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Research article

Evaluation of Abnormal Uterine Bleeding in Adolescents: Single Center Experience

Kızılcan Çetin S et al. Abnormal Uterine Bleeding in Adolescents

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What is already known about this topic?
- Anormal uterine bleeding (AUB) is adolescents' most common cause of gynecological problems.
- Since the adolescent age group is a transitional age group, both obstetricians and pediatricians have a role in treatment.
- There is no guideline for the management of AUB. An urgent treatment approach is significant for heavy bleeding.

What this study adds to the literature?
- The diagnostic and managemental differences were shown between those with and without heavy menstrual.
- We excluded patients with a previously diagnosed bleeding disorder. The frequency of hematological disease (Factor 7 deficiency) was 10.7%.
- Although *MTHFR* mutation frequency was 50%, it did not increase the risk of bleeding/thrombosis, and routine evaluation was unnecessary.

Abstract
Objective: Abnormal uterine bleeding (AUB) is adolescent girls' most common gynecologic complaint. This study aimed to determine the diagnostic and management differences between those with/without heavy menstrual bleeding.
Methods: We collected retrospective data such as follow-up, final control, and treatment regimen of adolescents aged 10-19 with the diagnosis of AUB. We excluded adolescents with known bleeding disorders at admission. We classified all subjects according to the level of anemia. Group 1 consisted of subjects with heavy bleeding (Hb<10 g/dl), and the rest with moderate and mild bleeding (Hb>10 g/dl) presented in Group 2. Admission and follow-up characteristics between the two groups were compared.
Results: In this study, we included 79 adolescent girls with a mean age was 14.3±1.8 years. 85% of all had a menstrual irregularity in the first two years after menarche. Anovulation was observed in 80%. 95% of group 1 had irregular bleeding in the two years ($p<0.01$). In all subjects, while 13 girls (16%) were diagnosed with PCOS, two adolescents (2%) had structural anomalies. No adolescents had hypothyroidism or hyperprolactinemia. Three (10.7%) were diagnosed with Factor 7 deficiency. Nineteen girls had *MTHFR* mutation. None had venous thromboembolism during at least six month-follow-up-period.
Conclusion: This study showed that 85% of AUB had occurred in the first two years. We found the frequency of hematological disease (Factor 7 deficiency) 10.7%. The frequency of *MTHFR* mutation was 50%. We thought this did not increase the risk of bleeding/thrombosis. Its routine evaluation was not necessarily due to the similarity in population frequency.
Keywords: Abnormal uterine bleeding, adolescents, anovulatory bleeding, heavy menstrual bleeding

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Introduction

Abnormal uterine bleeding (AUB) is defined as bleeding from the uterine corpus that is abnormal in duration, volume, frequency and/or regularity. Bleeding has an irregular pattern in duration, amount, and frequency. AUB affects 3-20% of women of reproductive age and is more common in adolescence (1). It constitutes an essential part of the problems in the adolescent age group (2-4). In 2011, the International Federation of Obstetrics and Gynecology (FIGO) defined AUB as menstrual bleedings that, uterine originated, unrelated to pregnancy, abnormal in the last six months (in terms of amount, frequency, or duration), irregular or regular but lasting more than eight days (3). The term dysfunctional uterine bleeding has been removed because the different terminologies are confusing. FIGO suggests the usage of the AUB term (5, 6).

Each menstrual cycle of healthy adolescents has a bleeding duration every 21-45 days, lasting 2-7 days, and the amount is about 30-40 ml (3-6 pads) per day (2, 7, 8). Menarche usually occurs between 12-13 years of age (2, 9). Menstrual cycles are 21-34 days by the third year after menarche, similar to adults in 60-80% of adolescents (2). Change of pad/tampon in less than a few hours, use of double pads, frequent soiling of laundry or linens, and clots more than 2,5 cm in diameter are signs of AUB (10). FIGO suggested the abbreviation PALM-COEIN [Polyp, Adenomyosis, Leiomyoma, Malignancy & Hyperplasia (structural causes); Coagulopathy, Ovulatory dysfunction, Endometrial, Iatrogenic and Not yet classified (non-structural causes)] for the etiology of AUB (3). Structural causes are very rare (1.3%-1.7%) in adolescence (11, 12).

Adolescents may not be aware that their bleeding patterns are abnormal since there may be irregularities in the menstrual cycle during the first two years following menarche. AUB and the factors that cause it can cause long-term health problems. It can affect the physical, emotional, social, and quality of life. It can cause absenteeism in education life and cause a decrease in academic achievement. Survey studies also support these ideas (13).

AUB is the most common cause of gynecological problems in adolescents and is an essential source of stress for adolescents and their families. Although common, this situation is rarely reported. Frequent and heavy menstrual bleeding requires urgent management, and a correct treatment approach is vital. Since the adolescent age group is transitional, obstetricians and pediatricians intervene. However, there is

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no standard guideline for management. This study aimed to determine the diagnostic and managemental differences between those with and without heavy menstrual bleeding by evaluating AUB in a large case series in adolescent girls.

Method

Study Population

This retrospective case series includes all adolescents aged 10-19 diagnosed with AUB at our institution between 2016 and 2021. The ethical committee of our university approved this study (Approval number: I5-378-21).

We retrospectively evaluated data: demographic, family history, complaints at presentation, AUB characteristics, examination findings in diagnosis and follow-up, laboratory and radiological evaluations, treatment regimen, and responses to treatments. We excluded adolescents with typical menstrual characteristics (frequency, duration, and bleeding intensity), previously diagnosed bleeding disorders.

The definition of AUB consists of frequent (interval shorter than 21 days), rare (longer than 45 days), prolonged (longer than seven days), or heavy (more than 80ml) menstrual cycle. Heavy bleeding was defined as using more than six pads per day for more than seven days or affecting daily activity(1). We used the parameters shown in Table 1 to define AUB.

The same procedure was used in the first step evaluation since our clinic's approach was performed with a standard protocol. Laboratory tests were evaluated to determine the severity of bleeding and the potential etiologies of heavy menstrual bleeding in all cases. The minimum laboratory evaluation included complete blood count, peripheral smear, ferritin level, prothrombin time (PZ), activated partial thromboplastin time (APTZ), and fibrinogen values. The vWD panel included functional tests for plasma von Willebrand factor (vWF), Vwf antigen, and factor VIII activity. If these were all normal, other factors were tested, too. In cases with small amounts of prolonged bleeding, human chorionic gonadotropin (hCG) and pelvic USG were performed to exclude pregnancy.

We investigated anemia findings and the duration of anemia in the history, physical examination, hemogram, peripheral smear, and patients' previous blood examination. Laboratory tests such as serum iron, total iron binding capacity, and serum ferritin value were assessed. If the serum iron was decreased and the total iron binding capacity increased, a diagnosis of iron deficiency was made, and the other causes of microcytic anemia were excluded.

Anovulation was defined as the following criteria: 1. Adolescents who had menstrual bleeding occurring more frequently than every 21 days or was excessive 2. Serum progesterone under < 0.5 ng/mL at diagnosis. 3. Exclusion of known causes of AUB.

We classified all subjects in terms of the level of anemia. Group 1 consisted of adolescents with heavy and severe bleeding (Hb<10 g/dl). The rest with moderate and mild bleeding (Hb>10 g/dl) were included in Group 2. Admission and follow-up characteristics between the two groups were compared.

AUB management was under the standard protocol. According to our protocol, the main aim of AUB management was to provide hemodynamic stability by correcting anemia until the detection of etiology. Anemia was classified as following: mild Hb>12 g/dl, moderate 10-12 g/dl, heavy 8-10 g/dl, and severe Hb <8 g/dl. Patients with mild/moderate menstrual bleeding were given NSAIDs, such as ibuprofen and naproxen sodium, to decrease bleeding flow. If the hemoglobin was 10-12 g/dl, iron supplementation with 60 mg elemental iron per day was given. For adolescents with heavy bleeding (Hb 8-10 g/dl), which means active bleeding, COCs containing at least 30 mcg of ethinyl E2 were given. We gave one pill every 8-12 hours until the menstrual bleeding ceased. Then we continued giving one pill daily until the Hb level increased more than 10 g/dl for 3-6 months. We hospitalized patients with Hb <7 g/dL and patients with Hb <10 g/dL who had active heavy bleeding and hemodynamic instability. We gave erythrocyte suspension transfusion and used COCs with 30-50 mcg ethinyl E2 once every six hours for 2-4 days, then once every eight hours for three days, and then the same amount every 12 hours for the next two days. When Hb level reached 10 g/dL, COCs were given in a cyclic pattern for three to six months until Hb level reached more than 10 g/dL. Supplementation of 60-120 mg elemental iron was given to all with Hb ≤10 g/dL. Progestin-only hormone therapy (medroxyprogesterone (10 mg/day) was given to the patients, who had a contraindication for estrogen therapy (such as thromboembolic disease, migraine with aura, hepatic dysfunction etc.). Additional antiemetic treatment was used when necessary. After initial management, we treated patients according to the underlying pathology of AUB.

Statistical analysis

All statistical analyses were performed using SPSS, version 21.0 (IBM Corp., Armonk, NY, USA). Data were expressed as the mean ± SD, median [minimum; maximum]. The Kolmogorov-Smirnov test evaluated the normality of variables. Descriptive analyses were presented using means and standard deviations for normally distributed variables. The student's t-test was used to compare the mean values of continuous variables. The Mann-Whitney U Test with appropriate confidence intervals compared the nonparametric measurements. A p-value of less than 0,05 showed a statistically significant result in all analyses.

Results

In this study, 79 adolescents were included. The mean age of all participants was 14.3±1.8 (10.7-17.9) years, and the menarche age was 11.9±1.4 (9.5-15.9) years. The age distribution was homogeneous between Group 1 and 2 (p=0. 01). While 64.6% had normal weight, 22.8% were obese, and 11.4% were underweight. 85% had a menstrual irregularity in the first two years after menarche. 95% of group 1 had irregular bleeding in the two years (p<0.01). The most common presenting symptoms were dizziness n=21 (27%) and syncope n=11 (14%). There was no history of anorexia and bulimia nervosa in any subjects. %32 had dense bleeding, and all had Hb <10 gr/dl. %48 had frequent bleeding, with whom %32 were in Group 1, and the rest of them were in Group 2. Anovulation was observed in 80%. While 13 girls (16%) were diagnosed with PCOS, two adolescents (2%)had structural anomalies (uterus didelphys). No adolescents had hypothyroidism or hyperprolactinemia. Two were on antiepileptics, and eight were on vitamin supplements (iron, vitamin d, b12). None caused bleeding.

In Group 1, 33% (n=25) had frequent bleeding, and 33% (n=25) had dense bleeding, which caused low-level Hb (<10 gr/dl). In all groups, anovulation (%80) was the main reason for AUB. The other etiology consisted of PCOS (%16), and Factor 7 deficiency (%5). 34% had a family history of PCOS and %6 had a family history of AUB (Table 2).

Twenty-eight of all were under close follow-up and assessment for hematological diseases. Three (10.7%) were diagnosed with Factor 7 deficiency. Two of them were in Group 1 and one was in Group 2. Noone had vWD or other Factor deficiency and platelate structural/ functional disorders. Thirty-four subjects with a suspected family history of thrombosis (history of immobilization, pregnancy, hormone therapy, etc.) and two proven thrombosis history (history of hospitalization due to venous thromboembolism), underwent genetic examination. 50% had *MTHFR* mutation (4 homozygous, 15 heterozygous) with no hyperhomocysteinemia. Prothrombin mutation or Factor V Leiden mutation was not detected. Noone had venous thromboembolism during at least six month-follow-up-period.

In terms of a treatment procedure, since Group 1 had patients with Hb < 10g/dl, they were on 3-4 tablets of combined oral contraceptive (COC) daily regimen until the bleeding ceased. 18 (22.8%) of Group 1 with heavy/severe bleeding needed erythrocyte transfusion. Half of the patients had heavy bleeding with each menstrual period since menarche. The most prolonged period between menarche and the onset of heavy bleeding was four years. Three of these patients required hospitalization in the intensive care unit. The bleeding was ceased in a mean of 2.77 (±0.86 [1; 5]) days following the initiation of treatment with COC. In the first month and a half, Hb increased above 10 g/dl. Oral iron supplementation was initiated in all patients. 4 (5%) patients required rehospitalization. All four had a history of maternal AUB, and none had a family history of bleeding disorders.

In group 2, NSAIDs (such as ibuprofen and naproxen sodium) decreased the duration and amount of bleeding in subjects with mild uterine bleeding (n=22) and subjects with normal hemoglobin. In adolescents with moderate uterine bleeding (n=14), iron supplementation with 60 mg of elemental iron per day and additional COC were initiated. 5 mg medroxyprogesterone acetate was started in two due to the family

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history of proven thromboembolism. Other patients were on 1-2 COC tablets with 0.15 mg desogestrel and 30 mcg ethinylestradiol per day. Except for eight of these patients, they were followed closely with outpatient treatment. In group 2, one patient had family history of AUB, 17 patients had family history of PCOS, two had family history of a bleeding disorder, and two had family history of thromboembolism. During the follow-up, 20 patients in the general group did not comply with the treatment during cyclic use. Non-compliance was observed in all patients (n=7, 8%) who presented with rebleeding. Three of them had bleeding disorders. Six of these patients required rehospitalization. The clinical and laboratory characteristics of all groups were shown in Table 2. Nausea was the only COC-related short-term adverse effect (n=16; 20%). Treatment with iron supplementation or COCs was successful in the short term in all groups.

Discussion

The regular menstrual cycle is an essential indicator of adolescent health. During the first two years of menarche, approximately half of the menstrual cycle is anovulatory. 75% of the cycles are ovulatory at the fifth year of menarche. A deficiency in progesterone secretion from the ovarian follicles and excessive E2 production cause anovulation. Endometrial proliferation is also the cause of unpredictable menstrual bleeding(2). Our study supported the literature that the most common cause of AUB in adolescents is anovulation (14-16). There was no history of excessive exercise in our cases. The literature has reported that obesity, anorexia, weight loss, PCOS, hyperprolactinemia, drugs such as steroids, phenothiazines, tricyclic antidepressants(3), and hypothyroidism cause AUB(17-19). In our study, all cases were evaluated for endocrinopathies. No endocrinopathies except PCOS were detected. Due to the study's retrospective nature, we could not assess the stress factor.

The second most common cause of AUB is coagulopathies, with a 5-28% frequency. Studies have reported that von Willebrand's Disease (vWD) was the most common pathology that causes coagulopathy in women, with a frequency of 5-48%. Other causes of coagulopathy are respectively: platelet dysfunction (2-44%), thrombocytopenia (13-20%), coagulation factor deficiencies (8-9%), leukemia, hypersplenism and hereditary bleeding disorder (11, 20-22). Reported studies in the literature included cases previously diagnosed with a bleeding disorder. Since we did not include them, the number of patients with bleeding disorders was low. However, our study implicated that patients with bleeding disorders could present with AUB for the first time. Three patients were diagnosed with Factor 7 deficiency. Two of them were in Group 1, and one was in Group 2. This distribution showed that Factor 7 deficiency could present both heavy and mild bleeding. Keeping this situation in mind is valuable for daily practice.

Although our study was retrospective, No pregnancy was observed. Invasive imaging methods were not needed because structural etiology was not common in adolescents. Incidental structural anomaly (uterus didelphys) was detected by pelvic USG in only two. We could not explain the relationship between this anomaly and AUB. These cases were also anovulatory too. The similar approach to each patient made our study valuable in examining the etiology and treatment management of AUB.

Severe AUB is in 10-20% of adult women and 37% of adolescents. A study of approximately 1000 healthy adolescents showed that 40% had heavy menstrual bleeding (23, 24). About half of our patient group consisted of heavy and severe AUB. Although it was a retrospective study, the approach procedure was the same for all patients since it was a single center. Providing hemodynamic stability, curring anemia, and maintaining regular cycles in all patients were our main goals in managing severe AUB. Three patients in the severe group had required intensive care unit follow-up. We followed up with heavy bleeding in the inpatient unit. In the literature, it has been emphasized that the basic approach in treatment is to stop bleeding, treat anemia, ensure a regular menstrual cycle, and increase the quality of life of the adolescent (25, 26).

Treatment options include iron supplementation, COCs, progesterone, NSAII, antifibrinolytics, desmopressin, and GnRH analogs (27). Supportive treatment options are antiemetics, iron, NSAII (naproxen, ibuprofen), antifibrinolytic (tranexamic acid, aminocaproic acid), other (danazol, ulipristal acetate, DDVAP) (28). The management is mainly based on the severity of bleeding and anemia. All were on COC, NSAII, and iron supplementation in our follow-up. The observed effect associated with COCs was nausea. We could not mention our experience with GnRH analogs and antifibrinolytic treatments in this study since subjects who were previously diagnosed with bleeding disorders and malignancies were excluded.

The heterozygous frequency of *MTHFR* mutation in Turkey is 40-50%, while the homozygous frequency is 3-6%. Detection of hyperhomocysteinemia in the presence of homozygous mutation causes a tendency to thrombosis. This mutation alone (without homocysteinemia) does not create a significant risk factor for thrombosis (29). While there is no difference in thrombosis risk in patients with heterozygous *MTHFR* mutation compared to the average population, it has been reported that the risk of thrombosis is very low with the use of COCs in cases with homozygous mutations (30). We found the frequency of *MTHFR* mutation as 50% similar to the frequency of the population. We have seen that this mutation did not increase the risk of bleeding/thrombosis, and we think routine evaluation is unnecessary.

Menstrual problems are significant in the adolescent age group. A study in Hong Kong determined that approximately one-third of adolescents had restricted daily activities during menstruation, and 12% could not attend school during this period. Almost 70% of the girls described dysmenorrhea, and 17.9% were hospitalized with heavy menstrual bleeding (31). A study of 1,000 healthy adolescents stated that 73% had menstrual irregularities. In addition, 37% had heavy menstrual bleeding, and 22% were stopped with medication. Furthermore, 38% had a family history of heavy menstruation, and half of them had heavy menstruation in their children (23). Those with heavy menstrual bleeding were more tired than adolescents with normal bleeding. Their ability to participate in physical education and sports was reduced. They could not go to school at least one day a month, and their hobbies and leisure activities were disrupted (32). In 60% of adolescents, heavy menstrual bleeding seriously affected their social activities (33). However, we did not have the chance to apply a scale to the adolescents. More than half of the patients were hospitalized, and this situation indirectly showed that their quality of life was affected, and AUB caused them to stay away from daily activities.

Study Limitations

The limitations of our study include the participants of a single center; however, all patients diagnosed in our center in five years were eligible. Multicenter national studies are significant for more generalizable results.

Conclusion

This study determined that 85% of AUB in adolescent girls were anovulatory in the first two years, 33% of cases had intense bleeding, and 23% required erythrocyte suspension. In addition, the frequency of hematological disease (Factor 7 deficiency) was 10.7%. Although *MTHFR* mutation frequency was 50%, we thought it did not increase the risk of bleeding/thrombosis, and routine evaluation was unnecessary since the frequency was similar in the population.

References

1. Munro MG, Critchley HO, Fraser IS, Committee FMD, Haththotuwa R, Kriplani A, et al. The two FIGO systems for normal and abnormal uterine bleeding symptoms and classification of causes of abnormal uterine bleeding in the reproductive years: 2018 revisions. International Journal of Gynecology & Obstetrics. 2018;143(3):393-408.
2. Elmaoğulları S, Aycan Z. Abnormal uterine bleeding in adolescents. Journal of clinical research in pediatric endocrinology. 2018;10(3):191.
3. Munro MG, Critchley HO, Broder MS, Fraser IS, Disorders FWGoM. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. International Journal of Gynecology & Obstetrics. 2011;113(1):3-13.

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4. Caufriez A. Menstrual disorders in adolescence: pathophysiology and treatment. Hormone Research in Paediatrics. 1991;36(3-4):156-9.
5. Fraser IS, Critchley HO, Broder M, Munro MG, editors. The FIGO recommendations on terminologies and definitions for normal and abnormal uterine bleeding. Seminars in reproductive medicine; 2011.
6. Fraser IS, Critchley H, Munro M, Broder M. Can we achieve international agreement on terminologies and definitions used to describe abnormalities of menstrual bleeding? Human reproduction. 2007;22(3):635-43.
7. World Health Organization multicenter study on menstrual and ovulatory patterns in adolescent girls. I. A multicenter cross-sectional study of menarche. World Health Organization Task Force on Adolescent Reproductive Health. J Adolesc Health Care. 1986;7(4):229-35.
8. ACOG practice bulletin: management of anovulatory bleeding. Int J Gynaecol Obstet. 2001;72(3):263-71.
9. Yaşa C, Uğurlucan FG. Approach to Abnormal Uterine Bleeding in Adolescents. Journal of clinical research in pediatric endocrinology. 2020;12(Suppl 1):1.
10. Haamid F, Sass AE, Dietrich JE. Heavy menstrual bleeding in adolescents. Journal of pediatric and adolescent gynecology. 2017;30(3):335-40.
11. Pecchioli Y, Oyewumi L, Allen LM, Kives S. The utility of routine ultrasound in the diagnosis and management of adolescents with abnormal uterine bleeding. Journal of pediatric and adolescent gynecology. 2017;30(2):239-42.
12. Claessens EA, Cowell CA. Acute adolescent menorrhagia. American journal of obstetrics and gynecology. 1981;139(3):277-80.
13. Fraser IS, Langham S, Uhl-Hochgraeber K. Health-related quality of life and economic burden of abnormal uterine bleeding. Expert Review of Obstetrics & Gynecology. 2009;4(2):179-89.
14. Rimsza ME. Dysfunctional uterine bleeding. Pediatr Rev. 2002;23(7):227-33.
15. ACOG Committee Opinion No. 349, November 2006: Menstruation in girls and adolescents: using the menstrual cycle as a vital sign. Obstet Gynecol. 2006;108(5):1323-8.
16. Gray SH, Emans SJ. Abnormal vaginal bleeding in adolescents. Pediatrics in Review. 2007;28(5):175.
17. Malik D, Musharaf D, Gupta D. PATTERN OF ABNORMAL UTERINE BLEEDING IN HYPOTHYROID FEMALES OF REPRODUCTIVE AGE GROUP–A PROSPECTIVE STUDY. European Journal of Molecular & Clinical Medicine. 2021;8(1):2204-8.
18. Barya S, Goyal S, Maheshwari S. Evaluation of Thyroid Dysfunction in Abnormal Uterine Bleeding. International Journal of Health and Clinical Research. 2021;4(2):142-4.
19. Pujari P, Shenoy H, Chellamma V. Evaluating Patterns Of Abnormal Uterine Bleeding (AUB) In Thyroid Dysfunction At A Tertiary Care Centre In North Kerala, India. International Journal of Health and Clinical Research. 2021;4(6):66-72.
20. Chi C, Pollard D, Tuddenham EG, Kadir RA. Menorrhagia in adolescents with inherited bleeding disorders. J Pediatr Adolesc Gynecol. 2010;23(4):215-22.
21. Shankar M, Lee CA, Sabin CA, Economides DL, Kadir RA. von Willebrand disease in women with menorrhagia: a systematic review. BJOG: An International Journal of Obstetrics & Gynaecology. 2004;111(7):734-40.
22. Díaz R, Dietrich JE, Mahoney Jr D, Yee DL, Srivaths LV. Hemostatic abnormalities in young females with heavy menstrual bleeding. Journal of pediatric and adolescent gynecology. 2014;27(6):324-9.
23. Friberg B, Kristin Örnö A, Lindgren A, Lethagen S. Bleeding disorders among young women: A population-based prevalence study. Acta obstetricia et gynecologica Scandinavica. 2006;85(2):200-6.
24. Karaman K, Ceylan N, Karaman E, Akbayram S, Akbayram HT, Kaba S, et al. Evaluation of the hemostatic disorders in adolescent girls with menorrhagia: experiences from a tertiary referral hospital. Indian Journal of Hematology and Blood Transfusion. 2016;32(3):356-61.
25. Benjamins LJ. Practice guideline: evaluation and management of abnormal vaginal bleeding in adolescents. Journal of Pediatric Health Care. 2009;23(3):189-93.
26. Sokkary N, Dietrich JE. Management of heavy menstrual bleeding in adolescents. Current Opinion in Obstetrics and Gynecology. 2012;24(5):275-80.
27. Hernandez A, Dietrich JE. Abnormal uterine bleeding in the adolescent. Obstetrics & Gynecology. 2020;135(3):615-21.
28. Frishman GN. Evaluation and treatment of menorrhagia in an adolescent population. Journal of minimally invasive gynecology. 2008;15(6):682-8.
29. Ozmen F, Ozmen MM, Ozalp N, Akar N. The prevalence of factor V (G1691A), MTHFR (C677T) and PT (G20210A) gene mutations in arterial thrombosis. Ulus Travma Acil Cerrahi Derg. 2009;15(2):113-9.
30. Sidney S, Petitti DB, Soff GA, Cundiff DL, Tolan KK, Quesenberry CP, Jr. Venous thromboembolic disease in users of low-estrogen combined estrogen-progestin oral contraceptives. Contraception. 2004;70(1):3-10.
31. Chan S, Yiu KW, Yuen PM, Sahota DS, Chung T. Menstrual problems and health-seeking behaviour in Hong Kong Chinese girls. Hong Kong Med J. 2009;15(1):18-23.
32. Wang W, Bourgeois T, Klima J, Berlan E, Fischer A, O'Brien S. Iron deficiency and fatigue in adolescent females with heavy menstrual bleeding. Haemophilia. 2013;19(2):225-.
33. Esen I, Oğuz B, Serin HM. Menstrual characteristics of pubertal girls: a questionnaire-based study in Turkey. Journal of clinical research in pediatric endocrinology. 2016;8(2):192.

Table 1. Definition of Abnormal Uterine Bleeding*

Parameter	Definition
Frequency	
Infrequent menstrual bleeding	One or two episodes in a 90-day period
Frequent menstrual bleeding	More than four episodes in a 90-day period
Regularity	
Irregular menstrual bleeding	Variation more than 20 days over a period of a year
Amenorrhea	No bleeding in a 90-day period
Amounf of flow	

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Heavy menstrual bleeding	Excessive blood loss which effects the woman's quality of life
Heavy and prolonged menstrual bleeding	Excessive blood loss exceeding eight days
Light menstrual bleeding	Bleeding less than 5 mL in a period
Duration of Flow	
Prolonged menstrual bleeding	Menstrual periods that exceed eight days on a regular basis
Shortened menstrual bleeding	Menstrual bleeding lasting less than two days
Density of menstrual bleeding According to Hemoglobin(Hb) level	
Severe (dense menstrual bleeding)	≤ 8 g/dL
Heavy (dense menstrual bleeding)	8-10 g/dL
Moderate	10-12 g/dL
Mild	≥12 g/dL

*The International Federation of Gynecology and Obstetrics Classification System (2,3)

Table 2. Clinical and Laboratory Features of Cases with Abnormal Uterine Bleeding

		General (n=79)	Group 1 (n=43)	Group 2 (n=36)	p
	Age (year)	14.3 ± 1.8	14.7 ± 1.7	13.8 ± 1.7	0.01*
	Menarche age(year)	11.9 ± 1.4	12.3 ± 1.4	11.5 ± 1.2	0.07*
	BMI (%)	109.3 ± 25.6	106.3 ± 21.7	112.5 ± 28.2	0.45*
	Underweight (<90%)	19	11	8	0.73**
	Normal (90-110%)	29	17	12	0.57**
	Overweight (110-12%)	10	4	6	0.33**
	Obese (>120%)	21	11	10	0.83**
Time	**Irregularity after menarche (n,%)**				
	<2years	67	41	26	<0.01**
	>2years	12	2	10	<0.01**
Bleeding Pattern	**frequent (n)**	38	25	13	0.05**
	dense(n)	25	25	0	<0.01**
	infrequent(n)	6	3	3	0.82**
Hb(gr/dl)	**Severe (≤ 8 g/dL) (n)**	26	26	0	<0.01**
	Heavy (8-10 g/dL) (n)	17	17	0	<0.01**
	Moderate (10-12 g/dL) (n)	14	0	14	<0.01**
	Mild (≥12 g/dL) (n)	22	0	22	<0.01*
Diagnostic Distribution	**Presence of hematological disease (n)**	3	2	1	0.66**
	Factor 7 deficiency (n)	3/28	2/16	1/12	0.72**
	vWH, other Factor deficiency (n)	0/28	0	0	-
	Platelet structural/functional disorders (n)	0	0	0	-
	MTHFR heterozygous	15/36	11/25	4/11	0.67**
	MTHFR homozygous	4/36	3/25	1/11	0.8**
	FVL (0/34)	0	0	0	-
	PHTRT (0/34)	0	0	0	-
	Anovulation(n)	63	34	29	0.55**
	PCOS (n)	13	7	6	0.96**
	Structural anomaly (n)	2	1	1	0.9**
	Hypothyroidism/ Hyperprolactinemia (n,%)	0	0	0	-

* Mann Whitney U Test; **studient's t test

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