GENERAL GYNECOLOGY

The prevalence of underlying bleeding disorders in patients with heavy menstrual bleeding with and without gynecologic abnormalities

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OBJECTIVE: The purpose of this study was to assess the prevalence of underlying bleeding disorders in women with heavy menstrual bleeding (HMB) with and without gynecologic abnormalities.

STUDY DESIGN: We performed a single-center prospective cohort study of 112 consecutive patients who were referred for heavy menstrual bleeding. Control subjects were 28 healthy volunteers who reported no HMB. Patients and control subjects had hemostatic testing in the first week after menstruation. Patients underwent gynecologic evaluation.

RESULTS: The median age was 42.5 years (range, 17—55 years) in patients and 40.0 years (range, 25—55 years) in control subjects. Forty-six percent of patients had anemia; the median pictorial bleeding assessment chart score was 271. Seven percent of the control subjects with a subjectively normal menstruation had anemia. Twenty-six percent of patients had gynecologic abnormalities, which was considered to explain HMB. Overall, we found an underlying bleeding disorder in 29% of the patients, which was comparable for unexplained and explained HMB (31% vs 27%; $P = .75$). We diagnosed 6 cases of Von Willebrand's disease, 4 cases of factor XI deficiency, and 1 case of factor VII deficiency. The only abnormalities that we found in control subjects were platelet aggregation defects (11% in control subjects vs 23% in patients). Patients had a significantly longer activated partial thromboplastin time compared with control subjects (26.5 vs 25.0 seconds; $P = .001$) that was caused by lower median levels of factor XI (100 vs 124 IU/dL; $P < .001$).

CONCLUSION: Bleeding disorders play an equally important role in the cause of both unexplained and explained heavy menstrual bleeding. A novel finding is the occurrence of low, but not deficient, levels of factor XI.

Key words: bleeding disorder, factor XI, heavy menstrual bleeding, menorrhagia, von Willebrand's disease

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Heavy menstrual bleeding (HMB) is a common problem. At least 5-10% of women in reproductive age seek medical attention for HMB.[1] The World Health Organization estimates that 18 million women worldwide are affected.[2] HMB is a common cause of iron deficiency anemia[3] and can affect a woman's quality of life, her study or work, and family and social interactions.[4]

HMB can be associated with a wide range of hemostatic disorders.[5,6] Von Willebrand's disease (VWD) has been recognized as an important cause and/or contributory factor.[7-9] Approximately 5-20% of the patients with HMB with no gynecologic abnormalities have VWD as an underlying bleeding disorder.[10,11] The prevalence in HMB of underlying bleeding disorders other than VWD (eg, platelet function defects) has yet to be established. Although a cyclic variation of hemostatic factor variables has been found,[12] with nadirs that occur during the menstrual and/or follicular phase, most previously reported studies have measured variables randomly throughout the menstrual cycle. This may result in over- or underestimation of the prevalence of a bleeding disorder.[10] Previous studies have focused on women with no gynecologic abnormalities. Whether women with HMB and gynecologic abnormalities (ie, uterine polyps and fibroid tumors) also have underlying bleeding disorders has not been assessed in earlier studies.[10]

We studied the prevalence of underlying bleeding disorders that included VWD, other coagulation disorders, and platelet defects in patients with HMB with and without gynecologic abnormalities; testing occurred in the first week after menstruation in routine Dutch gynecologic practice. We compared the data with healthy control subjects.

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MATERIALS AND METHODS

Patients

This is a single-center prospective cohort study that included consecutive patients who were referred to the gynecology clinic at the University Medical Centre of Groningen between March 2007 and December 2010, and who had a history of heavy, regular (every 23-39 days) menstrual periods. Exclusion criteria were pictorial bleeding assessment chart (PBAC) score <100, known bleeding disorders, use of any intrauterine device in the past 2 months, and treatment with anticoagulants, antifibrinolytics, nonsteroidal antiinflammatory agents, combined oral contraceptives, or progestogens. Referred patients who were eligible potentially received a structured questionnaire by mail to obtain information about baseline characteristics: medical, obstetric, and gynecologic history, and previous treatment for HMB. After reviewing the completed questionnaire, we excluded women with intermenstrual, irregular, and postcoital bleeding. Thereafter, the women had a gynecologic examination and transvaginal pelvic ultrasonography in the first week after menstruation. If we suspected a gynecologic abnormality during transvaginal ultrasonography (ie, a polyp, endometrial hyperplasia or submucous fibroid), we did an additional saline solution infusion sonogram and/or (diagnostic or therapeutic) hysteroscopy during the same consultation. One interviewer (H.M.K.) took the menstrual history, recorded the number of other bleeding symptoms[13] (relevant items of the Tosetto bleeding score [320])[13] such as easy bruising; nose, gum, postoperative, and postpartum bleeding, and bleeding after tooth extraction; the interviewer asked about a family history of bleeding disorders. Women with submucous uterine fibroid tumors >2 cm in diameter, uterine polyps, endometrial hyperplasia, or endometritis were classified as HMB with gynecologic abnormalities or explained HMB.[8,14]

The study was approved by the institutional review boards of the University Medical Centre of Groningen. Informed consent was obtained from all patients and control subjects.

Control subjects

The 28 healthy volunteers in our hospital were women with a subjectively normal menstruation and no use of hormonal treatment or intrauterine devices; their hemostatic test results in the first week after menstruation during follicular phase were used for comparison. Exclusion criteria were known bleeding disorders, treatment with anticoagulants or nonsteroidal antiinflammatory agents. Control subjects completed the same questionnaire as patients but had no gynecologic examination. We did not exclude control subjects on the basis of their PBAC score.

PBAC of menorrhagia

Before the first hospital visit, the patients were informed about the PBAC[15,16] by a letter that contained standard instructions; they completed the PBAC in the menses before the first hospital visit. HMB was defined as a PBAC score of ≥100 based on the scoring system of Higham et al.[15] The healthy volunteers also completed the pictorial chart in the first menses after blood samples were taken.

Laboratory measurements

A venous citrated blood sample was taken from all patients and control subjects in the first week after menstruation. In patients, the blood samples were taken before the gynecologic examination. Blood samples were also obtained for ABO blood group typing, complete blood cell counts, and ferritin and liver, kidney and thyroid function measurements.

Reagents that were used for activated partial thromboplastin time (aPTT; Dade Actin, FS Reagent), prothrombin time (PT, Dade Innovin Reagent) and fibrinogen (Dade Thrombin Reagent) were obtained from Siemens (Marburg, Germany). The 1-stage factor VIII, IX, XI, and XII assays were performed with aPTT reagent and factor deficient plasmas from Siemens. Von Willebrand factor antigen (vWF:Ag) was measured by enzyme-linked immunosorbent assay with polyclonal antiserum from DakoCytomation (Glostrup, Denmark), with von Willebrand factor ristocetin cofactor activity (vWF:Rco), and with von Willebrand reagent (lyophilized stabilized platelets and ristocetin) from Siemens in an optical aggregometer from Chrono-Log Corp (Haverton, PA).

Induced platelet aggregation that was measured by light transmission aggregometry (LTA; Chrono-Log Corp) was performed at 37.8°C in platelet-rich plasma with 5 different agonists: adenosine diphosphate (ADP), 3.3 μmol/mL; ristocetin, 1.2 mg/mL; arachidonic acid, 1.5 mmol/L; epinephrine, 1 μg/mL, and collagen, 1 μg/mL. In a subgroup (n = 48 women), we also performed LTA with lower ADP concentrations of 1.0, 1.5, and 2.0 μmol/mL. Aggregation tracings were performed for 10 minutes, and maximal percent aggregation was recorded. Reference values (mean ± 2SD) were estimated in the control group on log-transformed data; a decreased aggregation was defined as a maximal percent aggregation below the mean ± 2SD. The lower limit of normal reference values (mean ± 2SD) were 64% for ADP (3.3 μmol/mL), 72% for ristocetin, 70% for epinephrine, 70% for collagen, and 69% for arachidonic acid.

For the other hemostatic parameters, the normal ranges in our laboratory were as follows: PT, 9-12 seconds; aPTT, 23-33 seconds; fibrinogen, 1.7-4.0 g/L; factor VIII:C, 50-150 IU/dL; factor IX, 50-150 IU/dL; factor XI, 70-130 IU/dL; factor XII, 65-150 IU/dL; vWF:Ag, 50-150 IU/dL, and vWF:Rco, 50-150 IU/dL.

Values below the lower limit of normal reference range were confirmed by a second independent sample and were taken in the first week after the menstruation. A diagnosis of VWD was made if the vWF:Ag or vWF:Rco was <50 IU/dL in 2 measurements.

Statistical analysis

Mann Whitney *U* and χ^2 tests were used as appropriate. Because the levels of all hemostatic variables and percentage of maximal aggregation were not normally distributed, we log transformed them. Differences in log-transformed means between women with HMB and control subjects were evaluated by *t* tests. The analysis of variance test was used to