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- Autor contributions
  Svetlana M. Djukic performed the research and wrote the paper.
  Svetlana M. Djukic and Jovan P. Antovic designed the research study.
  Nebojsa Andjelkovic contributed essential reagents or tools.
  Aleksandar Djukic, Vladimir Vukomanovic and Ivana Simic Vukomanovic analysed the data.
Abstract

Background/Aim. Coagulation disorders could be a cause of menorrhagia in women of reproductive age. The aim was to estimate frequency of coagulation disorders and design an appropriate algorithm for detection of coagulation disorders.

Methods. We have investigated coagulation in 115 women (36.1 ± 9.6 years) with anamnestical data of menorrhagia, verified using semiquantitative method - Pictorial Bleeding Assessment Chart (PBAC) with score ≥ 100. Results. Menorrhagia has been objectively verified in sixty-four women (55.7%) and in comparison with those with normal menstruation, they had higher PBAC score of menstrual cycle (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 have been found in 12 (10.4%) women - decreased FIX:Ac in 4 (3.5%), decreased FVII:Ac in 1 (0.9%), decreased FX:Ac in 1 (0.9%), decreased FXI:Ac in 1 woman (0.9%), while 5 women (4.3%) matched criteria for mild VWD type 1. Women with coagulation disorders had prolonged PT (Md=13.1s, 12.2-14.8s vs Md=12.5s, 10.6-18.3s; p=0.032). Anemia was diagnosed at 61 women (53.0%). 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 can be seen as a contribution to the construction 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.

Key words: coagulation disorders, von Willebrand disease, menorrhagia, anemia.

Sažetak

Uvod/Cilj: Poremećaji koagulacije mogu da budu uzrok menorrhagije kod žena u reproduktivnom periodu. Cilj istraživanja je bio utvrđivanje učestalosti poremećaja koagulacije kod žena sa menorrhagijom 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 menorrhagije koja je verifikovana primenom semikvantitativne metode -Pictorial Bleeding Assessment Chart-(PBAC) sa skorom ≥ 100.

Rezultati. Menorrhagija je objektivno verifikovana kod 55,7% ispitanica. Pacijentkinja sa menorrhagijom su imale viši PBAC skor (Md=150,0 vs Md=50,0; p<0,001) ali ne i dužinu menstrualnog ciklusa (7,2±2,1 days vs.7,3±1,9 days; p>0,05). Poremećaji koagulacije su detektovani kod 12 (10,4%) ispitanica – snižena FIX:Ac kod 4 (3,5%), snažena FVII:Ac kod 1 (0,9%), snažena FX:Ac kod 1 (0,9%), snažena FXI:Ac kod 1 (0,9%) a 5 (4,3%) pacijentkinja je ispunjavalo kriterijume blage forme VWD tip 1. Ispitanice sa poremećajima koagulacije su imale produžen PT (Md=13,1s, 12,2-14,8s vs Md=12,5s, 10,6-18,3s; p=0,032). Anemija je dijagnostikovana kod 61 pacijentkinje. (53,0%). Najjači prediktor poremećaja hemostaze bio je postojanje objektivno verifikovane menorrhagije (količnik verovatnoće 0,018), a zatim prisustvo anemije (12,43), PT (2,35), dužina menstruacionog 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 bi bilo racionalno sprovesti kod pacijentkinja koje imaju menoragiju verifikovanu objektivnim metodama, PBAC skor > 100, produžen menstruacioni ciklus, anemiju i produženo PT.

**Ključne reči:** poremećaji koagulacije, von Willebrand-ova bolest, menoragija.

**Introduction**

Menorrhagia is fairly common problem among women of reproductive age. According to WHO 18 million women in the world aged 30 to 55 have this disorder. Objectively, menorrhagia is defined as menstrual blood loss exceeding 80mL per menstruation or heavy menstrual bleeding that lasts for more than 7 days. Diagnosis often is 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. Menorrhagia may result from anatomic, endocrinologic, iatrogenic and organic causes. 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%. The reported prevalence of von Willebrands disease (vWD) as the most frequent among them is 13%, based on a systematic review. The considerable proportion of women with menorrhagia is found to have single coagulation factor deficiencies such as factor 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 factor I, II, V, VII, X, XI, XIII. Coagulation abnormalities have a major impact on health-related quality of life, work impairment and health-care costs. Anemia is associated with menorrhagia and coagulation abnormalities in women of reproductive age. At least 20% of women with heavy menstrual bleeding experience anemia.

The aim 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 on them.

**Methods**

**Patients**

This clinical-laboratory study section included population of 115 women age 36.1 ± 9.6 years (range 15 to 58). 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)\textsuperscript{5,6}. Complete blood count (CBC), iron, TIBC, UIBC, bleeding time (BT) and coagulation analyses were performed as well as ABO blood group typing. 

**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) INR, fibrinogen (PT-Fibrinogen Recombinant, Hemosil, Instrumentation Laboratory Company-Lexington USA), D-dimer (D-dimer, Hemosil, Instrumentation Laboratory Company-Lexington USA), factor clotting activity (FII, FV, FVII, FVIII, FIX, FX, FXI) (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. Fisher exact test and Chi-square test were carried out for qualitative variables. With the help of direct logistic regression the predictive value of the model which includes some of the parameters tested was examined.

**Results**

**The frequency and characteristics of menorrhagia in the study population**

Sixty four women (55.7%) of the total number of patients (115) who had anamnetical data of menorrhagia, really 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.

**The frequency and characteristics of coagulation disorders in the study population**

In the examined population coagulation defects have been found in 12 women (10.4%) - decreased FIX; Ac in 4 (3.5%), decreased FVII: Ac in 1 (0.9%), decreased FX: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, SCOR, hematology, most of the coagulation factors) as well as expected. Patients with registered some of hemostasis disorders had prolonged PT (Md=13,1s, 12,2-14,8s vs Md=12,5s, 10,6-18,3s; p=0,032) (after adjustment for the presence of FVII and FX deficiency this finding was persistent for the entire group).

**Connection between menorrhagia and coagulation disorders**

Chi-square test of independence (with correction by Yeats) showed significant association between the existence of menorrhagia and the existence of disorders of hemostasis ($c^2$ (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 is significantly lower among patients who had no verified menorrhagia (1 of 51).

The frequency of anemia in the study population

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

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 at patients who state a history of the existence of menorrhagia is shown in the 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 is a semi-quantitative method of comparative analysis of used sanitary material with standard tables and calculation of PBAC score menstrual cycle (Pictorial Bleeding Assessment Chart) – PBAC. Obtained results are in the best correlation with the “golden standard” method of intensity of menstrual bleeding estimation by determining alkaline hematin. PBAC score of menstrual cycle (its intensity), but not its duration is higher in women with menorrhagia. Thus, intensity but not duration of menstrual cycle leads to greater blood loss at women with menorrhagia.

Patients with and without menorrhagia did not differ among themselves regarding examined factors of coagulation except for FVII. After adjustment for the presence of FVII deficiency this finding was persistent for the entire group. The existence of states and disorders which could influence activity of FVII were excluded: sepsis, malignity, transplantation of bone marrow, transitory deficit after surgery, procreation of antibodies on FVII, influence of circadian rhythm on activity FVII. Considering a short half-life of FVII, 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 several 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. 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 have hemostasis disorder. Some of the
most representative studies by Kadir and associates state the information about 17% of patients. The proportion of women with VWD is 6.25%. Meta-analysis by Shankar and associates that included a total of 11 study of 988 women, showed that the prevalence of VWD is in the range of 5% to 24%. The proportion of women with a deficit of individual coagulation factors is 6% for FIX and 2% for FVII, FX and FXI. Some reports showed that incidence of deficit of individual factors in women with menorrhagia is in the range of 1% to 4%, an average of 2.5%.

Our research showed that the PT has 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. Anemia was diagnosed at over a half of the patients included into the study. (53%) The study of Hutspardol and associates showed the similar average value of the PT in the group of patients with menorrhagia.

Anemia was diagnosed at over a half of the patients included into the study. (53%) The survey Philipp et al 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. Toseto and associates valorized some of the most common clinical manifestations of hemorrhagic syndrome for prediction of von Willebrand disease. 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, the 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 length of the menstrual cycle (1.16) and the value of PBAC score (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 increased 1.16 times and with each additional point in the score of menstrual cycle increased 1.02 time. These five parameters could also represent the strongest predictors for the presence of coagulation disorders.

Although including more patients and completing the study with additional researches which are primarily related to platelet function is mandatory, the results of our study can be seen as a contribution to the construction of a diagnostic algorithm for disorders of hemostasis, primarily VWD. Firstly it is necessary to estimate the abundance of menstrual cycles (PBAC), then, in second step, it is important on the basis of simple anamnesis (duration of menstrual cycle) and standard laboratory analyzes (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 detected in patients with menorrhagia and which are less likely to think about, because they have a subclinical manifestation and inapparent flow, and 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

The results can be seen as a contribution to the construction 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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The authors stated that they had no interests which might be perceived as posing a conflict or bias. Svetlana M. Djukic performed the research and wrote the paper. Jovan P. Antovic designed the research study. Nebojsa Andjelkovic contributed essential reagents or tools. Aleksandar Djukic, Vladimir Vukomanovic and Ivana Simic Vukomanovic analysed the data.

Conflict of interest

The authors fully declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

References:

**Table 1**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All (X±SD or Md, min-max, n=115)</th>
<th>Women with menorrhagia (X±SD or Md, min-max, n=64)</th>
<th>Women without menorrhagia (X±SD or Md, min-max, n=51)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>36.1±9.6 (15-55)</td>
<td>38.0 (15-55)</td>
<td>36.0 (17-58)</td>
<td>p&gt;0.05*</td>
</tr>
<tr>
<td>SCOR</td>
<td>100.0 (26-778)</td>
<td>150.0 (100-778)</td>
<td>50.0 (26-95)</td>
<td>p&lt;0.001*</td>
</tr>
</tbody>
</table>
Duration of menstrual bleeding (days) & 7.0 (4-28) & 7.0 (6-28) & 7.0 (4-12) & p>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) & p>0.05* \\
RBC (x10^{12}/L) & 4.28 (2.27-5.50) & 4.34 (3.30-5.50) & 4.73 (2.27-5.40) & p>0.05* \\
Hemoglobin (g/L) & 114.1±22.2 & 114.9±19.1 & 113.1±25.9 & p>0.05** \\
MCV (fL) & 81.8±10.1 & 83.1±9.8 & 81.3±10.6 & p>0.05* \\
Hematocrit & 0.350 (0.126-0.462) & 0.360 (0.225-0.462) & 0.359 (0.126-0.440) & p>0.05* \\
Platelets (x10^{9}/L) & 283.9±92.9 & 290.1±86.9 & 275.3±100.9 & p>0.05** \\

* Mann-Whitney U test  
** T test

Table 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Women with menorrhagia (X±SD or Md, min-max)</th>
<th>Women without menorrhagia (X±SD or Md, min-max)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding time (s)</td>
<td>120 (60-270)</td>
<td>90 (60-180)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>aPTT (s)</td>
<td>27.9 (22.4-46.2)</td>
<td>28.6 (21.3-49.1)</td>
<td>p&gt;0.05*</td>
</tr>
<tr>
<td>PT (s)</td>
<td>12.6 (10.8-15.0)</td>
<td>12.5 (10.6-18.3)</td>
<td>p&gt;0.05*</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>3.26±0.82</td>
<td>3.50±0.85</td>
<td>p&gt;0.05**</td>
</tr>
<tr>
<td>FII (%)</td>
<td>84.4 (50.9-149.0)</td>
<td>92.5 (52.0-182.0)</td>
<td>p&gt;0.05*</td>
</tr>
<tr>
<td>FV (%)</td>
<td>98.5 (50.0-213.0)</td>
<td>110.0 (50.0%-241.0)</td>
<td>p&gt;0.05*</td>
</tr>
<tr>
<td>FVII (%)</td>
<td>78.0±28.3</td>
<td>100.5±35.0</td>
<td>p&lt;0.001**</td>
</tr>
<tr>
<td>FVIII (%)</td>
<td>132.0 (39.0-525.0)</td>
<td>124.0 (22.0-596.0)</td>
<td>p&gt;0.05*</td>
</tr>
<tr>
<td>FIX (%)</td>
<td>79.6 (27.0-772.0)</td>
<td>79.2 (45.0-472.0)</td>
<td>p&gt;0.05*</td>
</tr>
<tr>
<td>vWFAc (%)</td>
<td>98.5 (26.2-182.0)</td>
<td>96.6 (38.5-279.0)</td>
<td>p&gt;0.05*</td>
</tr>
<tr>
<td>vWFAg (%)</td>
<td>111.5 (30.0-535.0)</td>
<td>95.8 (32.0-348.0)</td>
<td>p&gt;0.05*</td>
</tr>
</tbody>
</table>

* Mann-Whitney U test  
** T test
## Table 3
Prediction of the existence of hemostasis disorder at patients who state a history of the existence of menorrhagia (5 parameters)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Á</th>
<th>Standard error</th>
<th>Wald</th>
<th>Degrees of freedom</th>
<th>p</th>
<th>Quotient of probability</th>
<th>95% confidence interval for Quotient of probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>menorrhagia</td>
<td>4.024</td>
<td>1.470</td>
<td>7.495</td>
<td>1</td>
<td>0.006</td>
<td>0.018</td>
<td>0.001 - 0.319</td>
</tr>
<tr>
<td>anemia</td>
<td>2.520</td>
<td>0.965</td>
<td>6.816</td>
<td>1</td>
<td>0.009</td>
<td>12.427</td>
<td>1.874 - 82.404</td>
</tr>
<tr>
<td>SCOR</td>
<td>0.015</td>
<td>0.009</td>
<td>3.197</td>
<td>1</td>
<td>0.050</td>
<td>0.985</td>
<td>0.968 - 1.001</td>
</tr>
<tr>
<td>PT</td>
<td>0.856</td>
<td>0.422</td>
<td>4.102</td>
<td>1</td>
<td>0.043</td>
<td>2.353</td>
<td>1.028 - 5.384</td>
</tr>
<tr>
<td>Cycle duration</td>
<td>0.148</td>
<td>0.076</td>
<td>3.821</td>
<td>1</td>
<td>0.050</td>
<td>1.160</td>
<td>1.000 - 1.345</td>
</tr>
<tr>
<td>constant</td>
<td>13.196</td>
<td>5.460</td>
<td>5.742</td>
<td>1</td>
<td>0.016</td>
<td>0.000</td>
<td></td>
</tr>
</tbody>
</table>

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