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# Evaluation of Hemostasis Parameters in Adolescent Girls Presenting with Menometrorrhagia and Comparison with Healthy Adolescents

## Menometroraji ile Başvuran Ergen Kızlarda Hemostaz Değişkenlerinin Değerlendirilmesi ve Sağlıklı Ergenler ile Karşılaştırılması

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## Abstract

**Objective**: This study aims to investigate the presence of acquired and hereditary coagulopathies in adolescent girls presenting with increased menstrual bleeding.

**Material and Method**: The study consisted of 63 adolescent female patients (15.4±1.5 years) who applied to the pediatric clinic of our hospital due to increased menstrual bleeding and 74 healthy adolescent female who did not have any acute or chronic disease, did not use any medication in the last 14 days, and whose age and gender were the same as the study group. (15.5±1.5 years). Platelet count, all basal and advanced coagulation tests, platelet aggregation, and secretion tests were studied for each case included in the study.

**Results**: When basal and advanced coagulation tests, platelet aggregation, and secretion tests were examined, no significant difference was found between the study and the healthy control groups. On the other hand, in our study group with heavy menstrual bleeding, 4 (6.3%) patients were found to have impaired hemostasis (two patients with type 1 von Willebrand disease, one patient with immune thrombocytopenic purpura, and one patient with mild factor VIII deficiency).

**Conclusion**: Various hemostasis disorders, especially von Willebrand disease, could be detected in adolescents with heavy menstrual bleeding.

**Keywords**: Abnormal uterine bleeding, coagulation disorders, von Willebrand disease

## Öz

**Amaç**: Bu çalışmada menstrüel kanamasında artış ile başvuran ergen kızlarda edinsel ve kalıtsal pıhtılaşma bozukluklarının varlığının araştırılması amaçlandı.

**Gereç ve Yöntem**: Çalışmaya hastanemiz çocuk kliniğine artmış menstrüel kanama nedeniyle başvuran 63 ergen kız hasta (15,4±1,5 yıl) ile akut ve kronik bir hastalığı olmayan, son 14 gün içinde herhangi bir ilaç kullanmayan, yaş ve cinsiyetleri çalışma grubu ile eş olan 74 sağlıklı ergen sağlıklı kontrol grubu (15,5±1,5 yıl) olarak alındı. Çalışmaya dahil edilen her olgu için trombosit sayısı, tüm bazal ve ileri pıhtılaşma testleri, trombosit agregasyonu ve sekresyon testleri çalışıldı.

**Bulgular**: Bazal ve ileri pıhtılaşma testleri, trombosit agregasyon ve sekresyon testleri incelendiğinde ağır menstrüel kanaması olan çalışma grubu ile sağlıklı kontrol grubu arasında anlamlı fark bulunmadı. Öte yandan ağır menstrüel kanaması olan çalışma grubumuzda 4 (%6.3) hastada hemostaz bozukluğu (iki hastada tip 1 von Willebrand hastalığı, bir hasta immün trombositopenik purpura ve bir hastada hafif faktör VIII eksikliği) saptandı.

**Sonuç**: Ağır menstrüel kanaması olan ergenlerde, başta von Willebrand hastalığı olmak üzere çeşitli hemostaz bozuklukları saptanabilmektedir

**Anahtar Kelimeler**: Anormal uterin kanama, pıhtılaşma bozuklukları, von Willebrand hastalığı

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## INTRODUCTION

Abnormal uterine bleeding (AUB) is an important cause of physical and psychological morbidity that reduces the quality of life in women of all age groups. AUB is the most common reason for gynecological hospital admissions in the female adolescent age group.[1] Amenorrhea, irregular bleeding, intermenstrual bleeding, and excessive menstrual bleeding are the current classifications of the International Federation of Gynecology and Obstetrics (FIGO) in 2018. This classification aimed to use a standard terminology when describing abnormal bleeding. Heavy menstrual bleeding instead of menorrhagia and intermenstrual bleeding instead of metrorrhagia are used.[2] The most common clinical form of AUB in adolescents is excessive and prolonged menstrual bleeding. Undiagnosed patients with heavy menstrual bleeding may present with anemia, impaired quality of life, and even depression.[3]

Menstrual cycle disorders in adolescents can be caused by central, structural, gonadal, and systemic diseases.[4] Anovulation (46%) is the most common cause among adolescents admitted to the hospital due to menorrhagia in the USA, followed by; hematological disorders (33%), infections (11%) and chemotherapy (11%).[5] Coagulation disorders affect 20%–30% of female adolescents with hemoglobin levels below 10 g/dL, those who have heavy bleeding during their first menstruation, and those who have heavy bleeding that necessitates transfusion or hospitalization.[6] In female adolescents with coagulation disorders, increased menstrual bleeding may be the first reason for admission. The inability to perform detailed coagulation tests in routine laboratories often leaves the coagulation disorder in these patients undiagnosed. Studies have emphasized that, it is difficult to diagnose hereditary coagulation disorders that cause skin and mucosal bleeding, and that the tests used in screening and diagnosis might be not sensitive enough to detect mild coagulation disorders.[7]

Studies state that undiagnosed bleeding disorders may underlie intense or prolonged menstrual cycles and that these bleeding disorders should be investigated by clinicians.[8,9]

This study aims to investigate the presence of acquired and hereditary coagulation disorders by using coagulation system and platelet function tests in adolescent girls presenting with increased menstrual bleeding and to compare hemostasis tests with healthy adolescent girls of similar age group.

## MATERIAL AND METHOD

### Selection of Study the Groups

The “study group” included 63 adolescent female patients who applied to the pediatric clinic of our hospital due to increased menstrual bleeding. Girls with menstrual bleeding for more than 21 days and/or longer than 7 days and/or using more than 7 pads per day during menstruation were included in this group. 74 healthy adolescent girls, who did not have a chronic disease, did not have an acute infection at the time of admission, did not use any medication in the last 14 days, and were the same age as the patient group, were included in the "control group".[10,11] The chronological age of the patient group with heavy menstrual bleeding and the healthy control group, menstruation duration, frequency, bleeding between normal cycles, number of pads per day, previous bleeding history (e.g. bleeding from the nose, gastrointestinal bleeding, abnormal ecchymosis outside the usual places), history of drug use, hospitalization due to anemia, blood transfusion history, chronic disease history, family history of bleeding (heavy menstrual bleeding, epistaxis, gastrointestinal bleeding, bleeding such as abnormal ecchymosis outside the usual places) were questioned. The researchers, talking to the patient, asked her to fill out a questionnaire. The presence of gynecological pathology was investigated by suprapubic pelvic ultrasound and consultation at the obstetrics and gynecology clinic in all patients with heavy menstrual bleeding.

Our study was accepted with the decision of our Hospital Education and Coordination Board dated October 26, 2011, and numbered 3639. Written consent was obtained from the parents and adolescents included in the study.

### Equipment and Laboratory Methods

Venous blood samples from the study group included in our study and the healthy control group were taken from the antecubital vein by applying mild venous stasis to the upper arm between 8:00 and 10:00 in the morning after 12 hours of fasting.

An automatic hemocytometer (LH-780, Beckman Coulter, USA) calibrated daily was used for platelet count. For coagulation tests, 4 ml of blood were taken into standard tubes containing 0.5 ml (1 volume) of 0.109 M trisodium citrate solution, centrifuged at 3000 rpm for 10 minutes, and their plasmas were stored at -80°C until they were studied. Coagulation tests were performed daily using Stago STAR (Stago, France), and calibrated daily using kits, each compatible with the instrument. With the help of these instruments, plasma prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR), fibrinogen, thrombin time, factor (F) II, FV, FVII, FVIII, FIX, FX, FXI, FXII, von Willebrand factor (vWF), and ristocetin cofactor were studied in each patient. The reference intervals of the manufacturer were used for the reference intervals of the coagulation tests.

For platelet aggregation and secretion tests, 4 ml of blood were collected from the antecubital vein for each of two standard tubes containing 0.5 ml (1 volume) of 0.109 M trisodium citrate solution from the study and healthy control groups. The tests were performed on the same day, immediately after the blood was drawn, without waiting. Platelet aggregation, secretion tests, and ristocetin cofactor

tests were performed with a Chronolog Corporation model 700 (USA) brand device using optical aggregometry and lumiaaggregometry methods. In the study, collagen was diluted to 2 µg/ml; epinephrine, 5 µM; adenosine diphosphate, 5 µM; thrombin, one unit (30 µL); ristocetin, 1.25 mg/ml; and arachidonic acid at 0.5 µM concentrations were used as agonists.

On a patient-by-patient basis, the pediatric hematology specialist, the head of our hospital's hematology laboratory, evaluated the results of all complete blood count, basal coagulation tests, advanced coagulation tests, thrombocyte aggregation, and platelet secretion tests. The diagnosis was made by confirming the tests of the patients with defects in hemostasis tests at least twice.

### Statistical Analysis

Data analysis was done in the SPSS for Windows package program (11.5). The Kolmogorov-Smirnov test was used to determine whether continuous and discrete numerical variables showed a normal distribution. Data were presented as mean standard deviation or median (minimum-maximum) for continuous and discrete numerical variables and as several cases and percent for categorical variables.

The significance of the difference between the groups in terms of mean values were investigated using the Student' s t-test, and the significance of the difference in terms of median values were investigated with the Mann-Whitney U test. Categorical variables were evaluated with Pearson's chi-squared or Fisher's exact test.

For $P<0.05$, the results were considered statistically significant.

## RESULTS

The study group of [n=63, 12-18 years (15.4±1.5 years)] and control group [n=74, years (15.5±1.5 years) ] were in the similar age group (p>0.05). Body weight (study group 54.5±8.9 kg and control group 53.4±9.8 kg, p=0.481), height (study group 162.0±15.0 cm and control group 157.6 ±7.5 kg, p=0.028) and body mass index (study group 21.3±3.4 kg/m² and control group 21.5±3.4 kg/m², p=0.403) of the two groups were similar.

When the family history of bleeding was questioned, no difference was found between the two groups (**Table 1**). It was determined that 12.7% of the patients in the study group were using medication and 75% of these were using iron preparations for the treatment of iron deficiency anemia. This rate was similar in the healthy control group (p>0.05). There was no difference between the two groups in terms of receiving anemia treatment, hospitalization for anemia treatment, and blood transfusion(p>0.05). When the duration, frequency, and bleeding intensity of the menstruation in the study and control groups were questioned, a statistically significant difference was found (p<0.001) (**Table 1**).

**Table 1. Comparison of the study group with heavy menstrual bleeding and the control group in terms of clinical and menstrual characteristics**

| Variables | Study group (n=63) | Control group (n=74) | P |
|---|---|---|---|
| Bleeding history | 3 (4.8%) | 2 (%2.7) | 0.661‡ |
| Drug use | 8 (12.7%) | 9 (%12.2) | 0.924¶ |
| The drug used | | | - |
| Oral contraceptive | 2 (25.0%) | 1 (%11.1) | |
| Iron | 6 (75.0%) | 8 (%88.9) | |
| Anemia treatment | 25 (39.7%) | 23 (%31.1) | 0.293¶ |
| Hosptalization | 8 (12.7%) | 6 (%8.1) | 0.377¶ |
| Blood transfusion | 6 (9.5%) | 3 (%4.1) | 0.301‡ |
| Painful menstruation | 51 (81.0%) | 43 (%58.1) | 0.004 |
| Use of analgesics | | | 0.029 |
| No | 17 (33.3%) | 24 (55.8%) | |
| Yes | 34 (66.7%) | 19 (44.2%) | |
| Menstrual frequency | | | <0.001 |
| More than 21 days | 39 (61.9%) | 5 (6.8%) | |
| 21-28 day | 23 (36.5%) | 48 (64.9%) | |
| 28-35 day | 1 (1.6%) | 21 (28.4%) | |
| Menstrual duration | | | <0.001 |
| 3-4 day | 3 (%4.8%) | 25 (33.8%) | |
| 5-7 day | 24 (%38.1%) | 49 (66.2%) | |
| >7 day | 36 (%57.1%) | - | |
| Number of pads | | | <0.001 |
| 1-3 | 1 (1.6%) | 48 (64.9%) | |
| 4-5 | 11 (17.5%) | 26 (35.1%) | |
| 6-7 | 27 (42.9%) | - | |
| >7 | 24 (38.1%) | - | |

†Student's t-test, ‡Fisher's definitive test, ¶Pearson's Ki-Kare test

The platelet count of the study group and the control group had no difference (**Table 2**). However, a patient with a platelet count of $83x10^9$/L in the study group was followed up in the pediatric hematology department with the diagnosis of immune thrombocytopenic purpura (**Table 3**). When the study group and the control group were evaluated in terms of basal coagulation tests including aPTT, fibrinogen, and thrombin time, no significant difference was found. Although PT and INR variables were found to be statistically higher in the control group, they were not considered clinically significant. When the procoagulant proteins FII, FV, FVII, FVIII, FIX, FX, FXI and FXII, antiplasmin, vWF, and ristocetin cofactor values in the study group and the control group were compared, no significant difference was found (**Table 2**). On the other hand, in the study group, two patients were diagnosed with type 1 von Willebrand disease, and one patient was diagnosed with mild factor VIII deficiency (**Table 3**).

**Table 2. Comparison of the basal coagulation tests and procoagulant protein tests results of the study group and the control group**

| Variables | Study group (n=63) | Control group (n=74) | P |
|---|---|---|---|
| Platelet count ($10^9$/L) | 296±76.3 | 273±84.52 | 0.055† |
| Prothrombin time(sec) | 13.18±1.10 | 18.92±2.3 | <0.001† |
| INR (ratio) | 1.04±0.07 | 1.07± 0.28 | 0.383† |
| Activated partial thromboplastin time (sec) | 29.93±3.58 | 31.15±4.49 | 0.002† |
| Fibrinogen (mg/dL) | 299.35±58.6 | 298.68±57.6 | 0.946‡ |
| Thrombin time (sec) | 16.03±0.90 | 16.16±1.23 | 0.211† |
| FII (%) | 82.69±17.74 | 83.70±45.73 | 0.224† |
| FV (%) | 87.9±22.38 | 82.99±21.07 | 0.071† |
| FVII (%) | 77.49±21.87 | 78.44±19.24 | 0.786‡ |
| FVIII (%) | 157.84±116.75 | 156.6±85.13 | 0.276† |
| FX (%) | 81.54±18.9 | 80±15.49 | 0.595‡ |
| FXI (%) | 99.86±36.52 | 95.86±26.34 | 0.604† |
| FXII (%) | 89.24±30.60 | 93.17±20.21 | 0.387‡ |
| Antiplasmin (%) | 94±17.45 | 92.57±16.75 | 0.396† |
| vWF (%) | 111.36±33.07 | 109.94±38.59 | 0.820‡ |
| Ristocetin cofactor (sec) | 97.10±40.44 | 93.78±37.47 | 0.527 |

Abbreviations: dL, deciliter; F, factor; mg, milligram; sec, second; vWF, von Willebrand factor. INR: International normalized ratio, †Mann Whitney U test, ‡Student's t-test.

**Table 3. Clinical and laboratory features of four patients with coagulation disorder in adolescent girls with heavy menstrual bleeding**

| | ITP (1) | vWD (2) | vWD (3) | FVIII deficiency (4) |
|---|---|---|---|---|
| Age (year) | 15 | 14 | 14 | 15 |
| Menstrual duration (day) | >7 | >7 | >7 | >7 |
| Menstrual frequency | 21-28 day | 21 | more than 21 day | more than 21 day |
| Number of pads per day | >7 | >7 | >7 | >7 |
| History of bleeding | - | - | - | - |
| Family history of bleeding | - | - | - | - |
| Anemia treatment | + | + | + | + |
| Family history of bleeding | - | + | - | + |
| Hb (g/dL) | 10.6 | 12.4 | 10.6 | 10.5 |
| Platelets ($10^3$/L) | 83 | 319 | 211 | 399 |
| Ferritin (ng/mL) | 4 | 8 | 3 | 2 |
| PZ (sec) | 14 | 13 | 15.3 | 12.5 |
| INR (ratio) | 1.1 | 0.96 | 1.2 | 0.9 |
| aPTZ (sec) | 34.5 | 38.9 | 34.6 | 27.5 |
| FVIII (%) | 89 | 39 | 38 | 35 |
| VWF (%) | 78 | 37 | 27 | 90 |
| Ristosetin cofactör (sec) | 68 | 8 | 25 | 75 |

Abbreviations: dL, desiliter; F, factor; g, gram; Hb, hemoglobin; ITP, Idiopathic thrombocytopenic purpura; mL, mililiter; ng, nanogram; sec, second; vWD, vonWillebrand Disease.

Comparing the platelet aggregation tests of the study group and the control group, adenosine diphosphate (5 µM), collagen (2 µg/ml), epinephrine (5 µM), arachidonic acid (0.5 µM), ristocetin (1.25 mg) /dL) and stimulated platelet aggregation results were not significantly different. Platelet aggregation test stimulated with thrombin (30 µL) was found to be higher in the study group than in the control group (**Table 4**). When we compared the results of platelet secretion tests and ristocetin cofactor tests of the study group and the control group, no significant difference was found in terms of adenosine diphosphate, collagen, thrombin, and ristocetin-stimulated platelet secretion results. (p>0.05). The epinephrine-stimulated secretion values were found to be statistically higher in the control group than in the study group (p <0.001) (**Table 4**).

**Table 4. Comparison of platelet aggregation and secretion test results of study group and control group cases**

| Variables | Study group (n=63) | Control group (n=74) | P† |
|---|---|---|---|
| ADP-agr (5 µM) (%) | 76.7±18.47 | 80.31±19.67 | 0.320 |
| ADP-sek (nmol) | 1.72±0.98 | 1.72±0.89 | 0.895 |
| Kollajen-agr (2 µg/ml) (%) | 80.84±19.55 | 80.69±21.11 | 0.957 |
| Kollajen-sec (nmol) | 0.89±0.96 | 0.98±0.78 | 0.22 |
| Epinefrin-agr (5 µM) (%) | 70.81±23.74 | 75.65±20.34 | 0.322 |
| Epinefrin-sec (nmol) | 0.68±1.22 | 1.83±6.45 | <0.001 |
| Arachidonic acid-agr (0,5 µM) (%) | 76.06±22.55 | 75.54±23.05 | 0.991 |
| Arachidonic acid-sec (nmol) | 1.40±1.03 | 1.23±0.75 | 0.256 |
| Thrombin-agr (30 µL)(%) | 95.44±18.81 | 88.06±37.19 | 0.036 |
| Thrombin-sec (nmol) | 0.36±0.45 | 0.58±0.78 | 0.637 |
| Ristosetin-agr (1,25 mg/ml) (%) | 86.52±20.9 | 85.91±19.77 | 0.805 |
| Ristosetin-sec (nmol) | 0.08±0.28 | 0.05±0.15 | 0.056 |

Abbreviations: ADP, adenosine diphosphate; Agr, aggregation; mL, mililiter; mg; miligram; †Mann Whitney U test

## DISCUSSION

Bleeding disorders are frequently encountered conditions in adolescents presenting with heavy menstrual bleeding. The underlying causes of bleeding disease in adolescents presenting with this complaint are platelet function disorders (2-44%), von Willebrand deficiency (5-36%) and other factor deficiencies (such as Factor V, Factor VII, Factor XI) (8-9%).[10] Undiagnosed bleeding disorders may underlie intense or prolonged menstrual cycles and that these bleeding disorders should be investigated by clinicians.[8,9] In the first step, hemodynamic evaluation of the adolescent who presented with increased menstrual bleeding is assessed. It is stated that, first-line coagulation tests including PT, aPT, fibrinogen, together with hemogram, ferritin and if the history is suggestive further tests such as vWF, ristocetin cofactor and antigen level, FVIII-XIII levels should be performed.[12,13]

In these patients, excessive menstrual bleeding may be the first presentation of the coagulation disorder. Studies have reported that the frequency of coagulation disorders in adolescent and adult women with increased and irregular menstrual bleeding is between 17% and 50%, and von Willebrand disease is the most common among these disorders.[14-16] The relationship between increased menstrual bleeding and von Willebrand has been well known for a long time. However, it may be overlooked when the patient does not give a good history. It has been shown in various studies that von Willebrand disease is detected at a high rate in patients with increased menstrual bleeding.[10] In a study conducted with 99 patients with type 1 von Willebrand

disease in 4 different hemophilia centers in the USA, it was reported that 78% of the patients had prolonged and heavy bleeding. In this study, it was reported that 71% of the patients required medical treatment and 15% required hysterectomy.[17] In a study including 30 female patients with menometrorrhagia, the frequency of von Willebrand disease was found to be 20%.[18,19] Similarly, the incidence was found to be increased in the group of patients with heavy menstrual bleeding in our study

The inability to perform detailed hemostasis tests in routine laboratories often causes the coagulation disorder in these patients to remain undiagnosed. Studies have emphasized that it is difficult to diagnose hereditary coagulation disorders that cause skin and mucosal bleeding, and that the tests used in screening and diagnosis are not sensitive enough to detect mild coagulation disorders.[7] Therefore, in our study, basal and advanced coagulation tests, platelet aggregation, and platelet secretion tests were measured for each patient by using detailed hemostasis tests in adolescents with increased menstrual bleeding. In this study, which we conducted using detailed hemostasis tests, coagulation disorder was detected in 4 (6.3%) patients out of 63, who presented with increased menstrual bleeding. Two of the patients (3.2%) had type 1 von Willebrand disease. Of the remaining 2 patients, one (1.6%) had idiopathic thrombocytopenic purpura and the other had mild FVIII deficiency (1.6%) Hemophilia A (FVIII deficiency), and hemophilia B (FIX deficiency) are rare in women as they are X-linked recessive diseases. However, prolonged bleeding may occur in carrier women due to low FVIII and FIX levels. These people are called symptomatic carriers. Factor levels are usually between 6-35% and they can also be defined as mild hemophilia. Excessive bleeding may occur during menstruation or childbirth. The frequency of hemophilia carriage in women with increased menstrual bleeding is 1-4%. [20] However, there was no study in the literature reporting the rate of hemophilia carriage in adolescent girls. In our study, FVIII deficiency carrier found in one of the 63 patients in our study group with complaints.

While platelet aggregation tests were performed on all adolescents included in the study, collagen, ristocetin, thrombin, arachidonic acid, adenosine diphosphate, and epinephrine were used as agonists. When platelet function tests were compared for both groups, the thrombin (30 µL)-stimulated platelet aggregation test was found to be higher in the study group with heavy menstrual bleeding, and epinephrine-stimulated secretion values from platelet secretion tests were found to be statistically higher in the control group, but these results were not accepted as clinically significant. There is limited information in the literature about platelet function tests in patients with heavy menstrual bleeding. In a large-scale study including 2200 patients with heavy menstrual bleeding, congenital bleeding disorders were found in 337 patients, and it was shown that most of them (83.9%) had platelet dysfunction, and FVII, FX, FXII, and FXIII were detected in only one patient each.[21]

## CONCLUSION

Undiagnosed bleeding disorders may underlie intense or prolonged menstrual cycles. All patients presenting with the complaint of menometrorrhagia should be evaluated with a through history of family and personal coagulation disorders. We believe that screening tests may show great variability in patients with mild coagulation disorders, von Willebrand disease should be investigated, particularly, basal screening tests might not be sufficient for diagnosis, coagulation disorders may be detected in advanced hemostasis tests even though the screening tests are normal.

## ETHICAL DECLARATIONS

**Ethics Committee Approval:** The study was carried out with the permission of Ankara Training and Research Hospital Ethics Committee (Date: 26.09.2011, Decision No: 3639).

**Informed Consent:** All patients signed the free and informed consent form.

**Referee Evaluation Process:** Externally peer-reviewed.

**Conflict of Interest Statement:** The author has no conflicts of interest to declare.

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**Author Contributions:** All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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