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Clinical significance of diagnostic algorithm in detection of mild hemostasis disorders in women with menorrhagia

Klinički značaj dijagnostičkog algoritma u detekciji blažih poremećaja hemostaze kod pacijentkinja sa menoragijom

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Abstract

Background/Aim. Coagulation disorders could be a cause of menorrhagia in women of reproductive age. The aim of the study was to estimate frequency of coagulation disorders and design an appropriate algorithm for detection of coagulation disorders. **Methods.** We investigated coagulation in 115 women (36.1 ± 9.6 years) with anamnestic data of menorrhagia, verified using semiquantitative method - Pictorial Bleeding Assessment Chart (PBAC) with score ≥ 100. **Results.** Menorrhagia was objectively verified in sixty-four women (55.7%) and in comparison with those with normal menstruation they had higher PBAC score of menstrual cycle [median (Md) = 150.0 vs. Md = 50.0; $p < 0.001$] but not its duration (7.2 ± 2.1 days vs. 7.3 ± 1.9 days; $p > 0.05$). Coagulation defects was found in 12 (10.4%) women - decreased F IX: Ac in 4 (3.5%), decreased F VII: Ac in 1 (0.9%), decreased F X: Ac in 1 (0.9%), decreased F XI: Ac in 1 woman (0.9%), while 5 (4.3%) women matched criteria for mild von Willebrand disease (VWD) type 1. Women with coagulation disorders had prolonged prothrombin time (PT) [Md = 13.1 s, range: 12.2–14.8 s vs. Md = 12.5 s, range 10.6–18.3 s; $p = 0.032$]. Anemia was diagnosed in 61 (53.0%) women. The strongest predictor of the hemostasis disorder was menorrhagia (Quotient of probability 0.018), then anemia presence (12.43), PT (2.35), menstrual cycle duration (1.16) and the PBAC score (0.98). **Conclusion.** The results of the study indicate the need to form a diagnostic algorithm for hemostasis disorders, primarily VWD. Sophisticated analysis of hemostasis is required, especially if predictive factors of statistical models are detected: objectively verified menorrhagia, anemia, prolonged menstrual cycle, PBAC score > 100 and extended PT.

Key words:
von willebrand disease; hemostasis, disorders; anemia.

Apstrakt

Uvod/Cilj. Poremećaji koagulacije mogu da budu uzrok menoragije kod žena u reproduktivnom periodu. Cilj istraživanja bio je utvrđivanje učestalosti poremećaja koagulacije kod žena sa menoragijom i kreiranje odgovarajućeg algoritma za detektovanje poremećaja koagulacije. **Metode.** Ispitivani su parametri koagulacije kod 115 žena (36,1 ± 9,6 godina) sa anamnestičkim podatkom o postojanju menoragije koja je verifikovana primenom semi-kvantitativne metode - Pictorial Bleeding Assessment Chart (PBAC) sa skorom ≥ 100. **Rezultati.** Menoragija je bila objektivno verifikovana kod 55,7% ispitanica. Pacijentkinje sa menoragijom imale su viši PBAC skor [medijana (Md) = 150,0 vs. Md = 50,0; $p < 0,001$], ali ne i dužinu menstrualnog ciklusa (7,2 ± 2,1 dana vs. 7,3 ± 1,9 dana; $p > 0,05$). Poremećaji koagulacije bili su detektovani kod 12 (10,4%) ispitanica – snižene vrednosti faktora (F) IX: Ac kod 4 (3,5%), F VII: Ac kod 1 (0,9%), F X: Ac kod 1 (0,9%), F XI: Ac kod 1 (0,9%), a 5 (4,3%) pacijentkinja ispunjavalo je kriterijume blage forme von Willebrandove bolesti (VWB) tip 1. Ispitanice sa poremećajima koagulacije su imale produženo protrombinsko vreme (PT) [Md = 13,1 s (12,2–14,8 s) vs. Md = 12,5 s (10,6–18,3) s; $p = 0,032$]. Anemija je dijagnostikovana kod 61 (53,0%) pacijentkinje. Najjači prediktor poremećaja hemostaze bilo je postojanje objektivno verifikovane menoragije (količnik verovatnoće 0.018), a zatim prisustvo anemije (12.43), PT (2.35), dužina menstrualnog ciklusa (1.16) i vrednost PBAC skora (0.98). **Zaključak.** Rezultati istraživanja ukazuju na potrebu formiranja dijagnostičkog algoritma poremećaja hemostaze. Sofisticirane i skupe laboratorijske analize za dijagnozu poremećaja hemostaze bilo bi racionalno sprovesti kod pacijentkinja koje imaju menoraguju verifikovanu objektivnim metodama, PBAC skor > 100, produžen menstrualni ciklus, anemiju i produženo PT.

Ključne reči:
von Willebrand-ova bolest; hemostaza, poremećaji; anemija.

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Introduction

Menorrgahia is fairly common problem among women of reproductive age. According to *World Health Organization* (WHO) 18 million women in the world, aged 30 to 55, have this disorder [1]. Objectively, menorrhagia is defined as menstrual blood loss exceeding 80 mL *per* menstruation or heavy menstrual bleeding that lasts for more than 7 days [2]. Diagnosis is often made subjectively by patient self-report of excessively heavy menstrual bleeding, but correlation between anamnestic and objectively verified menorrhagia is poor. Data from literature suggested that approximately 10% of reproductive-aged women had objective evidence of menorrhagia, but studies based on self-reported information suggested that approximately 30% of women of reproductive age were afflicted with heavy menstrual bleeding [3, 4]. Menorrhagia may result from anatomic, endocrinologic, iatrogenic and organic causes [5–8]. Underlying bleeding disorders belong to the group of organic causes of menorrhagia and only have been recognized during the last two decades as a significant etiopathogenetic factor for menorrhagia formation. Frequency of hemostasis disorders in women with menorrhagia is in the range of 10% to 20% [9, 10]. The reported prevalence of von Willebrands disease (vWD) as the most frequent among them is 13%, based on a systematic review [11]. The considerable proportion of women with menorrhagia is found to have single coagulation factor deficiencies such as factor (F) XI deficiency (1–4%), carriers of hemophilia A and hemophilia B observed in approximately 1–4% of females with menorrhagia and less common deficiencies of factors I, II, V, VII, X, XI, XIII [12–15]. Coagulation abnormalities have a major impact on health-related quality of life, work impairment and health-care costs [16]. Anemia is associated with menorrhagia and coagulation abnormalities in women of reproductive age**.** At least 20% of women with heavy menstrual bleeding experience anemia [17].

The aim of the study was to estimate prevalence of coagulation disorders in females with menorrhagia as well as frequency of menorrhagia and its characteristics and design an appropriate algorithm for patients and define required laboratory tests for them.

Methods

Patients

This clinical-laboratory study included population of 115 women aged 36.1 ± 9.6 years (range 15 to 58 years). The main including criterion was anamnestic information about the existence of heavier and/or prolonged menstrual cycles. Excluding criteria were: the existence of endocrine diseases and diseases of genital and urethral tract which could be the cause of menorrhagia, treatment with antiplatelet and anticoagulant drugs within 2 weeks prior to the present study, known bleeding disorder, pregnancy. Informed consent was obtained from all patients. Menorrhagia was verified using semiquantitative method – Pictorial Bleeding Assessment Chart (PBAC) with score greater than 100 (which was equivalent to greater than 80 mL amount of blood loss measuring with alkaline hematin analysis of sanitary towels) [5, 6]. Complete blood count (CBC), iron, total ron binding capacity (TIBC), unsaturated iron binding capacity (UIBC), bleeding time (BT) and coagulation analyses as well as ABO blood group typing were performed.

Assays

Following coagulation tests were repeated on two occasions, before day 7 of the menstrual cycle on platelet poor plasma (fresh blood containing 3.2% sodiumcitrate anticoagulant centrifuged with 2500 G rpm for 15 minutes) on the ACL 9000: activated partial tromboplastin time (aPTT) (aPTT-SP liquid, Hemosil, Instrumentation Laboratory Company-Lexington USA), protrombin time (PT), (PT-Fibrinogen Recombinant, Hemosil, Instrumentation Laboratory Company-Lexington USA), *International normalized ratio* (INR), fibrinogen (PT-Fibrinogen Recombinant, Hemosil, Instrumentation Laboratory Company-Lexington USA), D-dimer (D-dimer, Hemosil, Instrumentation Laboratory Company-Lexington USA), factor clotting activity (F II, F V, F VII, F VIII, F IX, F X, F XI) (Factor deficient plasma, Hemosil, Instrumentation Laboratory Company-Lexington USA), von Willebrand factor antigen (vWFAg) (von Willebrand Factor Antigen, Hemosil, Instrumentation Laboratory Company-Lexington USA), von Willebrand factor activity (vWFAc) (von Willebrand Factor Activity, Hemosil, Instrumentation Laboratory Company-Lexington USA).

Statistical analysis and assessment

Statistical analysis was performed by SPSS 13.0. Mean and standard deviation were used to describe the variables. ANOVA test and *t*-test were used to analyze quantitative variables. The Fisher exact test and chi-square (χ^2) test were carried out for qualitative variables. With the help of direct logistic regression, the predictive value of the model including some of the parameters tested was examined.

Results

The frequency and characteristics of menorrhagia in the study population

Sixty four (55.7%) women of the total number of patients (115) with anamnestically data of menorrhagia, had objectively verified menorrhagia using semiquantitive method – Pictorial Bleeding Assessment Chart (PBAC) with score > 100 (equivalent > 80 mL blood). Characteristics of menorrhagia and hematologic tests results of patients with and patients without menorrhagia are shown in Table 1.

Coagulation tests results of patients with menorrhagia and patients without menorrhagia are shown in Table 2.

Table 1

Characteristics of menorrhagia and hematologic tests results of patients with and without menorrhagia

Parameters	All patients (mean ± SD or Md, min-max) (n = 115)	Women with menorrhagia (mean ± SD or Md, min-max) (n = 64)	Women without menorrhagia (mean ± SD or Md, min-max) (n = 51)	*p*
Age (years)	36.1 ± 9.6	38.0 (15–55)	36.0 (17–58)	> 0.05*
Score (points)	100.0 (26–778)	150.0 (100–778)	50.0 (26–95)	< 0.001*
Duration of menstrual bleeding (days)	7.0 (4–28)	7.0 (6–28)	7.0 (4–12)	> 0.05*
Iron level (imol/L)	9.8 (min 2.1, max 43.6)	8.6 (2.1–36.2)	8.1(5.2–43.6)	> 0.05*
RBC ($\times 10^{12}$/L)	4.28 (2.27–5.50)	4.34 (3.30–5.50)	4.73 (2.27–5.40)	> 0.05*
Hemoglobin (g/L)	114.1 ± 22.2	114.9 ± 19.1	113.1 ± 25.9	> 0.05**
MCV (fL)	81.8 ± 10.1	83.1 ± 9.8	81.3 ± 10.6	> 0.05*
Hematocrit (%)	0.350 (0.126–0.462)	0.360 (0.22–0.462)	0.359 (0.126–0.440)	> 0.05*
Platelets ($\times 10^{9}$/L)	283.9 ± 92.9	290.1 ± 86.9	275.3 ± 100.9	> 0.05**

RBC – red blood cells; MCV – mean cell volume; Md – median.
***Mann-Whitney *U*-test; **Student *t*-test.**

Table 2

Coagulation tests results of patients with menorrhagia and patients without menorrhagia

Parameter	Women with menorrhagia (mean ± SD or Md, min-max) (n = 64)	Women without menorrhagia (mean ± SD or Md, min-max) (n = 51)	*p*
Bleeding time (s)	120 (60–270)	90 (60–180)	> 0.05
aPTT (s)	27.9 (22.4–46.2)	28.6 (21.3–49.1)	> 0.05*
PT (s)	12.6 (10.8–15.0)	12.5 (10.6–18.3)	> 0.05*
Fibrinogen (g/L)	3.26 ± 0.82	3.50 ± 0.85	> 0.05**
F II (%)	84.4 (50.9–149.0)	92.5 (52.0–182.0)	> 0.05*
F V (%)	98.5 (50.0–213.0)	110.0 (50.0–241.0)	> 0.05*
F VII (%)	78.0 ± 28.3	100.5 ± 35.0	> 0.001**
F VIII (%)	132.0 (39.0–525.0)	124.0 (22.0–596.0)	> 0.05*
F IX (%)	79.6 (27.0–772.0)	79.2 (45.0–472.0)	> 0.05*
vWFAc (%)	98.5 (26.2–182.0)	96.6 (38.5–279.0)	> 0.05*
vWFAg (%)	111.5 (30.0–535.0)	95.8 (32.0–348.0)	> 0.05*

aPTT – activated partial thromboplastin time; PT – prothrombin time; F – factor; vWFAc – von Willebrand factor activity; vWFAg – von Willebrand factor antigen; Md – median.
***Mann-Whitney *U*-test; **Student *t*-test.**

The frequency and characteristics of coagulation disorders in the study population

In the examined population, coagulation defects were found in 12 (10.4%) women – decreased F IX: Ac in 4 (3.5%), decreased F VII: Ac in 1 (0.9%), decreased F X: Ac in 1 (0.9%), 1 woman (0.9%) was a hemophilia C carrier, while 5 women (4.3%) matched criteria for mild VWD type 1. Groups of patients with and without hemostatic disorders did not differ significantly with respect to the studied parameters (age, length of menstrual cycle, PBAC score, hematology, most of the coagulation factors) as expected. Patients with some of hemostasis disorders registered had prolonged PT [median (Md) = 13.1 s (12.2–14.8 s) vs. Md = 12.5 s (10.6-18.3 s); $p = 0.032$]. After adjustment for the presence of F VII and F X deficiency this finding was persistent for the entire group.

Connection between menorrhagia and coagulation disorders

Chi-square (χ^2) test of independence (with correction by Yeats) showed significant association between the existence of menorrhagia and the existence of hemostasis disorders [c^2 (1, n = 115) = 5.506, $p = 0.019$, fi = -0.247, Cramer`s V = 0.247]. Among patients with menorrhagia, 17.2% of them have hemostasis disorder, while the number was significantly lower among patients who had no verified menorrhagia (1 of 51).

The frequency of anemia in the study population

Anemia was diagnosed in 61 (53.0%) women. Taking into account the average values of hematological parameters, microcytic, hypochromic, hiposideremic anemia was present in all patients.

Table 3
Prediction of the existence of hemostasis disorder in patients who state a history of the existence of menorrhagia (5 parameters)

Parameters	Á	Standard error	Wald	Degrees of freedom	*p*	Quotient of probability	95% confidence interval for quotient of probability	
							lower limit	upper limit
Menorrhagia	-4.024	1.470	7.495	1	0.006	0.018	0.001	0.319
Anemia	2.520	0.965	6.816	1	0.009	12.427	1.874	82.404
PBAC score	-0.015	0.009	3.197	1	0.050	0.985	0.968	1.001
PT	0.856	0.422	4.102	1	0.043	2.353	1.028	5.384
Cycle duration	0.148	0.076	3.821	1	0.050	1.160	1.000	1.345
Constant	-13.196	5.460	5.742	1	0.016	0.000		

PBAC – Pictorial Bleeding Assessment Chart; PT – prothrombin time.

Predictive factors for the existence of hemostasis disorders in the study population

We investigated the predictive ability of the analyzed parameters in the detection of coagulation disorders. The model included five parameters: objectively verified menorrhagia, the presence of anemia, menstrual cycle duration, the value of PBAC score, menstrual cycle and PT.

Prediction of the existence of coagulation disorder in patients who stated a history of the existence of menorrhagia is shown in Table 3.

The strongest predictor of the coagulation disorder was objectively verified menorrhagia, which quotient of probability was 0.018, then anemia presence (12.43), PT (2.35), menstrual cycle duration (1.16) and the PBAC score (0.98).

Discussion

In more than half of patients (55.7%) who self-reported abundant and/or prolonged menstrual bleeding, menorrhagia was really diagnosed. Therefore, there is a need to apply an objective method for estimating intensity of menstrual bleeding. The most spread one is a semi-quantitative method of comparative analysis of used sanitary material with standard tables and calculation of the PBAC score [6]. Obtained results are in the best correlation with the "golden standard" method of menstrual bleeding intensity estimation by determining alkaline hematin [5]. PBAC score of menstrual cycle (its intensity), but not its duration, was higher in women with menorrhagia. Thus, intensity but not duration of menstrual cycle led to greater blood loss in women with menorrhagia.

Patients with and without menorrhagia did not differ among themselves regarding examined factors of coagulation except for F VII. After adjustment for the presence of F VII deficiency this finding was persistent for the entire group. The existence of states and disorders which could influence activity of F VII were excluded: sepsis [18], malignity [19], transplantation of bone marrow [20, 21], transitory deficit after surgery [22] procreation of antibodies on F VII [23–26], influence of circadian rhythm on activity F VII [27, 28]. Considering a short half-life of F VII, it seems that at patients with menorrhagia it was possible to deplete this vitamin K dependent glycoprotein during prolonged bleeding. Still, these results demand examination of more patients and additional tests.

Every tenth patient who stated a history of the existence of menorrhagia, had some of coagulation disorders (12 of 115 patients). The most frequent disorder is mild VWD type 1. A similar prevalence of specific hemostasis disorders was also obtained in representative studies [29]. On our territory data on coagulation disorders in women with menorrhagia are scarce and the current study is one of the first conducted in Serbia. In women with menorrhagia we detected mild VWD type 1 and mild forms of the deficit of individual factors, which incidence is not significantly different from other researches. Among patients with menorrhagia, 17.2% of them had hemostasis disorder. Kadir et al. [10], in one of the most representative studies, have stated that about 17% of patients had such disorder. The proportion of women with VWD is 6.25%. Meta-analysis by Shankar et al. [11] that included a total of 11 studies with 988 women, showed that the prevalence of VWD was in the range of 5% to 24%. The proportion of women with a deficit of individual coagulation factors was 6% for F IX and 2% for F VII, F X and F XI. Some reports showed that incidence of deficit of individual factors in women with menorrhagia was in the range of 1% to 4%, an average of 2.5% [14, 15].

Our research showed that PT had a significant role in predicting coagulation disorder. We found out that patients with a registered coagulation disorder had significantly higher values of PT in comparison with patients with normal hemostasis and almost all of them had menorrhagia. The study of Hutspardol et al. [30] showed the similar average value of PT in the group of patients with menorrhagia.

Anemia was diagnosed in over a half of the patients included into the study (53%). The survey by Philipp et al. [14] showed that 58% of patients with menorrhagia had anemia and in 4% of them substitution therapy of blood transfusions was applied.

We investigated the predictive ability of the analyzed parameters in the detection of coagulation disorders. There are numerous attempts to determine the importance of specific symptoms and signs in terms of predicting the existence of coagulation disorders. The consensus of international expert panel for the diagnosis and treatment of VWD and other disorders of hemostasis in women with menorrhagia, for the

prediction of hemostatic disorders in women with menorrhagia rely on symptoms and signs of clinical hemorrhage [31]. Toseto et al. [32] and Rodeghiero et al. [33] valorized some of the most common clinical manifestations of hemorrhagic syndrome for prediction of VWD. To consolidate multiple parameters in the prediction of hemostasis disorders in our research a direct logistic regression was conducted and the predictive model was postulated that, in addition to menorrhagia, emphasized the presence of anemia, duration of the menstrual cycle, the value of PBAC score and PT. The strongest predictor of the existence of coagulation disorders was presence of objectively verified menorrhagia (ratio of the probability 0.018), then the presence of anemia (12.43), PT (2.35), the menstrual cycle lenght (1.16) and the PBAC score value (0. 98). This practically means that the chance of existence of coagulation disorders in a group of patients who stated the history of menorrhagia was 55.56 times higher in those with objectively verified menorrhagia, 12.43 times higher if they had anemia, with each increase in PT for 1 second probability of having a coagulation disorder increased 2.35 times, for each day of prolonged menstrual cycles it increased 1.16 times and with each additional point in the score of menstrual cycle it increased 1.02 time. These five parameters could also represent the strongest predictors for the presence of coagulation disorders.

Although inclusion of more patients and completing the study with additional investigations primarily related to platelet function is mandatory, the results of our study can be seen as a contribution to form a diagnostic algorithm for disorders of hemostasis, primarily VWD. Firstly, it is necessary to estimate the abundance of menstrual cycles (PBAC), and then, in the second step, it is important on the basis of simple anamnesis (duration of menstrual cycle) and standard laboratory analyses (laboratory parameters for anemia and PT) to extract the group of patients in whom it is rational to implement a set of expensive diagnostic procedures. Sophisticated analysis of hemostasis is required in highly specialized centers, especially if predictive factors of statistical models were detected: objectively verified menorrhagia, anemia, prolonged menstrual cycle, PBAC score > 100 and extended PT.

This gradual approach would allow a rational, comprehensive and timely diagnosis of mild forms of hemostasis disorders often present in patients with menorrhagia which are less likely to think about, because they have a subclinical manifestation and inapparent flow. A special clinical significance they get only in life-threatening situations, such as trauma or surgery, when untimely detection of these disorders can lead even to fatal consequences.

Conclusion

Our results can contribute to the development of a diagnostic algorithm for disorders of hemostasis, primarily VWD. Sophisticated analysis of hemostasis is required, especially if predictive factors of statistical models were detected: objectively verified menorrhagia, anemia, prolonged menstrual cycle, PBAC score > 100 and extended PT.

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