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# Clinical management of woman with bleeding disorders: A survey among European haemophilia treatment centres

Karin P. M. van Galen[1] | Michelle Lavin[2,3] | Naja Skouw-Rasmussen[4] | Eva Ivanova[5] | Eveline Mauser-Bunschoten[1] | Marieke Punt[1] | Gerychová Romana[6] | Petra Elfvinge[7] | Roseline D'Oiron[8] | Rezan Abdul-Kadir[9]

[1]Van Creveldkliniek, University Medical Center Utrecht, University Utrecht, Utrecht, The Netherlands

[2]Irish Centre for Vascular Biology, School of Pharmacy and Biomedical Sciences, Royal College of Surgeons in Ireland, Dublin, Ireland

[3]Department of Haematology, Beaumont Hospital, Beaumont, Dublin, Ireland

[4]European Haemophilia Consortium, Brussels, Belgium

[5]Department of Haematology, University Hospital, Hradec Králové, Czech Republic

[6]Department of Gynaecology, University Hospital Brno, Brno, Czech Republic

[7]Department of Haematology, Karolinska University, Stockholm, Sweden

[8]Inserm U 1176, APHP Paris Saclay, Hôpital Bicêtre, Le Kremlin Bicêtre, France

[9]Department of Obstetrics and Gynaecology, Royal Free Foundation Hospital and Institute for Women's Health, University College London, London, UK

**Correspondence**
Karin P. M. van Galen, Van Creveldkliniek, University Medical Center Utrecht, University Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands.
Email: k.p.m.vangalen@umcutrecht.nl

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## Abstract

**Introduction:** The impact of bleeding for women with bleeding disorders (WBD) is of increasing focus and importance. Despite this, optimal management strategies are unclear and knowledge gaps persist.

**Aim:** To examine practices and define research priorities on diagnosis and management of WBD in Europe.

**Methods:** An electronic survey on clinical management of WBD was sent to 136 European haemophilia treatment centres (HTCs), including open questions on knowledge gaps and research priorities.

**Results:** Fifty-nine HTCs from 12 Western (WE) and 13 Central/Eastern European (CEE) countries completed the survey. Less than half runs a joint clinic (24 HTCs, 42%). Most centres without a joint clinic have a named obstetrician (81%) and/or gynaecologist (75%) available for collaboration. Overall 18/54 (33%) European HTCs do not offer preimplantation genetic diagnosis. Third trimester amniocentesis to guide obstetric management is available 28/54 HTCs (52%), less frequent in CEE compared to WE countries (5/17 vs 23/37, $P = .03$). 53% of HTCs (28/53) reported that only 0%-25% of WBD seek medical advice for heavy menstrual bleeding (HMB). An algorithm managing acute HMB in WBD is lacking in 22/53 (42%) HTCs. The main reported knowledge and research gaps are lack of awareness & education on WBD among patients and caregivers, optimal diagnostic strategies and effective multidisciplinary management of pregnancy & HMB.

**Conclusion:** Joint clinics, prenatal diagnostics and algorithms for managing acute HMB are lacking in many European HTCs. HMB may be an underestimated issue. This survey highlights the need to prioritize improvement of knowledge and patient care for WBD across Europe.

KEYWORDS

bleeding disorder, haemophilia, heavy menstrual bleeding, postpartum haemorrhage and reproduction, survey, von Willebrand disease

## 1 | INTRODUCTION

Issues faced by women with inherited bleeding disorders (WBD) were emphasized in a recent patient survey conducted by the European Hemophilia Consortium (EHC).[1] WBD experience substantial diagnostic delay and significant disease impact on their daily life. This is most evident for heavy menstrual bleeding (HMB), reported by more than half of these women. Considerations on management options require multidisciplinary and shared decision-making. Joint clinics, where women can consult with a haematologist, gynaecologist, nurse, psychologist/social worker, etc during one visit, will likely facilitate a personalized and combined plan of action to improve quality of life and social participation.[2]

Difficulties with reproductive decision-making are also major concern for WBD according to the EHC patient survey results.[1] The possibility of transmitting the genetic defect to offspring introduces the option of preimplantation diagnosis (PGD) in haemophilia.[3] During pregnancy, decisions on prenatal diagnostics (PND) need to be made, in early stages with the option to terminate pregnancy and in later stages to assist safe delivery. It is currently unknown to what extent PGD and PND are available for WBD across Europe, although diverse cultural and economic differences between countries may influence availability.

Women with bleeding disorders are at increased risk for postpartum haemorrhage (PPH), which occurs for example 2-3 times more often compared to the normal population in woman with von Willebrand disease (VWD) and carriers of haemophilia.[4-6] Optimal management strategies to prevent PPH and secure safe delivery for the possibly affected child are currently undefined. Close collaboration with other disciplines such as clinical geneticists, obstetricians, gynaecologists, neonatologists, paediatricians and anaesthetists is then important, but current practices on this aspect of care for WBD in European Haemophilia Treatment Centers (HTCs) are unknown.

Despite increasing attention in recent years, medical knowledge on WBD lags far behind that of men with haemophilia. However, bleeding disorders in general affect men and women equally. In order to address this gender-related gap, the European Association for Haemophilia and Allied Disorders founded the Women and Bleeding Disorders Working Group in September 2018 (EAHAD-WBD working group). Its aims are to gather knowledge and define research priorities on WBD to accelerate improvement of diagnosis and clinical management for WBD across Europe. The current survey aims to gain better insight into present-day clinical management of WBD in European HTCs and gather the most important knowledge gaps and research priorities felt by this community.

## 2 | METHODS

Between 9 May and 3 July 2019, an electronic survey on the multidisciplinary management of heavy menstrual bleeding (HMB) and pregnancy was sent to 136 certified European HTCs on behalf of the EAHAD. The survey consisted of multiple choice questions and two open questions on clinical knowledge gaps and research priorities for WBD and could be completed within ten minutes (full survey available on request). We asked for a single response per centre.

Differences in proportions were tested for significance with chi-square testing. Logistic regression was used to calculate odds ratio with 95% confidence interval (CI), and differences in proportions were considered statistically significant if the *P* value was <.05. Central themes from the open question responses were extracted by five working group members independently (KG, NR, PE, ML and RK) and by one external clinical researcher (MP). These themes were then merged into 3-5 main themes for each question by two authors who both received training in qualitative research (KG and MP) and confirmed by all authors in a final read back via email.

**TABLE 1** Baseline characteristics of the 59 respondents

| Characteristics | Number (%) |
|---|---|
| Haematologist | 35 (59%) |
| Paediatrician | 16 (27%) |
| Nurse | 1 (2%) |
| Other | 7 (12%) |
| Female sex[a] | 36 (63%) |
| Total number of patients with CBD[a] | |
| <100 | 4 (7%) |
| 100-500 | 32 (56%) |
| >500 | 21 (37%) |
| Number of female patients with CBD[a] | |
| <100 | 25 (44%) |
| 100-500 | 23 (40%) |
| >500 | 9 (16%) |
| Working at HTC in CEE | 20 (34%) |
| Working at HTC in WE | 39 (66%) |
| Patient population[a] | |
| Only children with CBD | 6 (11%) |
| Only adults with CBD | 15 (26%) |
| Both adults and children with CBD | 36 (63%) |

Abbreviations: CBD, congenital bleeding disorder; CEE, central or eastern european country; HTC, haemophilia treatment centre; WE, western european country.

[a]Based on 57 responses.

## 3 | RESULTS

The survey was completed by 59 HTCs from 12 Western (WE) and 20 HTCs from 13 Central/Eastern European (CEE) countries, representing a response rate of 43%. More HTCs from WE responded compared to CEE countries (n = 39 vs 20, Table 1). Responses were missing from four WE and four CEE countries (Figure 1 and Table S1). All HTCs reported treatment of WBDs. In total, 51 respondents


**FIGURE 1** Number of responding haemophilia treatment centres per country

answered both open questions regarding the main knowledge and research gaps in the clinical management of WBD.

### 3.1 | Respondents

The baseline characteristics of the respondents are summarized in Table 1. Most respondents were haematologists (59%), followed by (haematology) paediatricians (27%). More females responded (63%) compared to men; however, no information is available on the gender distribution of haemophilia treating physicians within the HTCs. More than a third of the respondents are employed at a large HTC (37% from HTC with >500 registered patients), and most HTCs treat both adults and children (63%).

### 3.2 | Joint clinics

A joint clinic for WBDs, defined as a multidisciplinary clinic where WBD can consult with a haematologist, obstetrician, gynaecologist, nurse, psychologist/social worker, etc during one visit, exists in 24 clinics (24/57, 42%, not confined to the large HTCs, information on a joint clinic missing in two respondents). Assessment of HMB during a joint clinic is reported in 19 centres (33%) and assessment of pregnancy in 18 centres (32%). Most respondents from HTCs without a joint clinic think it could be beneficial to organize such a clinic (66%). The majority of these centres did have a named obstetrician (81%) and/or gynaecologist (75%) available and a pathway to collaboration for managing pregnancy and HMB/other gynaecological issues, respectively.

### 3.2.1 | Barriers to organize a joint clinic for WBD

At least one barrier to organize a joint clinic is reported by 31 of the respondents without a joint clinic (94%), 15 respondents reported multiple barriers. Financial (10 respondents) and institutional barriers (20 respondents) were most frequently reported. None of the respondents reported lack of interest among patients as a barrier (Figure 2). Physician-imposed barriers were also frequently reported: 'Never thought of it' n = 5; 'Do not know how' n = 2; 'Lack of interest' n = 3; 'Not needed' n = 4; and 'Do not have the arguments needed to advocate for this' n = 3. In six respondents, physician-imposed barriers were the only imposed barrier to organize a joint clinic.

## 3.3 | Prenatal diagnostics

In total, 54 centres reported on the availability of PGD. Overall 18/54 (33%) European HTCs do not offer PGD. It is available onsite in 14 centres (26%) or there is a possibility for referral to another centre in 22 HTCs (41%). PGD availability is not different for CEE compared to WE countries. When taking the possibility for referral into account, PGD appeared slightly more often available in large (>500 patients) compared to smaller HTCs (16/21, 76%, vs 20/33, 61%, respectively, $P = .24$).

Non-invasive prenatal testing for foetal gender (Y-PCR) in maternal blood from 10 weeks gestation was reported to be available in 36 HTCs and ultrasound to assess foetal gender from 16 weeks gestation in 41 HTCs. Two respondents answered that no foetal gender assessment is available. The main method of prenatal diagnosis to terminate pregnancy in case of an affected child is chorionic villus sampling between 11 and 14 weeks of gestation (n = 32), followed by amniocentesis between 15 and 20 weeks (n = 13). Availability of third trimester amniocentesis to guide obstetric management was reported by 28/54 respondents (52%), although less frequent in CEE countries (5/17, 29%) compared to WE countries (23/37, 62%, $P = .03$). No difference appeared between large and smaller HTCs in this practice. If some or none of these prenatal diagnosis practices were available, the reported reason was mostly feasibility (n = 10), but sometimes also for cultural reasons (n = 6, exclusively CEE countries).

## 3.4 | Registries

Women with bleeding disorders are reported into a national registry in 31/53 HTCs, slightly more often in WE (12/17, 71%) compared to CEE countries (19/36, 53%).

## 3.5 | Heavy menstrual bleeding

Most respondents (28/53) reported that 0%-25% of WBD seek medical advice for HMB. A minority reported that more than half of the WBD seek advice for HBM (9/53), almost exclusively in the WE countries (8/9) and twice more often in large HTCs compared to smaller HTCs (6/20 vs 3/33, $P = .05$). An algorithm for the management of acute HMB in WBD is lacking in 22/53 (42%) HTCs, as often in WE and CEE countries. Paediatricians seem to have such an algorithm available more frequently since 10/13 paediatricians reported to have one, vs 21/40 non-paediatrician respondents (OR 3.0; 95% CI 0.72-13, $P = .13$).

Seventy per cent (37/53) of the HTCs uses a bleeding score, by far most frequently the ISTH BAT (29/53). In contrast, only 16 centres (30%) reported to often or always use the pictorial bleeding assessment chart (PBAC) to quantify menstrual blood loss and only 12% uses both the ISTH BAT and the PBAC.

## 3.6 | Knowledge and research gaps in the management of WBD

In total, 51 respondents answered the two open questions on, in their opinion, the main knowledge gaps and research priorities in the clinical management of WBD (raw data available on request). The extracted themes are described in Table 2. In summary, we identified lack of awareness & education on bleeding disorders among patients and caregivers, optimal diagnostic strategies and effective

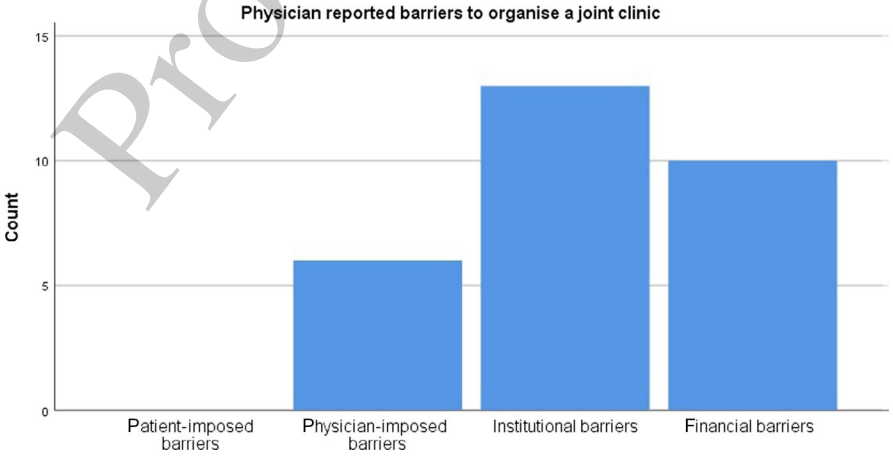


**FIGURE 2** Reported barriers to organize a joint clinic

**TABLE 2** Main themes extracted from the open questions on knowledge gaps and research priorities

| |
|---|
| What are the main knowledge gaps in the clinical management of WBD? |
| 1. Awareness & education: Lack of knowledge about bleeding disorders among patients, gynaecologists and other caregivers<br>2. Diagnostic challenges: Optimal path to reach a correct diagnosis?<br>3. Standardization of care: Need for effective multidisciplinary management of pregnancy and HMB |
| What are the main research priorities for improving the clinical management of WBD? |
| 1. Increase knowledge of caregivers on bleeding disorders and identify barriers for WBD to seek care<br>2. Find optimal diagnostic strategies<br>3. Investigate optimal management of pregnancy and HMB, including algorithms and new therapies<br>4. More data collection: Need for registries<br>5. Understand women-specific haemostasis |

multidisciplinary management of pregnancy & HMB as the main knowledge and research gaps.

## 4 | DISCUSSION

The presented survey results from 59/136 certified HTCs give an impression of the current state of clinical practice regarding WBD across a broad range of European HTCs. In this highly specialized clinical setting, joint clinics, prenatal diagnostics and algorithms for managing acute HMB are not widely available. Furthermore, HMB may be an underestimated issue.

Strengths of this study are that it is a large survey on behalf of EAHAD with a satisfactory response rate of 43% and represents both WE and CEE countries. This gives a good overview of current WBD clinical practice in certified European HTCs. Possible limitations are reporting bias, since a single response was requested per centre. The respondents were mostly haematologists/paediatricians who may be unaware of all facilities, especially regarding PND options. In general, less HTCs per CEE country responded compared to WE countries (Figure 1), which might give an overestimation of the quality of clinical care for WBD in general in CEE compared to WE countries.

In the large European patient survey by the EHC, WBD registered with HTCs were 2.2 times more likely to receive treatment compared to WBD in other hospital services.[1] Although the current HTC structures may facilitate treatment, the current survey among European HTCs highlights important areas for improvement. Whilst PND in reproductive decision-making is generally highly valued by patients,[7-10] substantial differences in availability of PND and PGD are evident. Furthermore, despite the EHC survey flagging HMB as a major concern in the majority of WBD,[1] most HTCs reported that only 0%-25% of WBD seek medical advice for it. This would suggest that either WBD are failing to report symptoms, or that HTC based physicians may not adequately assess for HMB in their patients; either way, a cultural change seems required.

The absence of a management algorithm for acute HMB in the majority of HTCs also underscores room for improving HMB care for WBD. The finding that paediatrics more often have such an algorithm available compared to adult haematologists is encouraging in that preparation for menarche should be central to the provision of care for adolescent WBD. In this current survey, no information is available on how these algorithms look like and to what extent they support local clinical practice. The PBAC score is hardly used which is unfortunate, since quantification of blood loss could help to give the women control and aid in the dialogue between the WBD and their physician, especially in young women who are less aware of a normal cycle bleed.[11] The finding that 20% of HTCs use a Tosetto/MCMDM version as their bleeding assessment tool (BAT) is of concern—as it is relatively insensitive for HMB since women must seek medical care before acquiring any scores for this domain.[12] If indeed only 0%-25% of WBD seek medical advice for HMB, as reported by most HTCs in this survey, then utilization of the Tosetto/MCMDM BAT would result in a score of 0 for the HMB domain, irrespective of the heaviness of their periods. This is not a helpful tool for HMB assessment.

The need for effective multidisciplinary management of pregnancy and HMB was highlighted as a main priority in this survey. Joint clinics are unarguably valued by WBD themselves and likely to have added value for clinical practice since they require close multidisciplinary collaboration and inherently knowledge exchange between healthcare professionals.[13] Physician-imposed barriers could be overcome by clear guidelines on the basis ingredients for such clinics. If joint clinics grow into common practice in an increasing proportion of HTCs, institutional barriers could also become easier to resolve. More scientific data should be generated to support this practice, including diagnosis and prospective outcome assessment of treatment algorithms and new therapies.

## 5 | CONCLUSION

Joint clinics, prenatal diagnostics and algorithms for managing acute HMB are not widely available in European HTCs. HMB may be an underestimated issue. The results of this survey highlight the need to prioritize improvement of knowledge and patient care for WBD across Europe.

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### DISCLOSURES

Karin van Galen received unrestricted research grants from CSL Behring and Bayer in the past and speakers fee from Takeda and Amgen. Michelle Lavin served on a speakers bureau for Shire and received research funding from Shire/Takeda, speakers fees from

Siemens Healthcare. Roseline D'Oiron served as a consultant for Baxalta/shire, Bayer, CSL Behring, LFB, NovoNordisk, Octapharma, Pfizer, Roche and Sobi, Spark and was invited speaker for Baxalta/shire, Bayer, CSL Behring, LFB, NovoNordisk, Octapharma, Pfizer, Roche and Sobi, Spark.

## ORCID

*Karin P. M. van Galen* https://orcid.org/0000-0003-3251-8595
*Michelle Lavin* https://orcid.org/0000-0003-2999-4216
*Marieke Punt* https://orcid.org/0000-0002-1891-5255
*Roseline D'Oiron* https://orcid.org/0000-0002-4843-7805
*Rezan Abdul-Kadir* https://orcid.org/0000-0002-2684-1006

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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