway. This leads to the assumption that a significant number of women with HMB without a proven disorder of the primary or secondary hemostasis (so-called bleeding disorder of unknown cause) may have a fibrinolytic disorder [15].

The proportion of women with HMB who consulted a physician was higher in our RBD cohort than that in the general population (82% vs 5%) [17]. The management of HMB in women with RBDs and other inherited bleeding disorders is, however, challenging due to the lack of high-quality research data and universally accepted standards of care [8,26]. Patients frequently need various treatment modalities before effective HMB control is reached [8]. In our cohort, the use of multiple treatment modalities (including surgical intervention) was not only needed in women with severe RBDs but was also frequently required in women with relatively mild RBDs. These observations are in agreement with earlier results from the RBiN study showing a high bleeding rate after tooth extractions, surgical interventions, and child delivery performed without periprocedural hemostatic treatment in patients with only mildly reduced activity levels of the deficient coagulation factor [1,5]. Furthermore, both the RBiN study and the *European Network of Rare Bleeding Disorders* have previously demonstrated only moderate to poor correlations between baseline coagulation factor activity levels and bleeding scores in the majority of RBDs [3,4].

In our cohort, 11% of women who were treated for their HMB underwent a hysterectomy (8/73 women). This percentage is lower than that in Dutch women with a (suspected) congenital platelet disorder (10/52; 19%) or moderate-severe von Willebrand disease (84/423; 20%) [18,21]. This may be explained by the fact that we included women with varying degrees of disease severity in the RBiN study: not only women who were referred because of a bleeding tendency but also women who were referred because of a positive family history or abnormalities in screening laboratory tests. In the women who underwent a surgical intervention for HMB, only 24% were treated with antifibrinolytics in the period before the intervention to reduce the amount of blood loss. Unfortunately, we do not know whether the RBD diagnosis was already established at time of intervention. However, these data highlight the importance of increasing awareness that HMB may be the first sign of a congenital bleeding disorder. Once an RBD is diagnosed early, the patient can be offered an individualized treatment plan. Consequently, the need to perform invasive procedures to treat severe HMB, such as endometrial ablation and hysterectomy, can probably be reduced. Moreover, a gynecologist should consider a hemostatic screening in all women in whom he/she plans to perform a hysterectomy.

In recent years, several initiatives have been developed to increase international awareness for a timely diagnosis and more optimal management of this specific patient group. The *European Association for Haemophilia and Allied Disorders* has founded the *Women and Bleeding Disorders Working Group*. This committee performed a large survey among 59 European hemophilia treatment centers in which investigation of therapies for HMB and the need for efficacious multidisciplinary treatment were defined as main priorities [27]. In addition, a joint initiative of the *European Association for Haemophilia and Allied Disorders* and *European Haemophilia Consortium* included an early recognition and optimal management of HMB as one of the 10 European principles of care for women and girls with inherited bleeding disorders [24]. Finally, the *Pediatric/Neonatal Thrombosis and*

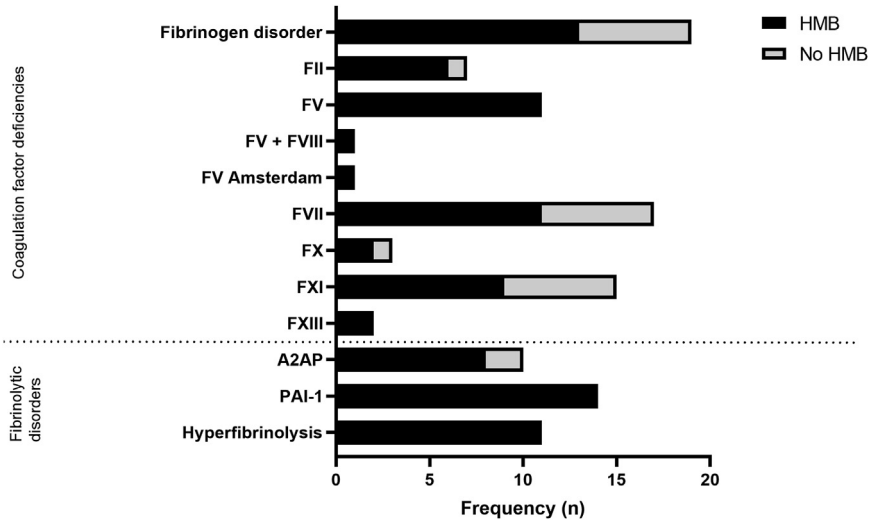

FIGURE 2 Prevalence of heavy menstrual bleeding per rare bleeding disorder. A2AP, alpha 2-antiplasmin; HMB, heavy menstrual bleeding; PAI-1, plasminogen activator inhibitor type 1.

Hemostasis and *Women's Health Issues in Thrombosis and Hemostasis* Scientific and Standardization Committees of the ISTH convened an international expert panel that assigned the hemostatic and non-hemostatic management of HMB as appropriate care consideration in women with bleeding disorders [26].

Our study has some limitations. First, as the RBiN study is a retrospective study, the exact volume of menstrual blood loss was not measured. Therefore, we could not use the classic HMB definition of menstrual blood loss of >80 mL per cycle [28]. Instead, we defined HMB as an HMB-specific ISTH BAT score ≥ 1. This definition has also been used in other studies [12,13]. In women with HMB who were still menstruating, we performed the PBAC to include a semi-quantitative assessment of menstrual blood loss [29]. In almost all of these women (97%, *n* = 33), the PBAC score was ≥185 suggesting that the prevalence of HMB in our cohort was not overestimated using ISTH BAT data. Moreover, the latest guideline of the *National Institute for Health and Care Excellence* also only uses subjective information in their new definition of HMB: "excessive menstrual blood loss which interferes with a woman's physical, social, emotional and/or material quality of life" [30]. Second, a potential problem in studies using patient-reported data is the risk of recall bias. Our data were not affected by differences in interviewing techniques or interpretation of patient-reported information as the same investigator interviewed all patients. Third, asymptomatic patients or patients with a mild bleeding phenotype may never be diagnosed with an RBD. This can potentially lead to selection bias. To reduce the risk of selection bias, we did not only include patients who were diagnosed after referral for a bleeding tendency but also heterozygous family members and patients diagnosed after an aberrant preoperative coagulation screening. Lastly, we unfortunately do not have information about possible contributing gynecologic risk factors for HMB such as uterine fibroids or adenomyosis.

In conclusion, HMB is common in women with rare coagulation factor deficiencies and fibrinolytic disorders. Both women with severe and relatively mild RBDs often report HMB. Women frequently used multiple different treatment modalities for their HMB. Hormonal therapy was mostly used, while hemostatic agents were prescribed less regularly. In the majority of women, HMB was already present since menarche. A significant delay in RBD diagnosis was observed in this group with a median age at diagnosis of 28 years. Prospective studies are required to collect more data on the optimal treatment of HMB in women with RBDs and to investigate how the delay between onset of HMB symptoms and RBD diagnosis can be reduced.

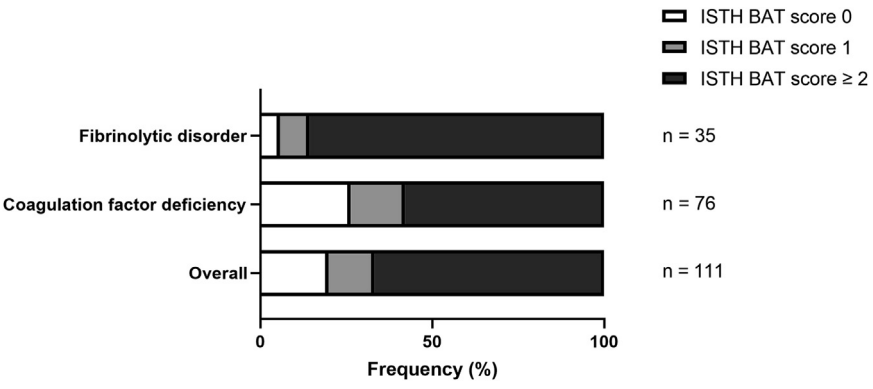

FIGURE 3 Heavy menstrual bleeding specific ISTH BAT scores in women with a fibrinolytic disorder, in women with a coagulation factor deficiency, and in the entire cohort. ISTH BAT, International Society on Thrombosis and Haemostasis Bleeding Assessment Tool.

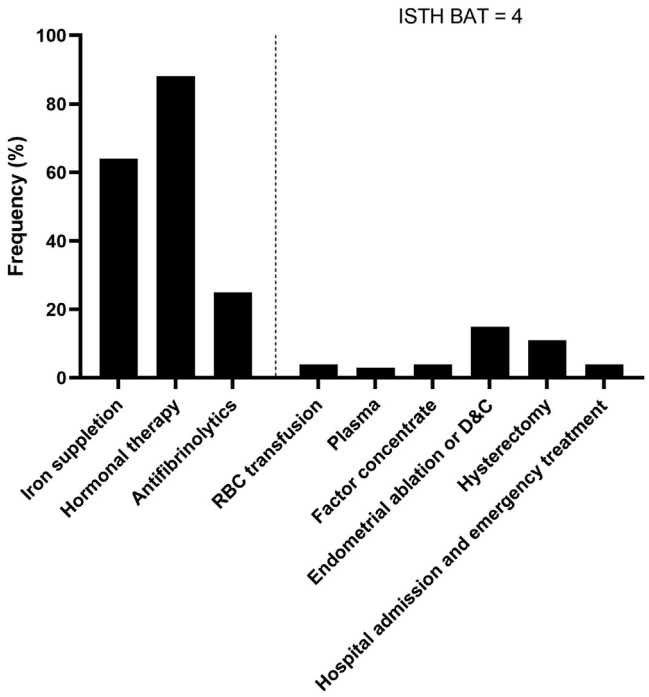

FIGURE 4 Treatment of heavy menstrual bleeding. This figure provides an overview of therapies used in the 73 women who ever required treatment for heavy menstrual bleeding. Women may have used more than one treatment type. D&C, dilation and curettage; ISTH BAT, International Society on Thrombosis and Haemostasis Bleeding Assessment Tool; RBC, red blood cell.

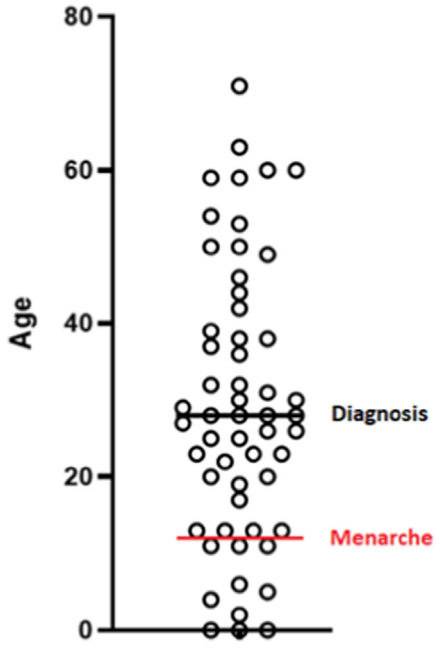

FIGURE 5 Age at diagnosis of the rare bleeding disorder in women with heavy menstrual bleeding since menarche. Each circle represents one woman. The black horizontal line represents the median age at diagnosis of the rare bleeding disorder in women with heavy menstrual bleeding since menarche. The red horizontal line represents the median age at menarche in Dutch girls [16].

APPENDIX

Members of the RBiN study group are D.P.M.S.M. Maas, J.L. Saes, K. Meijer, M.H. Cnossen, R.E.G. Schutgens, M. Peters, L. Nieuwenhuizen, P.L. den Exter, I.C. Kruis, W.L. van Heerde, and S.E.M. Schols.

AUTHOR CONTRIBUTIONS

K. Meijer, M.H. Cnossen, R.E.G. Schutgens, M. Peters, L. Nieuwenhuizen, P.L. den Exter, I.C. Kruis, W.L. van Heerde, and S.E.M. Schols are members of the steering committee that designed the study and are delegates from all Dutch hemophilia treatment centers and the NVHP patient society; N.M.A. Blijlevens is head of the department of Hematology in the Radboud University Medical Center and head of the RBiN project management team. O.W.H. van der Heijden is a gynecologist in the Radboud University Medical Center with expertise in women with bleeding disorders. J.L. Saes interviewed all patients; D.P.M.S.M. Maas analyzed the data; D.P.M.S.M. Maas, W.L. van Heerde, L. Nieuwenhuizen, and S.E.M. Schols wrote the manuscript; and all authors revised the manuscript and gave final approval.

DECLARATION OF COMPETING INTERESTS

K. Meijer reports speaker fees from Bayer and Alexion, participation in trial steering committee for Bayer, consulting fees from Uniqure, participation in data monitoring and endpoint adjudication committee for Octapharma. M.H. Cnossen's institution has received investigator-initiated research and travel grants as well as speaker fees over the years from the Netherlands Organisation for Scientific Research (NWO) and Netherlands National research Agenda (NWA), the Netherlands Organization for Health Research and Development (ZonMw), the Dutch Innovatiefonds Zorgverzekeraars, Stichting Haemophilia, Baxter/Baxalta/Shire/ Takeda, Pfizer, Bayer Schering Pharma, CSL Behring, Sobi Biogen, Novo Nordisk, Novartis, Roche, and Nordic Pharma, and for serving as a steering board member for Roche, Bayer and Novartis. All grants and fees go to the Erasmus MC as an institution. She is coordinator of Erasmus MC as a Health Care Provider within the European Reference Network (ERN) for rare hematological diseases EuroBloodNet and (co)leader of the local Erasmus MC Expert Centers for Rare Bleeding Disorders and Sickle Cell and Thalassemia Comprehensive Care Center. R.E.G. Schutgens reports grants from Bayer, Baxalta, Pfizer, and Novo Nordisk outside the submitted work. M. Peters reports a grant from Pfizer outside the submitted work. W.L. van Heerde reports financial support from Takeda, Bayer, Sobi and CSL Behring, and funding from Takeda and Bayer for Enzyre. The remaining authors declare no competing financial interests.

REFERENCES

[1] Maas DPMSM, Saes JL, Blijlevens NMA, Cnossen MH, den Exter PL, Kruis IC, Meijer K, Nieuwenhuizen L, Peters M, Schutgens REG, van Heerde WL, Schols SEM. Treatment of patients with rare bleeding disorders in the Netherlands: real-life data from the RBiN study. *J Thromb Haemost.* 2022;20:833–44.

[2] Menegatti M, Peyvandi F. Treatment of rare factor deficiencies other than hemophilia. *Blood.* 2019;133:415–24.

[3] Saes JL, Verhagen MJA, Meijer K, Cnossen MH, Schutgens REG, Peters M, Nieuwenhuizen L, van der Meer FJM, Kruis IC, van Heerde WL, Schols SEM. Bleeding severity in patients with rare bleeding disorders: real-life data from the RBiN study. *Blood Adv*. 2020;4:5025–34.
[4] Peyvandi F, Palla R, Menegatti M, Siboni SM, Halimeh S, Faeser B, Pergantou H, Platokouki H, Giangrande P, Peerlinck K, Celkan T, Ozdemir N, Bidlingmaier C, Ingerslev J, Giansily-Blaizot M, Schved JF, Gilmore R, Gadisseur A, Benedik-Dolničar M, Kitanovski L, et al. Coagulation factor activity and clinical bleeding severity in rare bleeding disorders: results from the European Network of Rare Bleeding Disorders. *J Thromb Haemost*. 2012;10:615–21.
[5] Maas DPMSM, Saes JL, Blijlevens NMA, Cnossen MH, den Exter PL, van der Heijden OWH, Kruis IC, Meijer K, Peters M, Schutgens REG, van Heerde WL, Nieuwenhuizen L, Schols SEM, RBiN study group. High prevalence of postpartum hemorrhage in women with rare bleeding disorders in the Netherlands: retrospective data from the RBiN study. *J Thromb Haemost*. 2023;21:499–512.
[6] Noone D, Skouw-Rasmussen N, Lavin M, van Galen KPM, Kadir RA. Barriers and challenges faced by women with congenital bleeding disorders in Europe: results of a patient survey conducted by the European Haemophilia Consortium. *Haemophilia*. 2019;25:468–74.
[7] Peyvandi F, Palla R, Menegatti M, Mannucci PM. Introduction. Rare bleeding disorders: general aspects of clinical features, diagnosis, and management. *Semin Thromb Hemost*. 2009;35:349–55.
[8] Curry N, Bowles L, Clark TJ, Lowe G, Mainwaring J, Mangles S, Myers B, Kadir RA. Gynaecological management of women with inherited bleeding disorders. A UK Haemophilia Centres Doctors' Organisation Guideline. *Haemophilia*. 2022;28:917–37.
[9] Presky KO, Kadir RA. Women with inherited bleeding disorders - Challenges and strategies for improved care. *Thromb Res*. 2020;196:569–78.
[10] Kadir RA, Edlund M, Von Mackensen S. The impact of menstrual disorders on quality of life in women with inherited bleeding disorders. *Haemophilia*. 2010;16:832–9.
[11] Rodeghiero F, Tosetto A, Abshire T, Arnold DM, Coller B, James P, Neunert C, Lillicrap D. ISTH/SSC bleeding assessment tool: a standardized questionnaire and a proposal for a new bleeding score for inherited bleeding disorders. *J Thromb Haemost*. 2010;8:2063–5.
[12] Atiq F, Saes JL, Punt MC, van Galen KPM, Schutgens REG, Meijer K, Cnossen MH, Laros-Van Gorkom BAP, Peters M, Nieuwenhuizen L, Kruip M, de Meris J, van der Bom JG, van der Meer FJM, Fijnvandraat K, Kruis IC, van Heerde WL, Eikenboom HCJ, Leebeek FWG, Schols SEM. Major differences in clinical presentation, diagnosis and management of men and women with autosomal inherited bleeding disorders. *EClinicalMedicine*. 2021;32:100726.
[13] Lavin M, Aguila S, Dalton N, Nolan M, Byrne M, Ryan K, White B, O'Connell NM, O'Sullivan JM, Di Paola J, James PD, O'Donnell JS. Significant gynecological bleeding in women with low von Willebrand factor levels. *Blood Adv*. 2018;2:1784–91. https://doi.org/10.1182/bloodadvances.2018017418
[14] Janssen CA, Scholten PC, Heintz AP. A simple visual assessment technique to discriminate between menorrhagia and normal menstrual blood loss. *Obstet Gynecol*. 1995;85:977–82. https://doi.org/10.1016/0029-7844(95)00062-v
[15] Valke L, Meijer D, Nieuwenhuizen L, Laros-van Gorkom BAP, Blijlevens NMA, van Heerde WL, Schols SEM. Fibrinolytic assays in bleeding of unknown cause: Improvement in diagnostic yield. *Res Pract Thromb Haemost*. 2022;6:e12681.
[16] Mul D, Fredriks AM, van Buuren S, Oostdijk W, Verloove-Vanhorick SP, Wit JM. Pubertal development in The Netherlands 1965-1997. *Pediatr Res*. 2001;50:479–86.
[17] Richtlijn Hevig menstrueel bloedverlies (HMB). In: Richtlijnendatabase FvMS, ed. *Nederlandse Vereniging voor Obstetrie en Gynaecologie*. NVOG); 2020.
[18] De Wee EM, Knol HM, Mauser-Bunschoten EP, van der Bom JG, Eikenboom JC, Fijnvandraat K, De Goede-Bolder A, Laros-van Gorkom B, Ypma PF, Zweegman S, Meijer K, Leebeek FW. Gynaecological and obstetric bleeding in moderate and severe von Willebrand disease. *Thromb Haemost*. 2011;106:885–92.
[19] James AH, Kouides PA, Abdul-Kadir R, Edlund M, Federici AB, Halimeh S, Kamphuisen PW, Konkle BA, Martínez-Perez O, McLintock C, Peyvandi F, Winikoff R. Von Willebrand disease and other bleeding disorders in women: consensus on diagnosis and management from an international expert panel. *Am J Obstet Gynecol*. 2009;201:12.e1–8.
[20] Gresele P, Orsini S, Noris P, Falcinelli E, Alessi MC, Bury L, Borhany M, Santoro C, Glembotsky AC, Cid AR, Tosetto A, De Candia E, Fontana P, Guglielmini G, Pecci A. Validation of the ISTH/SSC bleeding assessment tool for inherited platelet disorders: a communication from the Platelet Physiology SSC. *J Thromb Haemost*. 2020;18:732–9.
[21] Punt MC, Ruigrok ND, Bloemenkamp KWM, Uitslager N, Urbanus RT, Groot E, Kremer Hovinga ICL, Schutgens REG, van Galen KPM. Prevalence, burden and treatment effects of vaginal bleeding in women with (suspected) congenital platelet disorders throughout life: a cross-sectional study. *Br J Haematol*. 2022;196:215–23.
[22] Saes JL, Schols SEM, van Heerde WL, Nijziel MR. Hemorrhagic disorders of fibrinolysis: a clinical review. *J Thromb Haemost*. 2018.
[23] Knol HM, Mulder AB, Bogchelman DH, Kluin-Nelemans HC, van der Zee AG, Meijer K. The prevalence of underlying bleeding disorders in patients with heavy menstrual bleeding with and without gynecologic abnormalities. *Am J Obstet Gynecol*. 2013;209:202. e1–7.
[24] van Galen K, Lavin M, Skouw-Rasmussen N, Fischer K, Noone D, Pollard D, Mauser-Bunschoten E, Khair K, Gomez K, van Loon E, Bagot CN, Elfvinge P, d'Oiron R, Abdul-Kadir R. European principles of care for women and girls with inherited bleeding disorders. *Haemophilia*. 2021;27:837–47.
[25] Kadir RA, Economides DL, Sabin CA, Owens D, Lee CA. Frequency of inherited bleeding disorders in women with menorrhagia. *Lancet*. 1998;351:485–9.
[26] Zia A, Kouides P, Khodyakov D, Dao E, Lavin M, Kadir RA, Othman M, Bauman D, Halimeh S, Winikoff R, Revel-Vilk S. Standardizing care to manage bleeding disorders in adolescents with heavy menses-A joint project from the ISTH pediatric/neonatal and women's health SSCs. *J Thromb Haemost*. 2020;18:2759–74.
[27] van Galen KPM, Lavin M, Skouw-Rasmussen N, Ivanova E, Mauser-Bunschoten E, Punt M, Romana G, Elfvinge P, D'Oiron R, Abdul-Kadir R. Clinical management of woman with bleeding disorders: a survey among European haemophilia treatment centres. *Haemophilia*. 2020;26:657–62.
[28] Hallberg L, Högdahl AM, Nilsson L, Rybo G. Menstrual blood loss–a population study. Variation at different ages and attempts to define normality. *Acta Obstet Gynecol Scand*. 1966;45:320–51.
[29] Higham JM, O'Brien PM, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. *Br J Obstet Gynaecol*. 1990;97:734–9.
[30] National Institute for Health and Care Excellence. *Clinical Guidelines. Heavy menstrual bleeding: assessment and management*. London: National Institute for Health and Care Excellence (NICE); 2021.

SUPPLEMENTARY MATERIAL

The online version contains supplementary material available at https://doi.org/10.1016/j.jtha.2023.07.014