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UNCOVERING HIDDEN MORBIDITY: UNDIAGNOSED VON WILLEBRAND DISEASE AND IRON DEFICIENCY IN WOMEN WITH HEAVY MENSTRUAL BLEEDING

Ayman Ali[1], Ayesha Riaz[1], Beenish Gulshad[1], Hina Begum[1], Naeem Khattak[2]*

[1] Postgraduate Resident, Department of Obstetrics and Gynecology, Mardan Medical Complex, Medical Teaching Institution (MTI), Mardan, Pakistan.
[2] Department of Community Medicine, Bacha Khan Medical College, Medical Teaching Institution (MTI), Mardan, Pakistan.
*Corresponding Author: Naeem Khattak, Email: naeemkhattak520@gmail.com

ABSTRACT

Background: Heavy menstrual bleeding (HMB) is a common gynecological complaint associated with considerable morbidity. Despite its high prevalence, underlying bleeding disorders and iron deficiency often remain undiagnosed, resulting in delayed diagnosis and suboptimal management.

Objective: To determine the prevalence of undiagnosed von Willebrand factor (vWF) abnormalities, anemia, and iron deficiency among women presenting with heavy menstrual bleeding at a tertiary care hospital in Pakistan.

Methods: A hospital-based observational study was conducted among 312 women aged 15–49 years presenting with heavy menstrual bleeding at Mardan Medical Complex, Pakistan. Participants underwent standardized clinical assessment using the Pictorial Blood Loss Assessment Chart (PBAC), pelvic ultrasonography, hematological investigations, ferritin measurement, inflammatory marker assessment, and coagulation screening including von Willebrand factor testing where indicated. Data were analyzed using SPSS version 26.0 with non-parametric and categorical statistical tests; statistical significance was set at $p < 0.05$.

Results: Among the 312 participants, anemia (hemoglobin <120 g/L) was identified in 37.3%, while severe anemia was present in 9.5%. Iron deficiency was observed in 43.1% using a ferritin threshold of <15 µg/L, increasing to 72.2% when a cutoff of <30 µg/L was applied. Routine coagulation parameters were normal in nearly all participants; however, abnormal vWF activity was detected in 28 of 306 women (9.2%) without a previously diagnosed bleeding disorder. Women with reduced vWF activity also demonstrated significantly lower factor VIII levels ($p < 0.01$).

Conclusion: Women with heavy menstrual bleeding have a substantial burden of previously unrecognized iron deficiency and von Willebrand factor abnormalities that are not detected by routine coagulation testing. Incorporating ferritin assessment and targeted von Willebrand disease screening into the routine evaluation of HMB may facilitate earlier diagnosis and improve clinical outcomes.

KEYWORDS: Heavy menstrual bleeding; von Willebrand disease; von Willebrand factor; Iron deficiency; Anemia; Coagulopathy; Women's health.

INTRODUCTION

Heavy menstrual bleeding (HMB) is a common condition, with an estimated prevalence ranging from 10% to 30% (1). This condition, which is prone to result in health-compromising comorbidities, remains underdiagnosed and inadequately managed. A European survey revealed that 46% of afflicted women had never sought medical assistance for this issue, primarily due to the challenge women face in recognising the extent of their menstrual flow. Sociocultural factors also significantly influence women's likelihood of not reporting HMB, despite its effects on health and social well-being (2,3). Furthermore, there exists a widespread misconception regarding the essential investigations in this context among both women and healthcare professionals (4). Medical causes contributing to HMB have been identified and systematically classified by FIGO (the International Federation of Gynaecology and Obstetrics) in the PALM-COEIN system. This classification includes PALM (Polyps, Adenomyosis, Leiomyomas, and Malignancy or Atypical Endometrial Hyperplasia) and COEIN (Coagulopathies, Ovulatory Disorders, Primary Endometrial Disorders, Iatrogenic causes, and Not Otherwise Classified). HMB may also be associated with coagulation disorders, whether congenital (congenital bleeding disorders [CBD]) or acquired (5,6).

A menorrhagia-specific screening instrument has been recommended by the American College of Obstetricians and Gynaecologists and should be utilised more consistently (2). It includes fundamental coagulation assessments, measurements of Factor VIII (FVIII) activity and von Willebrand Factor (VWF) antigen and activity levels, as well as a comprehensive blood count and ferritin test.7 Indeed, HMB is the primary and occasionally the only symptom observed in adolescents with CBD, resulting in a significantly prolonged duration to diagnosis compared to boys with CBD.6 Furthermore, 70% of women diagnosed with von Willebrand disease (VWD) exhibit heavy

menstrual bleeding (HMB).8 Recommendations from the National Institute for Health and Care Excellence (NICE) suggest that a complete blood count and coagulation parameter assessments should be performed initially, prior to confirming or excluding iron deficiency through a ferritin assay.7 For the latter, the World Health Organisation (WHO) 15 µg/L cutoff for defining iron deficiency continues to be the most widely accepted criterion for hypoferritinemia in the latest 2020 guidelines,9 whereas thresholds of 20 or 30 µg/L are also referenced, and even 70 µg/L in the presence of inflammation.9 Regarding therapy, approaches differ among individual patients. Women diagnosed with CBD will receive appropriate management (desmopressin, tranexamic acid) but may also, similar to those without CBD, require hormone therapy or surgical interventions.Eight, ten, eleven Here, screening for coagulation abnormalities and anaemia was conducted in a substantial cohort of women referred for heavy menstrual bleeding at a specialised centre for haemostatic disorders. This facilitated a comprehensive characterisation of the clinical and biological features of HMB, as well as an assessment of the prevalence of CBD and iron deficiency within this population.

MATERIALS AND METHODS (REWRITTEN FOR MMC MARDAN)

Study Design and Setting

A hospital-based observational study was conducted in the Department of Obstetrics and Gynecology at Medical Teaching Institution (MTI), Mardan Medical Complex, Mardan, Pakistan. A dedicated evaluation pathway for women presenting with heavy menstrual bleeding (HMB) was implemented in the gynecology outpatient clinics and emergency department.

The study was approved by the Institutional Review Board of MTI Mardan Medical Complex. All eligible women were invited to participate.

Participants

Women aged 15–49 years presenting with complaints of heavy menstrual bleeding for at least three consecutive menstrual cycles were included. Heavy menstrual bleeding was defined using a pictorial blood loss assessment chart (PBAC) score ≥100.

Women who were pregnant, had known gynecological malignancy, were using anticoagulant therapy, or had chronic liver or renal disease were excluded.

Clinical Assessment

All participants completed a structured questionnaire capturing demographic data, menstrual history, reproductive history, medication use, and personal and family history of bleeding disorders. Bleeding severity was assessed using the Pictorial Blood Loss Assessment Chart (PBAC), where a score ≥100 was considered diagnostic of HMB. A modified bleeding assessment questionnaire adapted from the International Society on Thrombosis and Haemostasis (ISTH) bleeding assessment tool, covering symptoms such as epistaxis, gum bleeding, easy bruising, surgical bleeding, and postpartum haemorrhage.

Imaging Evaluation

All participants underwent pelvic or transvaginal ultrasonography as part of routine gynaecological assessment. Findings such as uterine fibroids, adenomyosis, endometrial abnormalities, and ovarian pathology were recorded to classify structural causes of bleeding.

Laboratory Investigations

Venous blood samples were obtained under aseptic conditions and analysed in the hospital laboratory. Haematological parameters like haemoglobin concentration and platelet count was assessed. Serum ferritin, C-reactive protein (CRP) to aid interpretation of ferritin was done. Coagulation screening was performed to assess the Prothrombin time (PT), Activated Partial Thromboplastin Time (aPTT), and Plasma fibrinogen levels. Where clinically indicated and feasible, additional testing for von Willebrand factor (vWF) antigen, vWF activity, and factor VIII activity was arranged through referral laboratories. Reference ranges were based on the institutional laboratory standards.

Statistical Analysis

Data was subjected to statistical analysis using SPSS Statistics, Version 26.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was assessed for normality. As the data were not normally distributed, they are reported as median with interquartile range (IQR). Categorical variables were presented as absolute frequencies and corresponding percentages (n, %). For inferential analysis, differences between study groups were evaluated using the non-parametric Mann-Whitney U test for continuous outcomes and Pearson's chi-square test for categorical outcomes. The threshold for statistical significance was established a priori at $p < 0.05$.

Ethical Considerations

Written informed consent was obtained from all participants before enrolment. Participants found to have anaemia or abnormal coagulation profiles were referred for appropriate medical or haematological management.

RESULTS

Participant Characteristics and Ultrasound Findings

During the study period, a total of 312 women presenting with heavy menstrual bleeding were enrolled. Pelvic or transvaginal ultrasonography was normal in 186 women (59.6%), while findings were inconclusive in 8 cases (2.6%). The most frequent structural abnormalities were uterine fibroids in 41 women (13.1%), adenomyosis in 38 (12.2%), and endometrial polyps in 19 (6.1%). Endometriosis was detected in only 5 women (1.6%).

A history of previous surgery was reported by 204 participants (65.4%), of whom 14 (4.5%) described excessive bleeding following a surgical procedure. The most common procedures were dental extractions (92 women, 29.5%), tonsillectomy or appendectomy (51, 16.3%), and gynecologic surgery (44, 14.1%). A history of cesarean section was reported by 28 women (9.0%).

Bleeding Severity and Clinical Profile

The median PBAC score was 298 (IQR 210–480) and the median bleeding assessment score was 3 (IQR 2–4). In 284 of 302 evaluable women (94.0%), heavy menstrual bleeding was the only bleeding symptom, without other spontaneous or surgical bleeding manifestations.

Iron Therapy and Blood Transfusion

A history of packed red cell transfusion was reported by 15 women (4.8%), while 26 (8.3%) had previously received intravenous iron therapy. Both transfusion and intravenous iron had been administered to 6 women (1.9%). Oral iron supplementation had been prescribed to 231 women (74.0%), and 96 (30.8%) reported previous use of tranexamic acid.

Table 1. Previous iron and transfusion therapy

Treatment	Total population (n = 312)
No transfusion / IV iron	265 (84.9%)
PRBC transfusion only	9 (2.9%)
IV iron only	26 (8.3%)
PRBC + IV iron	6 (1.9%)
Missing data	6 (1.9%)
Oral iron therapy	231 (74.0%)
No oral iron	73 (23.4%)
Missing data	8 (2.6%)

Coagulation Disorders

Routine coagulation screening (PT, aPTT, fibrinogen, and platelet count) was within normal laboratory ranges for almost all participants. One woman (0.3%) was diagnosed with a mild factor VII deficiency after a prolonged prothrombin time was identified.

Based on medical history, 6 women (1.9%) had a previously known congenital bleeding disorder: four with von Willebrand disease, one hemophilia carrier, and one with factor VII deficiency.

Women with a known bleeding disorder had significantly lower von Willebrand factor activity and factor VIII levels compared with those without a diagnosed disorder, while other clinical and hematological parameters were comparable.

Table 2. Comparison of women with and without known congenital bleeding disorders

Parameter	No CBD (n = 306)	CBD (n = 6)	P value
Age (years)	30 (22–38)	31 (24–35)	--
BMI (kg/m²)	23 (21–26)	24 (22–28)	--
PBAC score	300 (215–485)	295 (210–520)	--
Hemoglobin (g/L)	124 (116–131)	126 (121–130)	--
Platelets (×10⁹/L)	268 (232–315)	340 (250–402)	--

FVIII:C (IU/dL)	108 (92–128)	72 (60–85)	0.03
VWF activity (IU/dL)	85 (67–104)	38 (20–55)	0.01

von Willebrand Factor Screening in Previously Undiagnosed Women

Among the 306 women without a known bleeding disorder, abnormal von Willebrand factor activity was detected in 28 women (9.2%). Of these, 4 (1.3%) had levels ≤30 IU/dL (severe deficiency), 10 (3.3%) had levels between 31–40 IU/dL, and 14 (4.6%) had mildly reduced levels between 41–50 IU/dL.

These women had significantly lower factor VIII activity compared with women with normal von Willebrand factor levels ($p < 0.01$).

Anemia and Iron Deficiency

At the time of evaluation, anemia (Hb <120 g/L) was present in 114 women (37.3%), with severe anemia (Hb <100 g/L) in 29 (9.5%).

Iron deficiency (ferritin <15 µg/L) was observed in 132 women (43.1%), while 189 (61.8%) had ferritin <20 µg/L and 221 (72.2%) had ferritin <30 µg/L.

C-reactive protein values were normal in 258 of 312 women (82.7%). Elevated CRP (>5 mg/L) was observed in 54 women (17.3%), and was associated with anemia in 11 cases (3.5%).

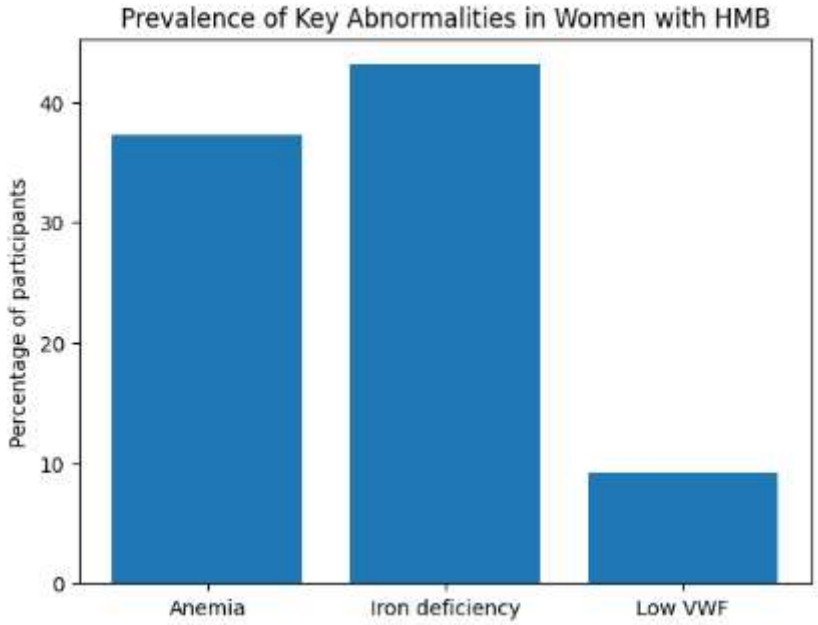

Figure 1. Prevalence of anemia, iron deficiency, and low von Willebrand factor activity among women presenting with heavy menstrual bleeding.

This bar chart shows the proportion of participants with anemia (Hb <120 g/L), iron deficiency (ferritin <15 µg/L), and reduced von Willebrand factor activity (<50 IU/dL).

DISCUSSION

This hospital-based observational study in Mardan, Pakistan, provides critical insights into the underlying causes of heavy menstrual bleeding (HMB) in a previously under-characterized population. Our principal findings reveal a dual burden of disease: a significant prevalence of both undiagnosed potential bleeding disorders and profound iron deficiency. Specifically, we found that while routine coagulation screening was largely uninformative, targeted testing identified abnormal von Willebrand factor (vWF) activity in 9.2% of women without a prior diagnosis. Furthermore, anemia was present in over a third of participants (37.3%), and iron deficiency was rampant, affecting 43.1% to 72.2% of women depending on the ferritin threshold used.

A key finding of our study is the high diagnostic yield of vWF screening in women presenting with HMB, even when it is their sole bleeding symptom. The 9.2% prevalence of low vWF activity in our cohort is consistent with rates reported in international studies, which range from 7.5% to 13% in similar populations (16, 17). This finding challenges the clinical practice of relying solely on a broader personal or family history of bleeding to prompt hematological investigation. In our study, 94% of women reported HMB as their only bleeding manifestation, underscoring the assertion by the American College of Obstetricians and Gynaecologists that HMB itself should

be considered a primary indicator for a potential congenital bleeding disorder (CBD) (2). The fact that routine tests like PT and aPTT were normal in nearly all participants further reinforces that these general screens are insufficient for detecting the most common CBDs, like von Willebrand disease (VWD), associated with HMB. Our results strongly advocate for the integration of specific vWF and Factor VIII activity testing into the standard evaluation pathway for HMB.

The second major finding is the staggering prevalence of iron deficiency and anemia, which persists despite a high rate of prior treatment. While the 37.3% rate of anemia (Hb <120 g/L) is alarming—more than double the estimated prevalence in the general female population (18)—the data on iron stores is even more concerning. Using the WHO threshold of 15 µg/L, 43.1% of women had depleted iron stores, and this figure rose to 72.2% with the more functionally relevant threshold of 30 µg/L (9, 19). This is particularly striking given that 74% of participants had previously been prescribed oral iron. This discrepancy highlights a significant gap in care, suggesting issues with patient adherence, inadequate dosage or duration of therapy, poor oral absorption, or a failure to address the underlying cause of blood loss. This chronic iron-deficient state, even in the absence of overt anemia, can have debilitating consequences on cognitive function, physical capacity, and overall quality of life (18, 19).

Clinical and Public Health Implications The findings from this study have direct implications for clinical practice in Pakistan and similar settings. First, they call for a paradigm shift in the initial workup of HMB, moving beyond gynecological assessment alone to include a standardized hematological evaluation. This should include a full blood count and, crucially, a serum ferritin level to accurately assess iron status. Second, specific screening for VWD with vWF antigen and activity levels should be considered for women with significant HMB (e.g., PBAC >100), irrespective of other bleeding symptoms. Identifying a CBD not only allows for targeted hemostatic therapy (e.g., desmopressin, tranexamic acid) but also has important implications for future surgical procedures and childbirth (10, 11). Finally, the high rate of persistent iron deficiency warrants more aggressive management strategies, including patient education on adherence, and consideration of intravenous iron therapy for women with severe depletion or intolerance to oral supplements.

Strengths and Limitations The primary strength of this study is its prospective design within a real-world clinical setting, utilizing standardized assessment tools like the PBAC and a modified ISTH bleeding questionnaire. The inclusion of a large, consecutive cohort of women enhances the external validity of our findings for similar tertiary care centers. However, we acknowledge several limitations. As a single-center study, our results may not be generalizable to the entire population of Pakistan. There is a potential for referral bias, as a specialized center may attract more severe or complex cases of HMB. Furthermore, while we screened for low vWF, comprehensive diagnostic confirmation of VWD (including multimer analysis or genetic testing) was not performed on-site, which may slightly over- or underestimate the true prevalence.

CONCLUSION

In conclusion, this study validates the strong association between heavy menstrual bleeding, underlying coagulopathies, and severe iron deficiency in a Pakistani cohort. It demonstrates that a substantial number of women with HMB suffer from undiagnosed conditions like VWD that are missed by routine coagulation tests. Our findings robustly support emerging international guidelines that advocate for a more comprehensive and integrated gyneco-hematological investigation of HMB. Implementing routine screening for both iron deficiency and von Willebrand disease is a critical step toward reducing the significant morbidity associated with this common and undertreated condition.

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