Coagulation hallmark indicators of menorrhagia in a comparative study between menorrhagic and healthy women attending Bungoma County Referral Hospital in Kenya

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Abstract

Background

Despite the significant burden of menorrhagia among women in Western Kenya, it remains unknown whether coagulation disorders are one of the important underlying causes of this condition in the region. This study evaluated the differences in coagulation profiles, associations between menorrhagia and coagulation profiles and compared the morphological features of platelets between menorrhagic patients and healthy women attending Bungoma County Referral Hospital in Kenya.

Methods

A comparative cross-sectional study of women [n = 428 (214 per group), aged 18–45 years] was performed. A Humaclot junior analyzer was used to evaluate prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time (PT), fibrinogen, and the international normalized ratio (INR). The platelet count was determined using Celtac F ME822K, and Leishman-stained blood films were analyzed using an Olympus light compound microscope. The Chi-square test was used to analyze categorical descriptive data. The Mann–Whitney U test was used to compare the data between the menorrhagic and control groups. Binary logistic regression was applied to determine the association between coagulation profile and menorrhagia incidence. The platelet morphological characteristics were reported as frequencies and percentages. Statistical significance was set at $p \leq 0.05$ indicated statistical significance.

Results

The results showed that a history of bleeding disorders ($p < 0.0001$), PT ($p < 0.0001$) and INR ($p < 0.0001$) were greater in menorrhagic women than in non-menorrhagic women. Menorrhagia was significantly associated with a high PT [OR = 2.129, 95% CI = 1.658–2.734; $p < 0.0001$] and INR [OR = 7.479, 95% CI = 3.094–18.080; $p < 0.0001$]. No morphological abnormalities in the platelets were observed in either healthy or non-menorrhagic women.

Conclusions

Family history of bleeding disorders, increased PT and INR are the hallmark indicators of menorrhagia in western Kenya. Therefore, routine assessment of the coagulation profile and history of bleeding disorders is critical for the diagnosis and management of menorrhagia.

Background

Menorrhagia is defined as heavy menstrual bleeding that exceeds 80 ml per cycle (1). It is a common disorder that, on average, affects 30% of women and has major negative social and economic ramifications (2). Having heavy periods significantly decreases women's quality of life, requires time away from work, involves surgical intervention, including hysterectomy, and ultimately has a substantial cost impact on the healthcare system (3).

Menorrhagia is a diagnosable ailment that needs to be treated to improve the quality of life of affected women (4). However, a significant number of menorrhagia cases are classified as idiopathic. Research has shown that when women are dissatisfied with their normal therapy options, they frequently choose significant surgery, such as hysterectomy (5). These women might benefit from a specialized method of diagnosis and treatment that emphasizes pertinent coagulation parameters. A series of activities known as the coagulation pathway results in hemostasis (6). This complex pathway promotes quick healing and prevents spontaneous bleeding by working with many clotting factors (7).

According to recent studies, many women between the ages of adolescence and premenopause often endure inexplicable menorrhagia (8). However, hemostatic concerns are commonly underestimated before patients undergo invasive surgical treatments. An international expert panel in obstetrics, gynecology, and hematology came to conclusions regarding the best ways to treat menorrhagia in females without a known bleeding disorder. The proposals call for a laboratory assessment of complete blood counts, platelet functions, and coagulation profiles in menorrhagia patients; however, more than 61% of patients presenting with menorrhagia are still categorized as having a nonstructural disorder without discernible coagulopathy as the cause of their condition (9). Menorrhagia may be caused by bleeding in as many as 17–20% of cases, according to recent American research (10). Nonetheless, coagulopathies are infrequently regarded as the cause of menorrhagia. A comprehensive history and clinical suspicion of an underlying bleeding issue in women who present with menorrhagia can help with the early identification and effective management of antepartum/postpartum hemorrhage (11). If there is no evident cause for menorrhagia, the coagulation profiles of all women should be checked (12). Coagulation problems are relatively common—1% of the general population is affected, and they can affect as many as 5% of gynecological patients (13). According to multiple studies conducted in Western countries, von Willebrand disease (vWD) is the most common hereditary blood disorder that causes menorrhagia (14). In addition, research from Southeast Asia indicates that the most common cause of menorrhagia is platelet dysfunction (15). In our opinion, we hypothesize that derangement in coagulation profiles which affect the integrity of the intrinsic, extrinsic and common pathways in coagulation cascade may be associated with menorrhagia. The explanations for coagulation problems and platelet dysfunction, which are some of the underlying causes of menorrhagia in women, are not well understood in Kenya. Furthermore, despite the substantial burden of menorrhagia in Western Kenya, the coagulation hallmark parameters of menorrhagic women compared to non-menorrhagic women are unknown. Therefore, this study determined the differences in selected coagulation parameters between menorrhagic and non-menorrhagic women. In addition, the present study investigated the associations between coagulation parameters and menorrhagia. Furthermore, the study determined the morphological characteristics of platelets from menorrhagic and non- women at Bungoma County Referral Hospital, Kenya.

Methods

Study site

The study was conducted at Bungoma County Referral Hospital (BCRH) in Bungoma County, coordinates 0.4213°N to 1.1477°N in latitude and 34.3627°E to 35.0677°E in longitude between December 2022 and September 2023. BCRH is a level 5 hospital located within the headquarters of Bungoma County in Western Kenya. This hospital is the main referral health facility for Bungoma County and its soundings, serving a population of 1,670,570 across an area of 2,206.9 km2 (16). Every year, approximately 6,000 patients visit the

BCRH gynecological clinic. Menorrhagia affects approximately 3% of all gynecological patients who visit the clinic according to Bungoma County Referral Hospital records (17).

Study design

This study used a comparative cross-sectional design.

Study population

The sample size formula for a quantitative comparative survey (18) was used to calculate the number of study participants. The sample size was 428 (214 per group). A systematic random sampling procedure was adopted, with every second person satisfying the inclusion criteria being selected until the sample size was reached.

Inclusion criteria

The study recruited adult women between the reproductive ages of 18 and 45 years. The women who came to the facility complaining of menorrhagia made up the cases. Healthy women were selected at random to serve as controls. A qualified gynecologist determined menorrhagia in each patient and established the clinical diagnosis based on the definition of menorrhagia (19).

Exclusion criteria

Women who experienced menorrhagia due to known causes, such as uterine fibroids or intrauterine contraception, were excluded from the study. Women with other known disorders that may alter coagulation parameters were excluded. Women who were found to be using any hemostasis-affecting medicines, as determined by a thorough clinical history by qualified clinicians, were also ineligible. Patients who had taken sylate or tranexamic acid within the previous three months, as well as other drugs known to manage bleeding difficulties, were ineligible.

Ethical considerations

The study was approved by the Maseno University Scientific and Ethical Review Committee (MUSERC) (#MUSERC/01166/22), and the authority to carry out the research was granted by the National Commission for Science, Technology, and Innovation (NACOSTI) (#NACOSTI/P/22/22573). Bungoma County Referral Hospital (#BDH/TP/B/VOL2) provided permission to perform the study. After being briefed on the study's specifics, each participant was requested to sign an informed consent form. The study's participants chose to participate voluntarily. A password was used to safeguard the completed data tools on the computer and in a locked area, and no personal information was collected from the participants.

Data collection

Recruitment and sample collection

The patients were composed of women who presented to the clinic complaining of menorrhagia. To act as controls, healthy women were selected at random. In each case, a qualified gynecologist diagnosed menorrhagia per the definition of menorrhagia (19). Using a screening procedure previously used by the Centers for Disease Control (CDC) (20), participants were classified into menorrhagic and non-menorrhagic women (20). Potential

study participants were provided a participant information sheet, and those who provided their consent participated in the sample collection activity.

For the coagulation profile, whole blood was collected from the participant and put in a vacuum tube containing 3.2% sodium citrate to ensure a 9:1 dilution of blood to the anticoagulant for prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), thrombin time (TT) and fibrinogen tests. Then, the tube was connected to the participant's distinctive identifying number. The sample(s) were delivered to the laboratory immediately after collection and spun for 5 minutes at 4000 rpm to ensure that the samples were platelet poor within four hours. The separated samples were stored at 2–8°C for 24 hours if not tested immediately. The coagulation test control materials were reconstituted following the manufacturer’s instructions. For thrombocyte count and morphology, whole blood was collected in a vacuum tube with ethylenediaminetetraacetic acid (EDTA), immediately inverted gently 8–9 times, and labeled with a unique number assigned to the participant. The phlebotomy order of drawing blood using evacuated tubes was followed by blood collection in sodium citrate, followed by blood collection in EDTA. Thin blood films for performing reflex testing when the analyzer results were flagged and determining the platelet cell morphology were immediately prepared and fixed using absolute ethanol (Sigma–Aldrich). The control materials were heated to room temperature and mixed well according to the manufacturer’s instructions before testing. The laboratory results were recorded on the study's standard data collection form.

Laboratory procedures

Coagulation profile parameters, including PT, aPTT, TT, fibrinogen, and the INR, were tested using a Humaclot Junior semiautomated coagulation analyzer (HUMAN Gesellschaft fur Biochemica and Diagnostica mbH Max Planck-Ring 2165205 Wiesbaden Germany) as previously described (21). The analyzer uses the photometric principle in which fibrin increases sample turbidity, which the photometer detects. After mixing the reagents with plasma, fibrinogen is converted into fibrin and coagulates. Thus, the optical density of the test sample changes, and the analyzer can detect the coagulation endpoint (22). Briefly, the procedure involved pipetting plasma into cuvettes and pre-warming, placing the appropriate reagents with a stirrer in a large central position, transferring the cuvette into a measuring position, adding pre-warmed individual reagents, and pressing the optic1 key to start running; the instrument read for 300 seconds, and the results were displayed on the screen in seconds.

For interpretation purposes, the reference ranges for the coagulation profile of adult women were adopted from the Bungoma County Referral Hospital Laboratory as follows: prothrombin time: 11.0 to 12.5 seconds; activated partial thromboplastin time: 30 to 40 seconds; thrombin time: 15–19 seconds; fibrinogen: 200 to 400 mg/dL; and international normalized ratio: 1.1 or less. The samples were examined simultaneously with abnormal and normal control plasma.

A Celtac F, MEK-8222 K analyzer (NIHON KOHDEN Corporation, 1-31-4 Nishiochiai, Shinjuku-ku, Tokyo 161–8560, Japan), as previously described (23), was used to determine the thrombocyte count. This analyzer measures thrombocytes by the electrical resistance sensing technique. For interpretation purposes, the reference ranges for the platelet count of adult women were adopted from the Bungoma County Referral Hospital Laboratory as follows: 150–450 $x10^9$/L. Low, normal, and high levels of control materials were analyzed before the samples were tested.

The morphology of the thrombocytes was evaluated using Leishman-stained blood films and optical light compound microscopy (Olympus ^{TM} Japan), as previously described (24), and the size, morphology, and granulation of the platelets were evaluated by looking for normal platelets, microplatelets, large/giant platelets, and hypogelular/agranular platelets. In instances when the thrombocyte count was a cause for concern, platelet aggregation was also examined to rule out pseudothrombocytopenia.

Quality assurance of the data

A qualified and competent phlebotomist was employed to collect blood samples, ensuring that the appropriate amount was collected to maintain the quality of the data. During preparation and testing, the collected samples were handled following the standard operating procedures of the Bungoma County Referral Hospital laboratory. For each sample, the analysis was carried out independently twice, and reliability was ensured by taking an average. Throughout the investigation, internal and external quality controls were checked and guaranteed. For example, slides were examined by two separate readers, and in the event of a discrepancy, a third reader was involved. To ensure accuracy, a second individual confirmed the results that were recorded. To ensure validity and further reliability, all the statistical tests were run at a Z score of 1.96 and a 95% level of significance.

Statistical analyses

Microsoft Spreadsheets were used to store the data. The Statistical Package for Social Science (SPSS V.26) (IBM Corporation, Chicago, Illinois, United States) was used for the analysis. The Shapiro–Wilk test was used to check for normality, and histograms and box plots were generated to verify the normality of the distribution of the data. The chi-square test was used to analyze categorical descriptive data that included residence, parity, occupation, family history of bleeding disorders, history of bleeding or gum bleeding, history of extended bleeding following tooth extraction, postoperative extended bleeding and history of prolonged bleeding following delivery or miscarriage. The Mann–Whitney U test was used to compare coagulation profiles between menorrhagic and non-menorrhagic women, as the data were not normally distributed. Since the current study included a categorical dependent variable, binary logistic regression was used to predict the association between menorrhagia and coagulation parameters. The platelet morphological characteristics are presented as frequencies and percentages. The frequency, median, and dispersion of the descriptive statistics are shown. For all analyses, statistical significance was established at $P \leq 0.05$.

Results

Demographic characteristics of the study population

The study recruited adult women (n = 428) between the ages of 18 and 45 [median (IQR); 33.5 (11.0) years]. There were 214 menorrhagic patients and an equal number of non-menorrhagic healthy women. The ages of the menorrhagic and non-menorrhagic women were comparable [median (IQR): 34.0 (6.0) years] and [median (IQR): 33.0 (14.0) years, $p = 0.209$]. In terms of place of residence, 136 (63.6%) menorrhagic women lived in rural areas, whereas 78 (36.4%) lived in urbanized areas. This was comparable ($p = 0.139$) to that of non-menorrhagic women, with 120 (56%) living in rural areas and 94 (44%) living in urban areas. In terms of parity, 177 (82.7%) menorrhagic women had previously had children, and 37 (17.3%) had never had children. This was comparable ($p = 0.390$) to that of non-menorrhagic women, which included 169 (79.0%) who had previously had children and 45 (21.0%) who had never had a child. In terms of occupation, 102 (47.7%) menorrhagic participants were

formally employed, and 112 (52.3%) were informally employed. This was comparable ($p = 0.846$) to that of non-menorrhagic participants, for whom 99 (46.13%) were formally employed and 115 (53.7%) were informally employed. All participants, menorrhagic and non-menorrhagic, were literate.

Among menorrhagic women, 202 (94.4%) had no family history of bleeding disorders, while 12 (5.6%) had. This percentage was significantly ($p < 0.001$) greater than that of non-menorrhagic women, with 214 (100%) having no family history of bleeding. In terms of a history of epistaxis or gum bleeding, 212 (99.1%) of the menorrhagic participants did not have one epistaxis or gum bleeding, whereas 2 (0.9%) had a history of epistaxis/gum bleeding. This was comparable ($p = 0.499$) to that of non-menorrhagic women, for whom 214 (100%) had no history of epistaxis or gum bleeding. In terms of a history of prolonged bleeding following delivery or miscarriage, 210 (98.1%) menorrhagic women did not have this history, whereas 4 (1.9%) had a history of prolonged bleeding following delivery. This was comparable ($p = 0.045$) to that of non-menorrhagic women, 214 (100%) of whom had a history of prolonged bleeding after delivery, as shown in Table 1. In summary, a greater percentage of menorrhagic women had a family history of bleeding disorders than did non-menorrhagic women, as shown in Table 1.

Table 1
Demographic characteristics of the study participants at Bungoma County Referral Hospital.

Demographic characteristic		Women with Menorrhagia (cases)	Women without menorrhagia (controls)	*p* value
Age		34.0 [6.0]	33.0 [14.0]	0.209[a]
Residence	Rural	136 (63.6%)	120 (56%)	0.139[b]
	Urban	78 (36.4%)	94 (44%)	
Parity	Ever had a child	177 (82.7%)	169 (79.0%)	0.390[b]
	Never had a child	37 (17.3%)	45 (21.0%)	
Occupation	Formally employed	102 (47.7%)	99 (46.3%)	0.846[b]
	Informally employed	112 (52.3%)	115 (53.7%)	
Literacy	Literate	214 (100%)	214(100%)	N/A
	Not literate	Nil	Nil	
Family history of bleeding disorders	Yes	12 (5.6%)	Nil	**< 0.001[b]**
	No	202 (94.4%)	214(100%)	
History of epistaxis or gum bleeding	Yes	2 (0.9%)	Nil	0.499[b]
	No	212 (99.1%)	214(100%)	
History of bleeding complications following tooth extraction	Yes	Nil	Nil	N/A
	No	214 (100%)	214(100%)	
Postoperative extended bleeding	Yes	Nil	Nil	N/A
	No	214 (100%)	214(100%)	
History of Prolonged bleeding following delivery or miscarriage	Yes	4 (1.9%)	Nil	0.123[b]
	No	210 (98.1%)	214(100%)	

The data provided are presented as the frequency and percentage unless otherwise stated. The frequency and proportion of ten demographic characteristics were tabulated for both menorrhagic and non-menorrhagic participants. [a] statistical significance was determined using Mann–Whitney U test. [b] Statistical significance of the differences was determined using the chi-square test. Nil means no demographic characteristic was seen in any of the participants for either the menorrhagic or non-menorrhagic categories. N/A indicates that the *p* value was not generated. A family history of bleeding disorders was significantly greater in menorrhagic women than in non-menorrhagic women.

Comparison of coagulation profiles between menorrhagic and non-menorrhagic women

The prothrombin time of menorrhagic women ranged between 11.0 and 16.40 seconds [median (IQR); 12.40 (2.40) seconds], with 176 (82.2%) patients having normal prothrombin times, whereas 38 (17.8%) patients had prothrombin times higher than the anticipated reference range of 11.0 to 12.5 seconds. This was significantly ($p < 0.001$) greater than that for women who presented without menorrhagia; their prothrombin time ranged between 11.0 and 14.90 seconds [median (IQR); 12.10 (0.50) seconds], with 211 (98.6%) having normal prothrombin times and 3 (1.4%) having high prothrombin times above the expected reference range of 11.0 to 12.5 seconds, as shown in Table 2.

The international normalized ratio of menorrhagic women ranged from 0.80 to 2.12 [median (IQR); 1.27 (0.51)], with 192 (89.7%) patients having normal INR levels and 22 (10.3%) having INR levels higher than the expected reference range of 1.1 or lower. These values were significantly ($p < 0.001$) greater than those of women who presented without menorrhagia [median (IQR); 0.80 [0.50], with 212 (99.1%) patients having normal INR levels and 2 (0.9%) patients having INR levels higher than the expected reference range of 1.1 or lower, as shown in Table 2.

The aPTT of menorrhagic women ranged from 30.05 to 39.97 seconds [median (IQR); 35.14 (5.80) seconds], with all 214 (100%) women having normal aPTT. This was comparable ($p = 0.106$) to that of non-menorrhagic women, whose aPTT ranged from 31.30 to 39.68 seconds [median (IQR); 34.68 [3.19] seconds], with 214 (100%) women having normal aPTT levels compared to the reference range of 30–40 seconds, as shown in Table 2.

The thrombin time of menorrhagic women ranged from 14.50 to 19.98 seconds [median (IQR); 17.39 (2.84) seconds], with 2 (0.9%) patients having lower TT levels, 209 (97.7%) patients having normal TT levels, and 3 (1.4%) patients having high TT levels compared to the normal range of 15 to 19 seconds. This was comparable ($p = 0.176$) to that of women who presented without menorrhagia, whose TT ranged from 15.22 to 18.89 seconds [median (IQR); 17.11 (1.89) seconds], with all participants having normal TT levels compared to the reference range of 15–19 seconds, as shown in Table 2.

The fibrinogen level of menorrhagic women ranged from 223.20 to 338.60 g/dL [median (IQR); 309.67 (81.44) g/dL], with all 214 patients having normal fibrinogen levels compared to the reference range of 200–400 g/dL. This finding was comparable ($p = 0.082$) to that of women who presented without menorrhagia, whose fibrinogen levels ranged from 200.30 to 409.56 g/dL [median (IQR); 311.92 (95.32) g/dL], with 212 (99.1%) participants having normal fibrinogen and 2 (0.9%) having high levels of fibrinogen compared with the reference range of 200–400 g/dL, as shown in Table 2.

The platelet counts of menorrhagic women ranged from 280–592 $x10^9$/L [median (IQR); 358 (75.00) $x10^9$/L], with 210 (98.1%) patients having a normal platelet count and 4 (1.9%) patients having a high platelet count compared to the reference range of 150–450 $x10^9$/L. These platelet counts were comparable ($p = 0.101$) to those of non- menorrhagic women, whose platelet count ranged from 290–448 $x10^9$/L [median (IQR); 366 (79.25) $x10^9$/L], with all 214 (100%) participants having a normal platelet count compared to the reference range of 150–450 $x10^9$/L, as shown in Table 2.

In summary, menorrhagic women had substantially greater PT and INR values than non-menorrhagic women did. The aPTT, TT, fibrinogen levels and platelet count were comparable between the two groups, as shown in Table 2.

Table 2
Comparison of coagulation profiles between menorrhagic and non-menorrhagic women, Bungoma County Referral.

Parameter	Women with Menorrhagia (cases)	Women without menorrhagia (controls)	*p* value
	Median (IQR)	Median (IQR)	
PT/seconds	12.40 (2.40)	12.10 (0.50)	**< 0.00001**
INR	1.27 (0.51)	0.80 (0.50)	**< 0.00001**
aPTT/seconds	35.14 (5.80)	34.68 (3.19)	0.106
TT/seconds	17.39 (2.84)	17.11 (1.89)	0.176
Fibrinogen/ng/dL	309.67 (81.44)	311.92 (91.32)	0.082
PLT count x 10^9/L	358.00 (75.00)	366.00 (79.25)	0.101

The data are presented as the medians (interquartile ranges) of coagulation parameters unless otherwise stated. Statistical significance was determined using the Mann–Whitney U test. A *p* value ≤0.05 was considered to indicate statistical significance. PT: prothrombin time, INR: international normalized ratio, aPTT: activated partial thromboplastin time, TT: thrombin time, PLT: platelet. PT and the INR were significantly greater in menorrhagic women than in non-menorrhagic women, but the aPTT, TT, fibrinogen and PLT were comparable.

Association between coagulation profile and menorrhagia

The association between coagulation profile and menorrhagia was modeled using a binary logistic regression model based on the distribution of coagulation parameters in the menorrhagic and non-menorrhagic groups. Using non-menorrhagic women as the reference group since they were deemed healthy and had coagulation profiles thought to be closer to the expected reference values, binary logistic regression analysis revealed that menorrhagia was associated with high PT [OR = 2.129, 95% CI = 1.658–2.734, $p < 0.0001$] and high INR [OR = 7.479, 95% CI = 3.094–18.080, $p < 0.0001$], as shown in Table 3.

Menorrhagia was not associated with aPTT [OR = 1.064, 95% CI = 0.976–1.161, $p = 0.158$]; TT [OR = 1.129, 95% CI = 0.961–1.325, $p = 0.139$]; fibrinogen [OR = 0.996, 95% CI = 0.992–1.000, $p = 0.062$]; or platelet count [OR = 0.998, 95% CI = 0.994–1.002, $p = 0.349$], as shown in Table 3.

In summary, menorrhagia was significantly associated with high PT and INR but was not associated with aPTT, TT, fibrinogen or platelet count, as shown in Table 3.

Table 3
Association between menorrhagia and coagulation profile, Bungoma County Referral Hospital

Parameter	Women category	OR	95% CI	*p value*
	Non - menorrhagia	Ref.	-	**-**
PT/Seconds	Menorrhagia	2.129	1.658–2.734	**< 0.0001**
	Non - menorrhagia	Ref.	-	**-**
INR	Menorrhagia	7.479	3.094–18.080	**< 0.0001**
	Non - menorrhagia	Ref.	-	-
aPTT/Seconds	Menorrhagia	1.064	0.976–1.161	0.158
	Non - menorrhagia	Ref.	-	-
TT/Seconds	Menorrhagia	1.129	0.961–1.325	0.139
	Non - menorrhagia	Ref.	-	**-**
Fibrinogen/ng/dL	Menorrhagia	0.996	0.992-1.000	0.062
	Non - menorrhagia	Ref.	-	**-**
PLT count x 10^9/L	Menorrhagia	0.998	0.994–1.002	0.349

Women (n = 428) were classified based on the presence or absence of menorrhagia. Binary logistic regression analysis was used to obtain odds ratios (ORs) and 95% confidence intervals (CIs). Values in bold are statistically significant at $p \leq 0.05$. PT: prothrombin time, INR: international normalized ratio, aPTT: activated partial thromboplastin time, TT: thrombin time, PLT: platelet. Menorrhagia was associated with high PT and INR but not with aPTT, TT, fibrinogen or PLT count.

Comparison of morphological characteristics of platelets between menorrhagic and non-menorrhagic women

In both menorrhagic and non-menorrhagic women, there were no microplatelets, large/giant platelets, or hyper-granular or agranular platelets, as shown in Table 4.

Table 4
Comparison of morphological characteristics of platelets in Leishman-stained preparations between menorrhagic and non-menorrhagic women, Bungoma County Referral

Platelet morphology characteristics	Menorrhagic women		Non-menorrhagic women	
	Frequency	%	Frequency	%
Normal platelets	214	100	214	100
Platelets with excessive anisocytosis	Nil	Nil	Nil	Nil
Micro-platelets	Nil	Nil	Nil	Nil
Large/giant platelets	Nil	Nil	Nil	Nil
Platelet with normal granules	214	100	214	100
Hyper-granular platelets	Nil	Nil	Nil	Nil
Agranular platelets	Nil	Nil	Nil	Nil

The data provided are presented as the frequency and percentage unless otherwise stated. The frequency and proportion of the seven platelet morphological characteristics were tabulated for both menorrhagic and non-menorrhagic participants. Nil means no morphological characteristic was observed in any of the participants for either the menorrhagic or non-menorrhagic categories.

Discussion

The present study aimed to determine the difference in coagulation parameters between menorrhagic and non-menorrhagic women at the gynecological clinic of Bungoma County Referral Hospital. The association between coagulation profile and menorrhagia was also determined. Furthermore, the morphological characteristics of platelets from menorrhagic and non-menorrhagic women were determined.

The demographic characteristics of the study participants were comparable between the two groups in terms of age, place of residence, parity, occupation, and literacy; however, menorrhagic women had a significantly greater family history of bleeding disorders than non-menorrhagic women. In the present study, menorrhagic women had a median age of 34 years, which was comparable to that of non-menorrhagic women, who had a median age of 33 years. This was higher than the median in the Sudanese study (25) and the Indian study (26), which focused solely on adolescents, and the study conducted at Kocaeli University Hospital (27), which focused on adolescents and young women. The selection criteria used in the current study, which included adult patients aged 18 to 45 years, may explain why these findings contrast with those of previous studies.

The residential areas of menopausal women (rural or urban) were not substantially different from those of non-menorrhagic women in the present study, which was similar to the findings of a study performed in Tanzania (28). The current study revealed that a greater number of menorrhagic women had ever had a child, even though there was no significant difference in terms of parity. These findings contradict those of a study conducted in the United States of America in which just one person had ever had a child. This disparity could be due to the difference in sample size, as the latter comprised only 38 participants. The current study revealed that a considerable number of menorrhagic women were informally employed, which was not significantly different

from the findings of non-menorrhagic women. These findings are consistent with research performed in Tanzania (28), which showed that 52.5% of menorrhagic women work as peasants.

The present study revealed that a family history of bleeding disorders was significantly more common among menorrhagic women than among non-menorrhagic women; however, approximately 3-fold more menorrhagic women did not have any family history of bleeding disorders. These findings are consistent with studies performed in Egypt (29), Sudan (25) and Sweden (30). Previous studies have shown a substantial association between idiopathic menorrhagia and a family history of heavy menstrual bleeding, suggesting that familial menorrhagia is an inherited feature (27). A family history of spontaneous or induced bleeding may increase the possibility of congenital bleeding, but multiple drugs can increase the risk of bleeding (31). However, some previous studies have demonstrated that one-third of menstrual bleeding problem diagnoses have no documented family history and can be caused by a random gene mutation (32). The high number of menorrhagic women without a family history of bleeding disorders can be attributed to the fact that a diagnosis of bleeding problems can develop completely unexpectedly due to a genetic mutation which still needs further explorations. In addition, some people may be unaware of a bleeding issue in their family if other relatives are undiagnosed or have different symptoms. In light of the present findings, it is recommended that a thorough assessment of the family history of bleeding in menorrhagic women be performed routinely. Furthermore, women in this category should be evaluated for the possibility of having a genetic mutation of F5 gene which have been found to cause factor V deficiency.

The present study revealed that a history of epistaxis or gum bleeding in menorrhagic women was comparable to that in non-menorrhagic women; however, 0.9% of menorrhagic women had a history of epistaxis or gum bleeding. Additionally, the study showed that the history of prolonged bleeding following delivery or miscarriage in menorrhagic women and non-menorrhagic women was comparable; however, 1.9% of menorrhagic women had a history of prolonged bleeding following delivery or miscarriage. These findings agree with studies performed in South Sudan (25) and Turkey (27), which demonstrated that some patients had a history of additional bleeding issues in addition to presenting with menorrhagia. These findings could be attributed to the fact that previous studies have suggested that familial menorrhagia is a hereditary characteristic (27). Based on the results of the present study, a history of bleeding disorders other than menorrhagia, such as epistaxis, gum bleeding, and prolonged bleeding after delivery or miscarriage, should be extensively evaluated in women presenting with menorrhagia.

In the present study, the PT and INR were considerably greater in menorrhagic women than in non-menorrhagic women and were associated with menorrhagia, but the aPTT was comparable between the two groups and was not associated with menorrhagia. This was consistent with the findings of a study conducted in Sudan (25), which demonstrated higher PT and INR in menorrhagic women than in non-menorrhagic women. These findings, however, contradicted those of a study undertaken in India (26), which revealed PT to be normal in all but abnormal in just one patient. These findings also contradicted a study conducted in the United States of America (15), which showed that PT levels were comparable between menorrhagic and non-menorrhagic women. The prolonged PT and INR and their association with menorrhagia in the current study could be attributed to the fact that women in the mid-luteal phase are more hypercoagulable than women in the early follicular phase (33). Most of those previous investigations associated prothrombin time with adenomyosis (34) but not directly with menorrhagia. However, prolonged PT and normal aPTT may reflect vitamin K deficiency caused by malnutrition, biliary obstruction, malabsorption syndromes, antibiotic use, or liver disease, which lowers clotting factor

synthesis (35). The prothrombin time test evaluates the extrinsic coagulation pathway (also known as the tissue factor pathway), which comprises factors VII, X, V, and II, while the aPTT evaluates the intrinsic pathway (also known as the amplification pathway or contact system), which consists of factors XII, XI, IX, VIII, X, V, and II(36). It is further postulated that if the aPTT is normal, then a prolonged PT could be due to factor VII deficiency (36). In light of the present findings, it is recommended that PT and the INR, together with other coagulation factors, be routinely evaluated in menorrhagic women.

In the present study, TT, fibrinogen and platelet count were comparable in menorrhagic and non-menorrhagic women and were not associated with menorrhagia. Despite these findings, menorrhagia can cause anemia, increase the risk of hypercoagulability, and eventually lead to thrombosis (37). Patients with dysfibrinogenemia can also experience combined hemorrhagic and thrombotic tendencies (38). Dysfibrinogenemia is a clotting disorder characterized by a range of structural defects in the fibrinogen molecule that result in aberrant fibrinogen function. It can be hereditary or acquired. (39). In female patients with hereditary afibrinogenemia, repeated severe intra-abdominal hemorrhages due to rupture of the Graafian follicle during ovulation have been reported (40). Patients with acquired dysfibrinogenemia frequently have no history of bleeding or clotting, and a family history of dysfibrinogenemia does not predict hematologic problems (40). Clinical symptoms of acquired dysfibrinogenemia range from acute bleeding or thrombosis to chronic thromboembolic pulmonary hypertension and renal amyloidosis. Menorrhagia, postoperative bleeding, epistaxis, postoperative wound dehiscence, deficient wound healing, gingival bleeding, hemorrhage, and mild soft-tissue hemorrhage are all possible presenting signs and symptoms (41).

Despite the current data indicating comparable platelet counts in menorrhagic and no menopausal women, it is important to highlight that platelet count, size, and morphology are usually normal in individuals with Glanzmann thrombasthenia, a hereditary qualitative condition that affects platelet function through failure of aggregation (42).

In the present study, neither large/giant platelets nor hyper-granular or agranular platelets were found in menorrhagic or non-menorrhagic women. Despite these findings, Bernard–Soulier syndrome can be linked to uncontrollable menorrhagia (43). Bernard-Soulier syndrome is a rare inherited bleeding disease distinguished by prolonged bleeding time, thrombocytopenia, and morphologically aberrant large platelets that fail to adhere to exposed collagen in hemostatic response. The platelet membrane is defective in GpIb-V and GpI-IX, with the predominant deficiency being the lack of a GpIb receptor for the Von Willebrand factor (43).

Overall, the PT, INR, and family history of bleeding disorders, among other parameters, should be evaluated in menorrhagic women as soon as possible to better understand the coagulation profile and diagnose this life-threatening condition so that prompt treatment can be provided. A more accurate classification of menorrhagia would most likely result in the identification of a broader range of characteristics that could indicate hemostatic diseases or other etiologies. However, our study was limited in that we did not assess von Willebrand factor, which is known to affect coagulation. Furthermore, the study did not perform platelet aggregometry as platelet function test to measure platelet response or aggregation to a panel of antagonists such as collage. A longitudinal study with a larger sample size could help to close the knowledge gap in determining and interpreting such an association.

Conclusion

The prothrombin time (PT) and internal normalized ratio (INR) are increased in menorrhagic than in non-menorrhagic women and are associated with menorrhagia. A family history of bleeding disorders was significantly greater in menorrhagic than in non-menorrhagic women. Thus, prothrombin time and the internal normalized ratio, which are coagulation parameters, and family history of bleeding disorders are hallmark indicators of menorrhagia according to the findings of the present study.

Recommendations

The study recommends that women who experience heavy menstrual bleeding have a coagulation profile, as well as a family history of bleeding and history of bleeding disorders other than menorrhagia assessed. This approach allows for a more accurate diagnosis of menorrhagia based on the identified coagulation hallmark indicators.

Abbreviations

aPTT
Activated partial thromboplastin time
BRCRH
Bungoma County Referral Hospital
CDC
Centre of Disease Control
CI
Confidence interval
EDTA
Ethylene diamine tetra-acetic acid
INR
International Normalized Ratio
IQR
interquartile range
MUERC
Maseno University Ethical Review Committee
NACOSTI
National Commission for Science Technology and Innovation
OR
Odds Ratio:PLT:platelet
PT
prothrombin time
RPM
revolution per minute
SPSS
statistical package for social science
TT
thrombin time.

Declarations

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Leonard Lusenaka contributed to the recruitment of the participants. Thomas Wekesa contributed by performing the sample collection exercise. Antony Sangolo and Emmanuel Khisa assisted in the operation of the samples and the data collection.

Authors' contributions

PMM, SKM, PK, and CO planned the study and participated in all the areas. SKM, PK, and CO oversaw the study. PMM and FM conducted the data analysis and developed the manuscript. SKM, PK, and CO reviewed the manuscript for philosophical insights. All the authors reviewed the final manuscript and approved it for submission.

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Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to compliance with ethical reviewer's guidelines but are obtainable from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the Maseno University Scientific and Ethical Review Committee (MUSERC). All study participants provided informed written consent to participate in the study.

Consent for publication

Not applicable.

Competing interests

Authors have no competing interests.

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