Title

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Journal

Haemophilia, 17

ISSN

13518216

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Publication Date

2011-07-01

DOI

10.1111/j.1365-2516.2011.02558.x

Peer reviewed

Haemophilia

Haemophilia (2011), **17** (Suppl. 1), 6–13 DOI: 10.1111/j.1365-2516.2011.02558.x

ORIGINAL ARTICLE

Surveillance of female patients with inherited bleeding disorders in United States Haemophilia Treatment Centres

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Summary. Inherited bleeding disorders are especially problematic for affected girls and women due to the monthly occurrence of menstrual periods and the effects on reproductive health. Although heavy menstrual bleeding (HMB) is the most common manifestation, females with inherited bleeding disorders (FBD) experience other bleeding symptoms throughout the lifespan that can lead to increased morbidity and impairment of daily activities. The purpose of this article is to describe the utility of a female-focused surveillance effort [female Universal Data Collection (UDC) project] in the United States Haemophilia Treatment Centres (HTCs) and to describe the baseline frequency and spectrum of diagnoses and outcomes. All FBD aged 2 years and older receiving care at selected HTCs were eligible for enrolment. Demographic data, diagnoses and historical data regarding bleeding symptoms, treatments, gynaecological abnormalities and obstetrical outcomes were analysed. Analyses represent data collected from 2009 to 2010. The most frequent diagnoses were type 1 von Willebrand's disease (VWD) (195/319; 61.1%), VWD type unknown (49/319; 15.4%) and factor VIII deficiency (40/319; 12.5%). HMB was the most common bleeding symptom (198/253; 78.3%); however, 157 (49.2%) participants reported greater than four symptoms. Oral contraceptives were used most frequently to treat HMB (90/165; 54.5%), followed by desmopressin [1-8 deamino-D-arginine vasopressin (DDAVP)] (56/165; 33.9%). Various pregnancy and childbirth complications were reported, including bleeding during miscarriage (33/43; 76.7%) and postpartum haemorrhage (PPH) (41/109; 37.6%). FBD experience multiple bleeding symptoms and obstetrical-gynaecological morbidity. The female UDC is the first prospective, longitudinal surveillance in the US focusing on FBD and has the potential to further identify complications and reduce adverse outcomes in this population.

Keywords: gynaecology, heavy menstrual bleeding, inherited bleeding disorders, obstetrics, von Willebrand disease, women

Introduction

Inherited bleeding disorders are especially problematic for affected girls and women due to the monthly occurrence of menstrual periods and the effects on reproductive health. Menstruation, pregnancy and childbirth present recurrent haemostatic challenges to females with inherited bleeding disorders (FBD). It is widely recognized that heavy menstrual bleeding

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Accepted after revision 6 April 2011

(HMB) is common among women with bleeding disorders [1]. However, HMB is not the only gynaecological or reproductive tract manifestation of these conditions; bleeding disorders may be associated with increased ovarian cysts, endometriosis, miscarriage, bleeding complications during pregnancy and postpartum haemorrhage (PPH) [1] often resulting in exposure to blood and blood products. Women with von Willebrand's disease (VWD) are more likely to experience PPH and have a maternal mortality rate 10 times higher than women without VWD [2].

Besides HMB, FBD experience other bleeding symptoms throughout the lifespan that can lead to impairment of daily activities. Epistaxis, bleeding after surgical procedures such as dental extraction and joint bleeds can affect girls, female adolescents, reproductive-aged and menopausal/postmenopausal women. Adverse psychosocial effects and reduced quality of life (QOL) have been reported [3,4]. However, the evidence that FBD are subject to increased morbidity and mortality has been based on a retrospective review in relatively small sample sizes. There has not been a longitudinal assessment to characterize the population and monitor relevant health outcomes over time. The implementation of surveillance for FBD will help to determine the impact of bleeding, stimulate the development of new treatments, and potentially influence clinical practices to reduce reproductive morbidity and improve outcomes. The purposes of this article are to describe the: (i) utility and development of a female-focused data collection effort in the US and (ii) baseline frequency and spectrum of diagnoses, symptoms and reproductive outcomes.

Materials and methods

The Centers for Disease Control and Prevention (CDC) Universal Data Collection (UDC) surveillance system has collected data annually on persons with bleeding disorders receiving care at 130 US HTCs since 1998 to characterize the population, monitor blood and blood product safety, and identify complications. The primary focus of UDC was to monitor outcomes among persons with haemophilia who are predominantly male. Women with VWD and factor deficiencies have been eligible to participate in UDC since its inception; to date, over 4 000 female HTC participants have enroled. However, the data collection instruments do not target any female-specific bleeding symptoms, such as HMB or reproductive outcomes. Therefore, the true burden of bleeding disorders among females in UDC has not been well described. There are still many questions about the scope and severity of HMB and other bleeding symptoms in females and the long-term effects of bleeding disorders on reproductive outcomes. To this end, a female module has been added to the UDC system to prospectively characterize females receiving care at HTCs and monitor bleeding and reproductive complications over time.

The female UDC module was developed by a multidisciplinary committee of experts from HTCs in collaboration with CDC over a period of 4 years. The module collects data on diagnoses, menstrual bleeding, non-obstetrical-gynaecological bleeding symptoms, treatment, and gynaecological and reproductive history. A registration form is completed at baseline and includes month and year of birth, race/ethnicity, diagnoses, age at diagnosis and history of bleeding symptoms, treatments and reproductive outcomes. An annual form is completed at baseline and again at subsequent clinic visits to obtain information on current symptoms, treatments and outcomes. The module was pilot-tested in 17 HTCs from January 2008 to June 2008 to obtain feedback from providers regarding the content of the module and the logistics of administering the form in clinics. HTC staff members assessed the utility of the module and individual data elements by completing evaluation forms. There was an overall agreement that the module was a useful supplement to the UDC. The feedback received from the pilot test was incorporated into the current version of the module.

The implementation of the female module began in September 2009. The female UDC committee requested participation from a minimum of two HTCs in each of the 12 regions that make up the US HTC network [5]. To further test the feasibility of administration, HTCs with both small and large patient bases and related staff capacity were explicitly solicited. Participation was based on the sites' ability to incorporate the female module into their clinic routine; 30 HTCs volunteered to participate, however, this report represents data, to date, from participants at 20 HTCs. All FBD aged 2 years and older receiving care at the HTCs were eligible for enrolment. Eligible bleeding disorders included VWD, factor deficiencies with factor levels <50% and platelet disorders. HTC care providers offered enrolment to all eligible females; participants or their parents or legal guardians gave informed consent. Providers administered the registration and annual visit forms, and collected a plasma specimen to test for infectious agents and other potential complications as a part of routine UDC blood and blood product safety surveillance [6]; only registration data are included in this preliminary analysis. The registration form consists of: (i) demographic information and source of referral to HTC, (ii) diagnoses and family history of bleeding disorders, (iii) history of bleeding symptoms and resulting provider interventions, (iv) treatment history for bleeding problems, (v) history of gynaecological abnormalities and reproductive outcomes, and (vi) history of menopause and menopause-related treatment for bleeding. The protocol was reviewed and approved by institutional review boards at CDC and the individual sites. These baseline data represent data entered, to date, from participants enroled throughout December 2010. To minimize recall

bias, HMB analyses were restricted to menstruating females and did not include women who identified themselves as menopausal. Data on pregnancy outcomes included females who had achieved menarche and reported at least one pregnancy. Frequencies were tabulated using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

Participant characteristics and diagnoses

A total of 319 participants were included in this analysis. Participant demographics and characteristics are shown in Table 1. The mean age of participants was 26.5 years (range 2–83); 250 (78.4%) were non-Hispanic White and 145 (45.5%) patients were aged 18–44 years. A positive family history of a bleeding disorder was reported by 190 (59.6%) females. Patients were referred to the HTC by a variety of sources; 75 (23.8%) were referred by paediatricians, 58 (18.4%) by family members and 55 (17.5%) by haematologists. One hundred and fifty-six (51.5%) females were <13 years at the time of diagnosis. A positive history of anaemia was reported by 141 (44.2%) participants. Table 2 shows the frequency of various coagulation disorders among FBD. The most frequent diagnosis was type 1 VWD (195/319; 61.1%), followed by VWD type unknown (49/319; 15.4%) and factor VIII deficiency (40/319; 12.5%). Although 235 (73.7%) females had a single haemostatic defect, 62 (19.4%) were diagnosed with two or more haemostatic defects.

Table 1. Patient characteristics of females with bleeding disorders (n = 319).

	n	n (%)
Mean age at registration, years (range)	319	26.5 (2–83)
Age group (in years)		
2–12	319	61 (19.1)
13–17		61 (19.1)
18–44		145 (45.5)
45–55		23 (7.2)
>55		29 (9.1)
Race/ethnicity		
White (non-Hispanic)	319	250 (78.4)
Other		69 (21.6)
Family history		
Yes	319	190 (59.6)
No		86 (27.0)
Unknown		43 (13.4)
Age at diagnosis (in years)		
2–12	303	156 (51.5)
13–17		56 (18.5)
18–44		78 (25.7)
45–55		7 (2.3)
>55		6 (2.0)
Referral source		
Paediatrician	315	75 (23.8)
Family member		58 (18.4)
Haematologist		55 (17.5)
Family practitioner		31 (9.8)
Obstetrician-gynaecologist		20 (6.4)
Other		76 (24.1)
History of anaemia		
Yes	319	141 (44.2)
No		15 (4.7)
Unknown		163 (51.1)
Mean age at menarche, years (range)	253	12.1 (7–18)

Bleeding symptoms and treatment history

One hundred and sixty-five (76.0%) menstruating females (n = 217) reported HMB that required a protection change at least every 2 h on the heaviest day; 95 (57.6%) of these patients required some level of health care provider intervention (Table 3). Provider interventions included consultation, medications, surgeries, procedures, blood products, transfusions and hospitalization. Of 119 females who had been pregnant at least once, 63 (52.9%) reported bleeding with pregnancy and/or postpartum. Fifty-one (81.0%) of the participants who reported bleeding during pregnancy and/or delivery required provider intervention as a consequence of bleeding. Other frequently reported symptoms included excessive bruising (174/319; 54.5%), epistaxis (154/319; 48.3%) and bleeding from minor cuts (153/319; 48.0%). Less common but more serious bleeding was noted in terms of central nervous system (CNS) bleeding (9/319; 2.8%) and joint bleeding (51/319; 16.0%); the most common diagnosis among females reporting a history of joint bleeding was type 1 VWD (24/51; 47%). Provider intervention was frequent for bleeding after surgery (102/119; 85.7%), CNS bleeding (7/9; 77.8%) and joint bleeding (37/51; 72.5%). Two hundred and nine (65.5%) participants reported a history of three or more bleeding symptoms; 157 (49.2%) participants reported greater than four symptoms. A variety of treatment modalities were used to treat HMB and are listed in Table 4. Of the 165 menstruating females who reported a history of HMB, oral contraceptives were the most frequently used (90/

Table 2. Distribution of coagulation disorders (n = 319).

	n (%)
VWD	
type 1 VWD	195 (61.1)
type 2 VWD	25 (7.8)
type 3 VWD	14 (4.4)
VWD type Unknown	49 (15.4)
Factor VIII	40 (12.5)
Platelet disorders	15 (4.7)
Factor VII	11 (3.4)
Factor IX	11 (3.4)
Connective tissue disorders	10 (3.1)
Hereditary haemorrhagic telangiectasia (HHT)	4 (1.3)
Factor XI	3 (0.9)
Plasminogen activator inhibitor-1 (PAI-1) deficiency	3 (0.9)
Fibrinogen deficiency	2 (0.6)
Factor V	2 (0.6)
Factor X	2 (0.6)
Factor XIII	2 (0.6)
Missing diagnoses	22 (6.9)

VWD, von Willebrand's disease.

Table 3. Frequency of bleeding symptoms and provider intervention (n = 319).

	n (%) reported symptom	n (%) required provider intervention
More than one nosebleed per year lasting 10 min or longer	154 (48.4)	75 (48.7)
Oral mucosal bleeding lasting 10 min or longer	93 (29.4)	43 (46.2)
Bleeding during or after dental procedures of concern to healthcare provider	111 (35.1)	73 (65.8)
Bleeding from minor cuts lasting 5 min or longer	153 (48.0)	23 (15.0)
Bruises larger than a quarter size occurring at least once a month without trauma	174 (54.5)	13 (7.5)
Bleeding after surgery of concern to health care provider	119 (37.3)	102 (85.7)
Menstrual bleeding that required protection change at least every 2 h on heaviest day*	165 (76.0)	95 (57.6)
Bleeding during pregnancy and/or postpartum of concern to health care provider†	63 (52.9)	51 (81.0)
Joint bleeding	51 (16.0)	37 (72.5)
Muscle bleeding	28 (8.8)	13 (46.4)
CNS bleeding	9 (2.8)	7 (77.8)
GI bleeding	37 (11.6)	23 (62.6)

CNS, central nervous system; GI, gastrointestinal.
*Restricted to 217 menstruating females.
†Restricted to 119 females who had pregnancy.

165; 54.5%), followed by desmopressin [1-8 deamino-D-arginine vasopressin (DDAVP)] (56/165; 33.9%) and antifibrinolytics (40/165; 24.2%). The levonorgestrel-releasing intrauterine system (LNG-IUS) was used by five (3.0%) females. Twenty-one (10.6%) menstruating and menopausal females who reported a history of HMB (n = 198) underwent hysterectomy specifically to control HMB; the mean age of hysterectomy was 35.7 years (range 20–51).

Gynaecological and reproductive history

Participants reported seeking professional health care for abnormalities with their menstrual cycle, especially pain during menses (110/217; 50.7%), irregular menstrual cycles (102/217; 47.0%) and breakthrough spotting (85/217; 39.2%); other gynaecological diagnoses included bleeding ovarian cysts, endometriosis and fibroids (Table 5). Of the 253 females who had reached menarche, 119 (47%) females had been pregnant at least once and there were a total of 302 pregnancies. Two hundred and seven (68.5%) pregnancies resulted in full-term deliveries, 59 (19.5%) in first or second trimester miscarriage and 24 (7.9%) in preterm delivery (Table 6). Eight (2.6%) pregnancies were terminated electively and four (1.3%) were ectopic, tubal or molar. Thirty-seven (32.7%) females experienced bleeding complications during pregnancy. Of the 43 females who reported miscarriages, 33 (76.7%) experienced a problem with bleeding during miscarriages. Forty-one (37.6%) participants reported a history of PPH of concern to a healthcare provider.

Table 4. Treatments used for HMB (n = 165).

	n (%)
Oral contraceptives	90 (54.5)
Desmopressin	56 (33.9)
Antifibrinolytics	40 (24.2)
Blood or plasma products	12 (7.3)
Clotting factor products	10 (6.1)
Endometrial ablation	7 (4.2)
Levonorgestrel IUD	5 (3.0)
Uterine artery embolization	3 (1.8)
Platelet transfusion	1 (0.6)

HMB, heavy menstrual bleeding; IUD, intrauterine device.

Discussion

The implementation of a targeted surveillance effort among female HTC patients provides the opportunity to characterize the severity and scope of the disorders, symptoms and outcomes; identify risk factors for outcomes of interest; and identify future research questions. For male patients with haemophilia, the UDC has been a valuable system to describe the burden

Table 5. Frequency of gynaecological abnormalities among menstruating females (n = 217).

	n (%)
Pain during menses	110 (50.7)
Irregular cycles	102 (47.0)
Breakthrough spotting	85 (39.2)
Mid-cycle abdominal pain	61 (28.1)
Bleeding ovarian cysts	31 (14.3)
Endometriosis	26 (12.0)
Fibroids	19 (8.8)
Uterine or cervical polyps	11 (5.1)
Uterine or cervical cancer	6 (2.8)

Table 6. Frequency of pregnancy outcomes in 119 females (n = 302).

	n (%)
Full-term delivery	207 (68.5)
First trimester miscarriage	42 (13.9)
Preterm delivery	24 (7.9)
Second trimester miscarriage	17 (5.6)
Elective termination	8 (2.6)
Ectopic, tubal or molar	4 (1.3)
Bleeding during miscarriage*	33 (76.7)
Bleeding during pregnancy†	37 (31.1)
Bleeding postpartum‡	41 (37.6)

*Restricted to 43 females reporting history of miscarriage.
†Restricted to 119 females who had pregnancy.
‡Restricted to 109 females reporting delivery.

of disease and monitor complications [7]. The female UDC, on the other hand, is the first prospective, longitudinal surveillance in the US focusing on FBD and will provide insight into the diversity of disease expression, healthcare utilization, treatment patterns and health outcomes in this population.

The baseline data demonstrate that FBD experience a considerable burden of disease as a result of HMB, other bleeding symptoms and obstetrical complications. The prevalence of HMB among FBD has been reported to vary from 10% to 100% [8] with a higher proportion (≥80%) in women with VWD. In our surveillance of women with a variety of bleeding disorders, nearly 80% reported HMB and over half of these women required intervention, including hysterectomy in 10.6% of the cases.

This surveillance provides the first ever nationwide data on treatment patterns for FBD in the US. Oral contraceptives and the haemostatic agents DDAVP and antifibrinolytics were the most common treatments used for HMB. However, the haemostatic agents seemingly were underused as approximately 34% of patients reported using such agents. It is not clear if that was because a proportion of those patients were experiencing non-bleeding disorder-related HMB such as fibroids or had anovulatory HMB that led the caregiver to use hormonal based measures instead. It is also not clear whether the underutilization of DDAVP reflects in part the experience of HTC caregivers that DDAVP may not be as effective treatment for bleeding disorder-related HMB or possibly low patient preference due to cost and side effects [9]. Previous treatment studies have suggested a very high efficacy of DDAVP for VWD-related HMB, but response was based on subjective patient assessment [10,11]. Subsequent studies using more objective measures of menstrual blood loss such as the pictorial blood assessment chart (PBAC) or spectrophotometric assessment have demonstrated a lesser degree of efficacy for DDAVP [12,13]. However, a recent cross-over study of intranasal (IN)-DDAVP compared with the antifibrinolytic agent tranexamic acid (TA) did show a statistically significant decrease in menstrual flow by PBAC as well as improvement in QOL with IN-DDAVP [14].

The underutilization of antifibrinolytics in our population is probably explained by the lack of availability of TA in the USA. In Europe, TA has been the preferred non-hormonal agent for HMB in general (with or without a bleeding disorder) for decades based on several well-conducted studies summarized in the Cochrane reviews [15]. In the cross-over study of IN-DDAVP and TA, TA reduced menstrual flow and improved QOL to a greater degree than IN-DDAVP. The US Food and Drug Administration (FDA) approved a new sustained release form of TA (Lysteda™; Ferring Pharmaceuticals, Parsippany, NJ, USA) in December 2009 [16]. The introduction of TA to the US offers an efficacious treatment option for FBD. One-tenth of our patients had undergone a hysterectomy to control their HMB, which also underscores the need to adopt effective, non-surgical therapies. The mean age of hysterectomy in our population was more than 10 years younger than the national average [17]. It should be noted that the proportion of hysterectomies reported in this cohort appears to be congruent with smaller single institution studies reported in the last decade [18,19].

Our present surveillance of HMB treatments also highlights the underutilization of the LNG-IUS for HMB. In Europe, LNG-IUS appears to be the preferred hormonal measure to control HMB [20,21]; this was also recently reported in a consensus conference of international experts in gynaecology and haematology [22]. Although the LNG-IUS (Mirena®; Bayer HealthCare Pharmaceuticals Inc., Wayne, NJ, USA), has been available in the US for intrauterine contraception since 2000, the indication for treatment of HMB was not approved until October 2009 [23]. Over time, we expect LNG-IUS usage to increase among FBD with HMB. Recently, Chi *et al.* updated their experience of the LNG-IUS for inherited bleeding disorder-related HMB. They reported a significant decrease in PBAC scores as well as improvements in haemoglobin, ferritin and QOL [24].

Besides HMB, there were a number of other gynaecological conditions reported in this cohort such as pain during menses, mid-cycle spotting, irregular menstrual cycles, haemorrhagic ovarian cysts, endometriosis and fibroids. Although the occurrence of these gynaecological conditions has been reported in VWD [18,19,25], they also appear to be prevalent in other inherited bleeding disorders. Irregular bleeding reported in approximately half of our patients is an interesting observation. Intuitively, women with underlying bleeding disorders may have worse bleeding when they have anovulatory irregular cycles. Thus, haemostatic and hormonal therapies combined would appear appropriate for FBD with such irregular and heavy menstrual bleeding. A recent study showed that TA was an effective treatment for anovulatory HMB in terms of decreasing bleeding severity by 90% from baseline [26].

Our data demonstrate that pregnancy and childbirth in this population are subjected to various complications. Pregnancy in FBD affects not only the mother but also her foetus. Adverse pregnancy outcomes included miscarriages, preterm deliveries and ectopic pregnancies. The major obstetrical manifestations reported were bleeding during pregnancy, miscarriages and PPH. PPH is the leading cause of maternal mortality in the world [27] and FBD appear to be at an increased risk. In a CDC study of 102 women with VWD, 59% of women reported a history of PPH compared with 21% of controls [25]. An analysis of a large US inpatient hospital database also showed that women with VWD

were more likely to experience PPH [2]. The female UDC is the largest surveillance of pregnancy outcomes of FBD, to date, and will provide an opportunity to optimize management during this critical period. Identifying this subset of women at risk for PPH could prevent morbidity and mortality at the time of delivery by either providing appropriate prophylaxis or being prepared for aggressive intervention in the case of haemorrhage. Further collaboration between obstetricians and haematologists is necessary to provide appropriate care to these patients to reduce the occurrence of PPH and other adverse events [28,29].

Delayed diagnosis of FBD has been considered a barrier to timely treatment and a signal of late recognition by healthcare providers. A previous CDC survey of 75 women with VWD reported that the average age of diagnosis was 23 years and the average time from the onset of first symptom to clinical recognition was 16 years [30]. Referral to the HTC was primarily by a haematologist (31%) or gynaecologist (17%). The current surveillance data indicate that the average age of diagnosis was 15.4 years and nearly 52% of the participants were diagnosed with a bleeding disorder by the age of 12 years. Paediatrician and family members seem to be the major referral sources. The majority of our population had a family history of bleeding disorders, which may partially explain the high percentage of referrals from family members and some early diagnoses. Over 30% of participants were not diagnosed until 18 years or older. Although some awareness and education messages may be reaching the paediatric professional community, there is still a need to reinforce the importance of early recognition of bleeding symptoms and early diagnosis. Future publications will include analyses of clinical characteristics in the various age groups.

A modified bleeding assessment tool based on the Vicenza score was used in the female UDC to assess bleeding symptoms in females with bleeding disorders [31]. Although menstrual bleeding, bruising and bleeding with pregnancy were the most common reported symptoms, a high percentage required provider intervention for various kinds of bleeding episodes. Of interest, 16% of the females reported joint bleeding. These findings of increased bleeding symptoms wherein nearly 50% had ≥4 bleeding symptoms underscore the morbidity of a bleeding disorder in females beyond the obstetrical and gynaecological issues they may encounter. As the sample size increases, we plan to compare our symptom score with the Vicenza score.

Our initial findings from the female UDC have some limitations primarily due to the relatively small sample size, to date, that precludes meaningful comparison of bleeding symptoms and treatment outcomes between diagnoses. The bleeding tendencies of females with FVIII and factor IX deficiencies still remain unclear, as are their effect on obstetrical and gynaecological morbidity. As data continue to accrue, future analyses will explore comparisons between diagnoses, trends in treatment and age-related presentation of disease. As the initial data collection was retrospective, there is potential recall bias. We did limit the menstrual history recall to those women who are presently menstruating. Nonetheless, this surveillance relies on self-reported data, which may overestimate morbidity. It is not known how many eligible patients were seen at participating HTCs and what proportion elected to participate; the females enroled may represent the most severe, symptomatic cases. Nonetheless, the pronounced morbidity in terms of multiple non-obstetrical-gynaecological bleeding symptoms as well as obstetrical-gynaecological bleeding symptoms with a relatively high proportion requiring provider intervention is a reminder that continued public and healthcare provider awareness, surveillance and care of such women is crucial. Furthermore, our preliminary results suggest a need for provider education regarding effective management options (in particular TA and the LNG-IUS) in hopes of improving gynaecological morbidity and QOL. Our data also suggest a need for improved management protocols for affected women undergoing childbirth.

Conclusion

Public health surveillance of FBD is essential to identify risk factors and complications. This longitudinal data collection will inform clinical practice as well as the development of interventions to reduce adverse outcomes. The burden of bleeding disorders appears to be pronounced among reproductive aged females, which has implications for QOL and maternal and foetal outcomes. National and international attention, support and resources are needed to address this public health problem. The increased morbidity among FBD is not limited to females in the US; consequently, we look forward to harmonizing our database with international registries with hopes of improving care and research for women worldwide.

Disclosures

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

PAK has acted as a paid consultant to CSL Behring and to Ferring Pharmaceuticals; both companies manufacture products for the treatment of menorrhagia in women with bleeding disorders. CSL markets and manufactures Stimate and Humate P; Ferring manufactures Lysteda. The remaining authors have no interests which might be perceived as posing a conflict or bias.

This article is part of a supplement supported by an unrestricted educational grant from CSL Behring.

Acknowledgements

We would like to thank the following female UDC coordinators and their respective HTCs and staff for their commitment and participation: Maura Malone Dumas, Dartmouth-Hitchcock Hemophilia Center; Latoya Lashley, Boston Hemophilia Center-Children's Hospital; Jennifer LaFranco, Mary M. Gooley Hemophilia Center; Donna Arden, Charleston Area Medical Center; Karen Panckeri, Penn Comprehensive Hemophilia Center; Anita Smith and Annie Everhart, Wake Forest School of Medicine; Susan Peterson and Elviana Tur, University of Kentucky Hemophilia Treatment Center; Julie Thomas, Vanderbilt University Medical Center; Jayme Harvey, Indiana Hemophilia and Thrombosis Center; Laura Carlson, Michigan State University Center for Bleeding Disorders and Clotting Disorders; Sue Curoe, University of Minnesota Medical Center-Fairview; Rosie Howard, Rush University Medical Center; Elaine Reeves, Oklahoma Center for Bleeding Disorders; Aleida Stark, Texas Children's Hemophilia and Thrombosis Center; Debbie Nelson, Kansas City Regional Hemophilia Center; Mary Lou Damiano, Arizona Hemophilia and Thrombosis Center; Candace Lee, Rady Children's Hospital of San Diego; Jeri Tucker, Children's Hospital Orange County; James Riddel, Children's Hospital Oakland; Kathrynn Mosley, Oregon Hemophilia Treatment Center.

This work was supported by a cooperative agreement with the Centers for Disease Control and Prevention, USA.

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