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Biochemical, Metabolic, and Cardiovascular Factors Associated With Anemia Severity and Hemoglobin Recovery in Women With Heavy Menstrual Bleeding: A Prospective Cohort Study

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Zubia Bugti [1], Safia Ewaz Ali [1, 2], Ayisha Ejaz Bhutta [3], Shazia Baloch [4], Waqar Ahmed [5], Tariq Hussain [6], Naveed Shuja [7]

1. Department of Obstetrics and Gynecology, Unit I, Sandeman Provincial Hospital, Quetta, PAK 2. Department of Obstetrics and Gynecology, Bolan Medical Complex Hospital (BMCH), Quetta, PAK 3. Department of Obstetrics and Gynaecology, Kettering General Hospital, Kettering, GBR 4. Department of Obstetrics and Gynaecology, Bolan Medical Complex Hospital (BMCH), Quetta, PAK 5. Department of Cardiology, Khatam-un-Nabiyeen Trust (Regd.) Hospital, Sargodha, PAK 6. Department of Biochemistry, Bakhtawar Amin Medical and Dental College, Multan, PAK 7. Department of Biochemistry, Continental Medical College (CMC), Lahore, PAK

Corresponding author: Naveed Shuja, rananaveedshuja@gmail.com

Abstract

Background: Heavy menstrual bleeding (HMB) commonly contributes to anemia in reproductive-aged women. This study investigated clinical, biochemical, metabolic, and cardiovascular factors associated with baseline hemoglobin and subsequent recovery, while describing endometrial histopathology in a clinically selected subgroup.

Methodology: In this prospective observational cohort study, 150 women aged 18-49 years with HMB-associated anemia were enrolled at Sandeman Provincial Hospital in Quetta, Pakistan, in March 2026 and followed for 12 weeks. Assessments included pictorial blood loss assessment chart (PBAC) scores, iron status markers, C-reactive protein levels, metabolic indices, and cardiovascular measurements. The primary longitudinal outcome was the absolute change in hemoglobin level. Multivariable linear regression was used to assess associations, and histopathological findings were evaluated descriptively when clinically indicated.

Results: Mild, moderate, and severe anemia were present in 34 (22.7%), 97 (64.7%), and 19 (12.7%) participants, respectively. Of the 150 women, 140 (93.3%) completed follow-up. Mean hemoglobin levels increased from 9.76 to 11.91 g/dL, and 89 women (63.6%) achieved an increase of at least 2.0 g/dL. Higher PBAC scores and resting heart rates, as well as lower ferritin concentrations, were associated with lower baseline hemoglobin levels. Intravenous iron use and concurrent bleeding-control treatment were associated with greater changes in hemoglobin levels. Comparisons of endometrial histopathological findings were exploratory.

Conclusions: Menstrual blood loss and ferritin levels were associated with baseline anemia, whereas an elevated resting heart rate may reflect physiological compensation. Treatment associations were observational and do not establish comparative efficacy. Independent validation is needed before these findings can be applied as predictive criteria.

Categories: Obstetrics/Gynecology, Hematology, Endocrinology/Diabetes/Metabolism
Keywords: cardiovascular parameters, endometrial histopathology, heavy menstrual bleeding, hematological response, insulin resistance, iron-deficiency anemia, serum ferritin

Introduction

Heavy menstrual bleeding (HMB) is a prevalent gynecologic condition that has significant implications for quality of life and health. The definition is clinical, based on the blood loss that affects the physical, emotional, social, and material well-being of the patient, not just on volume [1]. Chronic blood loss causes iron deficiency and consequently decreases erythropoiesis, leading to iron-deficiency anemia, fatigue, and reduced functional capacity [2-4]. Uterine anomalies, ovulatory dysfunction, endometrial pathologies, and other systemic hemostatic diseases are responsible for HMB [1,5]. Anemia and iron depletion also affect quality of life [6]. Women reporting comparable bleeding may nevertheless have different hemoglobin concentrations, motivating evaluation of additional biochemical and physiological correlates [6].

Iron deficiency continues to be a key component in assessing anemia in HMB. Both serum ferritin (which measures iron stores) and transferrin saturation (which measures the available iron) should be evaluated in conjunction with hematologic indices and the clinical context [7-9]. Current guidelines focus on the diagnosis of iron deficiency and treatment of anemia, as well as the underlying bleeding disorder [10,11]. In inflammatory conditions, ferritin may rise despite low iron stores, partly due to changes in iron handling

and hepcidin-mediated mechanisms [12]. Consequently, the combined assessment of these parameters could be more useful in the characterization of baseline hematological status, namely, bleeding burden, iron indices, and inflammatory measurements [12].

The pictorial blood loss assessment chart (PBAC) is a semiquantitative assessment of menstrual blood loss that is based on the amount of sanitary product saturation and other characteristics of the bleeding [13]. While a useful tool in routine assessment, the score can vary depending on reporting behavior and characteristics of sanitary products [14]. While hemoglobin is inversely related to estimated blood loss, other clinical conditions, duration of bleeding, and iron stores may also contribute to this relationship. The association of PBAC with hemoglobin should therefore be studied in conjunction with laboratory markers and not as an independent prediction rule [14].

Disturbances in metabolism can also affect reproductive physiology. Obesity, insulin resistance, and disturbed glucose regulation may affect ovulation and endometrial proliferation and have been linked to endometrial hyperplasia in premenopausal women [15]. The presence of low-grade inflammation associated with metabolic dysfunction may affect iron metabolism; however, the independent association of low-grade inflammation with anemia among women with HMB is not clear. Fasting glucose, glycated hemoglobin, and the homeostatic model assessment of insulin resistance (HOMA-IR) allow for characterization of metabolic status, but these measures should be interpreted as exploratory correlates rather than evidence of a direct effect on bleeding or anemia [16].

As the supply of oxygen decreases, cardiovascular compensation, such as an increase in cardiac output and heart rate, can occur due to anemia. These changes may be accompanied by palpitations, dyspnea, dizziness, and exercise intolerance. Resting heart rate (HR) and blood pressure (BP) are easily assessable clinical observations but are not specific for anemia and can be affected by hydration, medications, anxiety, pain, and underlying cardiovascular conditions. A correlation between heart rate and hemoglobin may thus represent physiological stress in the context of anemia but is not necessarily causally related to the heart rate itself.

Endometrial histopathology can be useful for identifying causes of persistent or unexplained abnormal uterine bleeding, such as polyps, endometrial hyperplasia, and inflammatory or functional endometrial changes [5,15]. However, biopsy is used in selected cases based on clinical indications. Women selected for biopsy may therefore differ systematically from those who were not sampled. Because biopsy selection was clinically determined and potential confounding was not fully addressed, associations between histopathological findings and anemia or treatment response should be considered exploratory [17].

To achieve hematologic recovery, iron replacement is needed, as well as a reduction in ongoing menstrual blood loss. Oral or intravenous iron may be administered according to clinical need, alongside pharmacologic or procedural measures to reduce uterine bleeding [16-19]. Comparisons of treatment modalities are especially susceptible to confounding by indication because clinicians choose treatment based on the severity of anemia at the start of treatment, symptoms, and other clinical needs. Longitudinal assessment can only describe changes in hemoglobin and iron indices; it cannot provide evidence for the efficacy of one approach over another without randomization or the provision of a comparator [18].

This study examined factors associated with baseline hemoglobin in women with HMB-associated anemia, focusing on PBAC score, ferritin, C-reactive protein (CRP), HOMA-IR, and resting heart rate. The longitudinal objective was to assess factors associated with absolute hemoglobin change over 12 weeks, including the observed route of iron administration and concurrent bleeding-control treatment. Secondary outcomes included changes in ferritin and PBAC scores, and the proportions achieving hemoglobin normalization (⩾12.0 g/dL) and an increase in hemoglobin of ⩾2.0 g/dL. Descriptive analysis of the endometrial histopathological findings was carried out in clinically selected patients. Greater bleeding burden and lower ferritin were expected to accompany lower baseline hemoglobin; CRP and HOMA-IR were examined as potential additional correlates, while resting heart rate was regarded as a possible physiological consequence of anemia.

Materials And Methods

Study design and setting

This prospective observational cohort study was conducted in the Department of Obstetrics and Gynecology, Unit I, Sandeman Provincial Hospital, Quetta, Pakistan, in academic collaboration with Continental Medical College, Lahore, Pakistan. Participants were enrolled in March 2026 and followed for 12 weeks, through June 2026. Baseline clinical, laboratory, and cardiovascular measurements were related to hemoglobin concentration, and observed treatments were evaluated in relation to subsequent changes. Management followed routine clinical practice; treatment allocation was not randomized. Study reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations [20].

Study population and sampling technique

Women aged 18-49 years were eligible if they had clinically defined HMB and a baseline hemoglobin concentration below 12.0 g/dL. Adverse effects of menstrual blood loss on physical, emotional, social, or daily functioning constituted the definition of HMB, and PBAC was used to quantify the severity of bleeding but not as a specified eligibility cutoff. Those with bleeding due to pregnancy or the postpartum period, known hemoglobinopathies, malignancy, advanced chronic kidney disease, or known nongynecological causes of anemia were excluded. Urgent care patients were treated on a clinical basis, and clinical stabilization was prioritized over research procedures. Consecutive, nonprobability sampling during the predetermined March 2026 recruitment period yielded 150 participants. The sample size was based on recruitment feasibility; no a priori sample-size or power calculation was documented. The severe-anemia subgroup included 19 women. The numbers screened and excluded before enrollment were not available for reporting. A minimum HMB duration and any eligibility restrictions based on previous hormonal or iron treatment were not specified in the available study information.

Clinical and gynecological assessment

Demographic and clinical data collected at enrollment consisted of age, body mass index (BMI), parity, reproductive and menstrual history, prior anemia treatment, medical comorbidities, and signs and symptoms of diminished oxygen-carrying capacity. Menstrual blood loss was measured using the pictorial blood loss assessment chart (PBAC), a semiquantitative tool measuring the saturation of sanitary products and other menstrual bleeding characteristics [13]. Symptoms assessed included fatigue, weakness, dizziness, palpitations, dyspnea on exertion, and decreased exercise tolerance. Gynecologic examination and pelvic ultrasonography were performed as clinically indicated. If diagnostic data were available, causes of abnormal uterine bleeding were classified according to the PALM-COEIN system of the International Federation of Gynecology and Obstetrics [1].

Hematological and biochemical evaluation

Baseline hematological parameters included hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, and red cell distribution width. Serum ferritin and transferrin saturation were used to evaluate iron status, and CRP was quantified to interpret ferritin levels. Anemia was classified according to the World Health Organization criteria for nonpregnant women: mild (11.0-11.9 g/dL), moderate (8.0-10.9 g/dL), and severe (<8.0 g/dL) [21]. Hemoglobin was also assessed as a continuous variable to retain information across the severity spectrum.

Metabolic assessment

Metabolic evaluation comprised BMI, FPG, glycated hemoglobin (HbA1c), and fasting insulin. Insulin resistance was calculated using the homeostatic model assessment of insulin resistance (HOMA-IR), which was defined as the product of fasting insulin (μIU/mL) and FPG (mg/dL), divided by 405 [22]. HOMA-IR was analyzed continuously. These metabolic indices were considered exploratory correlates, not established causal determinants of anemia. BMI was not used in the multivariable model and was therefore not assessed for independent associations with either hemoglobin outcome.

Cardiovascular assessment

Cardiovascular assessment included resting heart rate, systolic and diastolic blood pressure and symptoms that may be indicative of reduced cardiovascular tolerance to anemia. Hemodynamic measurements were made at rest to minimize the immediate effects of exertion. The clinical assessment included the presence of palpitations, exertional dyspnea, and dizziness. Resting heart rate was assessed as a continuous variable and correlated with baseline hemoglobin as well as outcome variables over time. Other cardiovascular investigations were only carried out if clinically indicated. All these interventions were regarded as potential correlates or physiological effects of anemia, and not as proof of cardiovascular disease.

Endometrial histopathological evaluation

Histopathological evaluation of the endometrium was carried out only when clinically indicated due to persistent or unexplained abnormal uterine bleeding, the presence of risk factors, or an inadequate response to initial treatment. Tissue samples were classified as proliferative endometrium, secretory endometrium, endometrial polyp, endometrial hyperplasia, or chronic endometritis. In the sampled subgroup, the number of each finding and the percentage of participants achieving a hematological response were presented. Due to the nonrandom selection of tissue samples and the small numbers in diagnostic groups, these analyses were descriptive and were not used to draw independent prognostic or causal associations. Findings should not be extrapolated to participants who did not have an endometrial sample obtained.

Treatment protocol and follow-up assessment

Clinical management was customized according to baseline anemia, iron status, gynecologic findings, and other routine management needs. Iron replacement was provided orally or intravenously, as indicated, and additional medical or procedural measures were employed as needed to decrease menstrual bleeding. The route of iron administration and concurrent bleeding-control treatment were recorded; treatment

assignment was not randomized. The participants were evaluated again after 12 weeks, and hemoglobin, serum ferritin, and PBAC scores were measured. Iron formulation and elemental dose, treatment duration, adherence, the specific bleeding-control intervention, and packed red blood cell transfusion exposure were not reported in sufficient detail for inclusion in the multivariable models. For this reason, associations by treatment category were interpreted with caution, as differences in underlying clinical severity and confounding by indication may persist.

Outcome measures

The main longitudinal outcome was absolute hemoglobin change (g/dL), defined as the 12-week hemoglobin concentration minus the baseline concentration (measured continuously among participants with paired hemoglobin measurements). Baseline anemia severity was described using World Health Organization categories [21]. Secondary measures comprised the percentage of participants with a hemoglobin increase of ⩾2.0 g/dL (binary hematological response), the percentage of participants whose hemoglobin normalized to ⩾12.0 g/dL, and changes in serum ferritin and PBAC scores. Multivariable models were created to assess clinical and biochemical correlates of baseline hemoglobin and the change in hemoglobin observed at follow-up. Histopathology was analyzed descriptively only in participants who had endometrial samples obtained for clinically indicated reasons. The binary response indicator was not analyzed as the outcome of a regression model but was summarized descriptively.

Statistical analysis

Data were analyzed using IBM SPSS Statistics (version 26.0, IBM Corp., Armonk, NY). Continuous variables that were approximately normally distributed were reported as mean ± standard deviation, and those that were skewed were reported as median and interquartile range. Categorical variables were reported as numbers and percentages. Graphical and normality-based methods were used to check distributional assumptions. One-way analysis of variance or the Kruskal-Wallis test was used for continuous variables, and the chi-square or Fisher's exact test was used for categorical variables, as appropriate, for group comparisons by anemia severity category. Paired-samples t-tests or Wilcoxon signed-rank tests were used to assess changes from baseline to 12 weeks, as appropriate to the data distribution. All tests were two-sided, with $P < 0.05$ considered statistically significant for the principal analyses.

Multivariable linear regression was carried out for two continuous outcomes. Model A examined baseline hemoglobin ($n = 150$) in relation to PBAC score, serum ferritin, CRP, HOMA-IR, and resting heart rate. These variables represented bleeding burden, iron status, inflammation, metabolic status, and potential cardiovascular adaptation, respectively. Model B assessed the relationship between hemoglobin change at 12 weeks ($n = 140$) and baseline hemoglobin, PBAC score, CRP, HOMA-IR, intravenous iron versus oral iron, and concurrent bleeding-control treatment. Adjusted regression coefficients, 95% confidence intervals (CIs), and *P*-values were reported. During model evaluation, factors such as linearity, influential observations, and residual behavior were taken into account. Model B required complete paired outcome data; sensitivity analyses for missing data were not presented. No causal adjustment for treatment selection was made using propensity scores or other methods. Histopathological results were treated descriptively because biopsy selection was determined by clinical indications and the number of patients in each subgroup was small. These were explanatory association models rather than validated prediction models.

Ethical considerations

The study received Institutional Review Board approval (No. 09/IRB/CMC) before recruitment. Written informed consent was obtained from participants. Confidentiality was achieved by using coded identifiers, limiting access to clinical data, and reporting overall results. Study participation did not supplant the standard of care; investigations and treatments were performed as clinically appropriate. The study was carried out in accordance with the principles of the Declaration of Helsinki [23].

Results

Baseline demographic, clinical, and hematological characteristics

The cohort comprised 150 women with HMB-associated anemia. Mean age was 35.9 ± 7.3 years, mean BMI was 27.1 ± 4.7 kg/m^2, and mean baseline hemoglobin was 9.78 ± 1.44 g/dL. Mild anemia was observed in 34 participants (22.7%), moderate anemia in 97 (64.7%), and severe anemia in 19 (12.7%). Median PBAC scores increased from 233 (IQR, 195-265) in the mild-anemia group to 331 (IQR, 294-404) in the severe-anemia group ($P < 0.001$). Median ferritin decreased from 17.1 ng/mL (IQR, 12.9-20.8) to 10.3 ng/mL (IQR, 9.0-16.0; $P = 0.008$). Resting heart rate increased across severity categories ($P < 0.001$). There were no statistically significant between-group differences in age, BMI, transferrin saturation, CRP, HOMA-IR, or systolic blood pressure. Baseline characteristics are presented in Table *1*.

Variable	Mild (*n* = 34)	Moderate (*n* = 97)	Severe (*n* = 19)	*P*-value
Age, years	35.9 ± 6.9	36.0 ± 7.5	35.3 ± 7.1	0.958
BMI, kg/m²	27.3 ± 4.0	26.9 ± 4.8	27.7 ± 5.4	0.785
Hemoglobin, g/dL	11.57 ± 0.32	9.64 ± 0.82	7.25 ± 0.66	-
PBAC score	233 (195-265)	284 (237-330)	331 (294-404)	<0.001
Serum ferritin, ng/mL	17.1 (12.9-20.8)	15.0 (11.3-17.9)	10.3 (9.0-16.0)	0.008
Transferrin saturation, %	18.8 ± 5.2	17.7 ± 3.8	16.7 ± 4.0	0.333
CRP, mg/L	2.79	2.62	2.31	0.137
HOMA-IR	2.16	2.21	2.32	0.935
Resting heart rate, beats/min	70.8 ± 6.9	80.2 ± 6.0	88.4 ± 8.1	<0.001
Systolic blood pressure, mmHg	122.1 ± 7.9	121.7 ± 11.0	116.5 ± 9.5	0.060

TABLE 1: Baseline demographic, biochemical, metabolic, and cardiovascular characteristics according to anemia severity (n = 150).

Values are presented as mean ± standard deviation or median (interquartile range), except for CRP and HOMA-IR, for which only single summary values were reported without a specified measure of dispersion or summary-statistic type. Comparisons used one-way analysis of variance or the Kruskal-Wallis test, as appropriate. Hemoglobin was used to define anemia severity groups and was therefore not tested as an independent between-group comparison.

BMI, body mass index; PBAC, pictorial blood loss assessment chart; CRP, C-reactive protein; HOMA-IR, homeostatic model assessment of insulin resistance

Hematological improvement and treatment response

Of 150 enrolled women, 140 (93.3%) completed the 12-week assessment, and 10 (6.7%) lacked complete follow-up measurements. Oral iron was administered to 110 participants (73.3%) and intravenous iron to 40 (26.7%); 97 women (64.7%) received an intervention directed at reducing menstrual blood loss. Among the 140 women with paired measurements, mean hemoglobin increased from 9.76 ± 1.46 g/dL to 11.91 ± 1.71 g/dL, a mean increase of 2.15 g/dL (95% CI, 2.04-2.26; $P < 0.001$). Hematological response (increase ⩾2.0 g/dL) occurred in 89 women (63.6%), and hemoglobin normalized (⩾12.0 g/dL) in 72 (51.4%). Median ferritin increased from 15.0 to 38.7 ng/mL, while median PBAC decreased from 279 to 91 (both $P < 0.001$). Paired changes are summarized in Table *2*; participants without paired data were excluded from these longitudinal estimates.

Variable	Baseline	12 weeks	P-value
Hemoglobin, g/dL	9.76 ± 1.46	11.91 ± 1.71	<0.001
Serum ferritin, ng/mL	15.0 (11.2-18.5)	38.7 (32.0-46.8)	<0.001
PBAC score	279 (234-328)	91 (62-140)	<0.001
Hemoglobin increase ≥2.0 g/dL	-	89 (63.6%)	-
Hemoglobin normalization ≥12.0 g/dL	-	72 (51.4%)	-
Hematological non-response	-	51 (36.4%)	-

TABLE 2: Changes in hematological and menstrual bleeding parameters after 12 weeks of treatment (n = 140).

Values are presented as mean ± standard deviation, median (interquartile range), or frequency (percentage). Baseline and follow-up measurements were compared using paired-samples t-tests or Wilcoxon signed-rank tests. Response percentages were calculated among the 140 participants with complete follow-up measurements.

PBAC, pictorial blood loss assessment chart

Endometrial histopathological findings and treatment response

Endometrial histopathology was assessed in 65 participants (43.3%) according to clinical indications. Proliferative endometrium was identified in 24 (36.9%), secretory endometrium in 14 (21.5%), endometrial polyps in 13 (20.0%), hyperplasia without atypia in eight (12.3%), and chronic endometritis in six (9.2%). Complete follow-up was available for 60 sampled women; 39 (65.0%) met the hematological response threshold. Observed hematological responses were 18 (85.7%) for proliferative endometrium, 4 (80.0%) for chronic endometritis, 4 (57.1%) for hyperplasia without atypia, 7 (50.0%) for secretory endometrium, and 6 (46.2%) for endometrial polyps. These estimates were descriptive because biopsy selection was clinically determined and several categories contained few participants. No independent prognostic interpretation was made. Histopathological results are presented in Table *3*.

Histopathological finding	Total, *n* (%)	Follow-up, *n*	Responders, *n* (%)
Proliferative endometrium	24 (36.9)	21	18 (85.7)
Secretory endometrium	14 (21.5)	14	7 (50.0)
Endometrial polyp	13 (20.0)	13	6 (46.2)
Hyperplasia without atypia	8 (12.3)	7	4 (57.1)
Chronic endometritis	6 (9.2)	5	4 (80.0)
Total	65 (100.0)	60	39 (65.0)

TABLE 3: Endometrial histopathological findings and hematological treatment response.

Data are presented as frequency (percentage). Response percentages were calculated using the number of participants with complete follow-up within each histopathological category. Hematological response was defined as a hemoglobin increase of ≥2.0 g/dL at 12 weeks.

Factors associated with anemia severity and hematological recovery

In Model A, PBAC score, serum ferritin, and resting heart rate were associated with baseline hemoglobin after adjustment for the other included variables. Each 50-point higher PBAC score corresponded to 0.23 g/dL lower hemoglobin (adjusted coefficient -0.23; 95% CI, -0.35 to -0.10; $P < 0.001$). Each 5 ng/mL higher ferritin concentration corresponded to 0.17 g/dL higher hemoglobin (0.17; 95% CI, 0.03-0.30; $P = 0.017$). Every 10 beats/min higher resting heart rate corresponded to 0.91 g/dL lower hemoglobin (-0.91; 95% CI, -1.15 to -0.66; $P < 0.001$). Neither CRP nor HOMA-IR was significantly associated with baseline hemoglobin after adjustment ($P = 0.810$ and $P = 0.407$, respectively). The associations are summarized in Table *4*.

Predictor	Adjusted coefficient (95% CI)	*P*-value
Model A: Baseline hemoglobin (*n* = 150)		
PBAC, per 50-point increase	-0.23 (-0.35 to -0.10)	<0.001
Ferritin, per 5 ng/mL increase	0.17 (0.03 to 0.30)	0.017
Resting heart rate, per 10 beats/min increase	-0.91 (-1.15 to -0.66)	<0.001
HOMA-IR, per unit	-0.04 (-0.15 to 0.06)	0.407
CRP, per mg/L	-0.01 (-0.08 to 0.07)	0.810
Model B: Hemoglobin change at 12 weeks (*n* = 140)		
PBAC, per 50-point increase	-0.06 (-0.13 to 0.01)	0.113
Intravenous versus oral iron	0.50 (0.27 to 0.74)	<0.001
Menstrual bleeding-control treatment	0.37 (0.17 to 0.58)	<0.001
Baseline hemoglobin, per g/dL	0.09 (0.02 to 0.16)	0.015
CRP, per mg/L	-0.03 (-0.08 to 0.02)	0.182
HOMA-IR, per unit	0.01 (-0.05 to 0.07)	0.763

TABLE 4: Multivariable linear regression analysis of factors associated with baseline hemoglobin concentration and 12-week hemoglobin change.

Values are presented as adjusted, unstandardized regression coefficients with 95% confidence intervals. Model A examined baseline hemoglobin (*n* = 150); Model B examined absolute hemoglobin change from baseline to 12 weeks among participants with complete paired measurements (*n* = 140). The analyses are explanatory and have not been validated for individual-level prediction. All tests were two-sided; *P* < 0.05 was considered statistically significant.

PBAC, pictorial blood loss assessment chart; CRP, C-reactive protein; HOMA-IR, homeostatic model assessment of insulin resistance; CI, confidence interval

In Model B, intravenous rather than oral iron administration was associated with a greater 12-week hemoglobin change (adjusted coefficient, 0.50 g/dL; 95% CI, 0.27-0.74; *P* < 0.001). Concurrent bleeding-control treatment was similarly associated with a greater change (0.37 g/dL; 95% CI, 0.17-0.58; *P* < 0.001). Higher baseline hemoglobin was positively associated with subsequent change (0.09 g/dL per 1 g/dL; 95% CI, 0.02-0.16; *P* = 0.015). Baseline PBAC, CRP, and HOMA-IR were not significantly associated with change after adjustment. As treatment was selected clinically and not randomly, these findings represent adjusted associations and cannot demonstrate a causal benefit of one intervention over another (Table *4*).

Discussion

This prospective cohort evaluated the relationships of bleeding burden, iron status, metabolic and cardiovascular measures, and clinically indicated histopathology with anemia and 12-week hematological recovery. Higher PBAC scores and resting heart rates were associated with lower baseline hemoglobin, whereas higher ferritin was associated with higher hemoglobin. Hemoglobin and ferritin increased, and reported bleeding declined during follow-up. Greater hemoglobin change was associated with intravenous iron use and concurrent bleeding-control treatment, but clinical treatment selection precludes causal conclusions. Histopathological comparisons remained descriptive [1-3].

The inverse association between PBAC and baseline hemoglobin is consistent with the established relationship between ongoing menstrual blood loss, iron depletion, and anemia [2,3]. Median PBAC scores increased across anemia severity categories, and each 50-point higher score corresponded to 0.23 g/dL lower baseline hemoglobin after adjustment. Nevertheless, PBAC is a semiquantitative measure affected by individual reporting and sanitary-product characteristics [13,14]. These findings support integrating a bleeding history with laboratory assessment; they do not establish a diagnostic PBAC cutoff or validated prediction rule [4,5].

Ferritin was positively associated with baseline hemoglobin, and median concentrations declined from 17.1 ng/mL in the mild-anemia group to 10.3 ng/mL in the severe-anemia group [6]. Ferritin reflects iron stores but can also be influenced by inflammation; assessment alongside transferrin saturation and the clinical context remains important [7-12]. The relatively low reported CRP summary values may have limited the

ability to detect an adjusted association, although CRP dispersion was not reported. The rise in ferritin concentration during follow-up should also be interpreted with care, as iron administration (especially recent intravenous iron) may affect the ferritin measurement [7,8].

Resting heart rate was inversely associated with baseline hemoglobin in the adjusted regression model. This association may reflect compensatory cardiovascular responses to reduced oxygen-carrying capacity; the observational analysis does not establish directionality or causation [9-11]. Specificity is further compromised by pain, anxiety, hydration level, medication use, and concomitant cardiovascular disease. Therefore, resting HR should not be considered a predictor of the etiology or a validated predictor of the severity of anemia. No significant association with either outcome was observed in the reported models for CRP or HOMA-IR. These nonsignificant estimates do not exclude modest associations, particularly in this sample of limited size. BMI was not included in the models, and thus any independent relationship with obesity was not tested [12-14].

Histopathological findings included proliferative and secretory endometrium, polyps, hyperplasia without atypia, and chronic endometritis [5,15]. Observed response proportions varied across diagnostic categories; however, biopsy was performed only when clinical findings indicated the need for sampling. This selection process may increase the proportion of the subgroup with persistent bleeding or suspected pathological causes, and small cell counts result in poor precision. These data, therefore, provide information on the patients sampled but do not demonstrate differences in prognosis among the different diagnoses or provide estimates applicable to all women with HMB [16].

Among 140 participants with paired measurements, mean hemoglobin increased from 9.76 to 11.91 g/dL, while median ferritin increased and median PBAC scores decreased. In the adjusted model, the treatment-route and bleeding-control coefficients were both positive. Randomized studies and systematic reviews have assessed iron replacement and management of HMB [16-19], but the results of those studies do not translate into causal estimates for the present observational comparisons. Treatment selection was clinically determined by baseline severity and other factors not fully captured by the regression model [17]. The changes observed may have been influenced by differences in regimen, duration, adherence, previous treatment, or transfusion exposure. Moreover, the lack of an untreated comparison group means that the possibility of regression to the mean and natural variation in menstrual bleeding cannot be ruled out as alternative sources of within-person improvement [18].

The strengths of the study are the prospective follow-up, the high percentage of complete outcome measurements (140, 93.3%), the analysis of hemoglobin as a continuous variable and in the World Health Organization severity categories, and the measurement of CRP to help interpret ferritin levels [19]. Histopathology was treated appropriately as exploratory because sampling was clinically selected. Limitations include the single-center setting, the lack of a documented a priori power calculation, the feasibility-based sample size, with only 19 participants (12.7%) having severe anemia, and the 12-week follow-up period, which does not confirm sustained recovery [20]. No qualifying minimum duration of HMB or explicit eligibility restrictions based on previous hormonal or iron treatment were specified. Ten enrolled participants (6.7%) lacked complete 12-week measurements and were excluded only from analyses requiring paired follow-up data; no missing-outcome sensitivity analysis was reported [21]. Detailed information on iron formulations, iron doses, treatment duration, adherence measures, types of bleeding-control interventions, or red blood cell transfusion exposure was not included in the reported analyses. Treatment groups were not randomly allocated, PBAC was subjectively reported, there may have been unknown confounding factors, regression to the mean was a possibility, and selection bias in endometrial sampling may have occurred, restricting causal interpretation and generalizability. The regression models were not externally validated and should not be used for individual clinical prediction [22,23].

Conclusions

In women with HMB-related anemia, higher reported blood loss and lower serum ferritin were associated with lower baseline hemoglobin levels. Higher resting heart rate was also associated with lower hemoglobin and may reflect physiological compensation rather than a causal determinant. During the 12-week follow-up, there was an increase in hemoglobin and ferritin levels and a decrease in bleeding reported. Any differences in hemoglobin observed between different methods of iron administration and bleeding-control treatment are not proof of comparative treatment efficacy. In the reported models, there was no significant association between CRP and HOMA-IR and the outcomes; the independence of the effects of obesity or histopathological diagnoses was not established. These findings support integrated clinical assessment, and further validation is needed for their clinical application in individual prediction or decision-making.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Naveed Shuja, Zubia Bugti, Safia Ewaz Ali, Ayisha Ejaz Bhutta, Shazia Baloch, Waqar Ahmed, Tariq Hussain

Acquisition, analysis, or interpretation of data: Naveed Shuja, Zubia Bugti, Safia Ewaz Ali, Ayisha Ejaz Bhutta, Shazia Baloch, Waqar Ahmed, Tariq Hussain

Drafting of the manuscript: Naveed Shuja, Zubia Bugti, Safia Ewaz Ali, Ayisha Ejaz Bhutta, Shazia Baloch, Waqar Ahmed, Tariq Hussain

Critical review of the manuscript for important intellectual content: Naveed Shuja, Zubia Bugti, Safia Ewaz Ali, Ayisha Ejaz Bhutta, Shazia Baloch, Waqar Ahmed, Tariq Hussain

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Continental Medical College (CMC) issued approval 09/IRB/CMC. Participants gave written informed consent before their inclusion in the study. Confidentiality was ensured by coding participant identifiers, limiting access to participant clinical data, and presenting the results as grouped data. Diagnostic investigations and therapeutic interventions were done on clinical indications and at the institution's discretion, and participation in the study did not replace the standard of care provided. The investigation was done according to the ethical principles of the Declaration of Helsinki. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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