

WOMEN AND HEMOPHILIA: ASSESSMENT OF THE BLEEDING PHENOTYPE - ANALYSIS OF THE BRESCIA COHORT

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Background and Aims. Female genetic carriers of hemophilia face an increased risk of bleeding manifestations that have historically been underestimated or correlated with plasma factor levels only. Despite the updated ISTH nomenclature, many symptomatic women and girls remain undiagnosed and lack access to specialized Hemophilia Treatment Centers (HTCs). This work aimed to implement a proactive multidisciplinary screening pathway at the ASST Spedali Civili di Brescia to analyze the clinical, genetic, and phenotypic profiles of a female cohort of obligated and potential genetic carriers of hemophilia A and B, facilitating earlier diagnosis and personalized management.

Methods. A screening protocol was established involving both the Pediatric and Adult HTCs in Brescia. The population (N=33) was stratified according to ISTH definitions into: Women and Girls with Hemophilia (WGH, N=12, factor levels <40 IU/dL) and Hemophilia Carriers (HC, N=14, factor levels ≥40 IU/dL); we added the category of Potential Carriers (PC, N=7), including women and girls who weren't obligated genetic carriers and were waiting for genetic confirmation tests. The bleeding phenotype was assessed using the ISTH-Bleeding Assessment Tool (ISTH-BAT), with a specific focus on Heavy Menstrual Bleeding (HMB). Laboratory testing included coagulation factors VIII and IX (FVIII/FIX) levels determined via one-stage (OSA) and chromogenic substrate (CSA) assays, VWF assays (antigen and activity), an iron status evaluation (serum iron, serum ferritin) and routine hemocoagulative tests (complete blood count, prothrombin time, activated partial thromboplastin time, fibrinogen).

Results. The proactive screening successfully identified eight WGH (66% of the subgroup) previously unknown to the HTC, emphasizing the underdiagnosis of the condition even within known hemophilia families. An abnormal bleeding phenotype (pathological ISTH-BAT and/or HMB) was identified in 24.2% of the total cohort, with higher prevalence in WGH (41.6%) compared to HC (14.2%). Clinical data

analysis confirmed that HMB is the most frequent and impactful symptom, accounting for 40% of the total ISTH-BAT variance – occasionally leading to chronic iron deficiency, even in cases with sub-pathological ISTH-BAT scores. In accordance with the published literature, no direct linear correlation was found between FVIII/FIX levels and bleeding severity, suggesting that other factors may influence the phenotype.

Conclusions. A significant percentage of symptomatic carriers remain unrecognized. The lack of a clear correlation between laboratory factor levels and clinical symptoms reinforces the necessity of adopting validated clinical tools like the ISTH-BAT and prioritizing menstrual history in the diagnostic workup. Our findings strengthen the importance of implementing proactive, family-based screening pathways – essential to ensure gender equity in hemophilia care and to prevent hemorrhagic complications during critical life events, such as surgery, menarche, childbirth, or the transition to perimenopause.

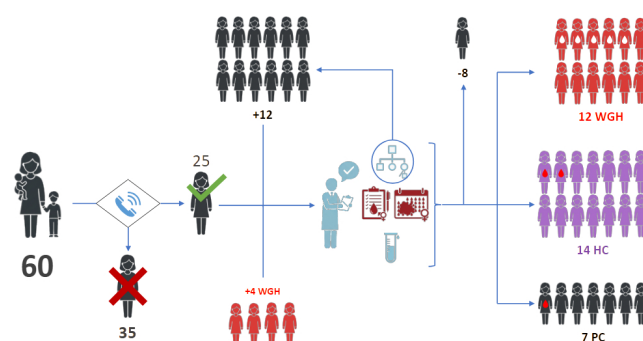


Figure 1. Integrated screening protocol and clinical outcomes infographic
From an initial cohort of 60 mothers of PWH, 25 were enrolled via telephone triage (35 were unavailable/declined). The cohort was supplemented by 12 family members identified through pedigree analysis and 4 previously known cases. The workup included bleeding assessment (ISTH-BAT and/or HMB) and laboratory assays. After 8 patients were lost to follow-up, final stratification identified 12 WGH, 14 HC, and 7 PC. Overall, 8 subjects presented an abnormal bleeding phenotype (symbolized by the drop icon).

Legend

PWH: Patient with Hemophilia; WGH: Women and Girls with Hemophilia; HC: Hemophilia Carriers; PC: Potential Carriers (waiting for genetic confirmation); HMB: Heavy Menstrual Bleeding.