

Evaluation of Abnormal Uterine Bleeding in Adolescents: Single Center Experience

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What is already known on this topic?

Anormal uterine bleeding (AUB) is the most common cause of gynecological problems in adolescence. Since the adolescent age group is a transitional age group, both obstetricians and pediatricians have a role in clinical management. There is no guideline for the management of adolescent AUB. However, heavy bleeding requires urgent treatment.

What this study adds?

Diagnostic and management differences were identified between girls with and without heavy menstrual bleeding. Despite excluding patients with a previously diagnosed bleeding disorder, the frequency of factor VII deficiency was around 4%. Although *MTHFR* mutation frequency was 50% in girls with a history suggestive of thrombosis, it did not appear to increase the risk of bleeding/thrombosis and we suggest routine evaluation is unjustified.

Abstract

Objective: Abnormal uterine bleeding (AUB) is the most common gynecologic complaint in adolescent girls. The aim of this study was to identify the diagnostic and management differences between those with/without heavy menstrual bleeding.

Methods: Retrospective data was collected from adolescents aged 10-19 years, diagnosed with AUB. Adolescents with known bleeding disorders at admission were excluded. All girls were classified according to the degree of anemia; group 1 had heavy bleeding [hemoglobin (Hb) <10 g/dL] and group 2 had moderate or mild bleeding (Hb >10 g/dL). Admission and follow-up characteristics were compared between the two groups.

Results: The cohort consisted of 79 girls with a mean age of 14.3 ± 1.8 years and mean age of menarche of 11.9 ± 1.4 years, with 85% experiencing menstrual irregularity in the two years after menarche, rising to 95.3% in group 1 ($p < 0.01$). Anovulation was evident in 80% of the cohort. Of these 79 girls, 13 (16.5%) had polycystic ovary syndrome and two (2.5%) had structural anomalies (uterus didelphys). Three girls (group 1, $n = 2$) had previously undiagnosed clotting factor VII deficiency; no other clotting deficiencies were diagnosed. Nineteen of 34 (56%) with personal ($n = 2$)/family history of thrombosis had *MTHFR* mutation. None had venous thromboembolism during follow-up of >6 months.

Conclusion: The majority of AUB (85%) occurred in the first two years after menarche. A small proportion (3.8%) had undiagnosed clotting factor deficiency. The frequency of *MTHFR* mutation was 50% in girls with history of thrombosis; however this did not increase the risk of bleeding/thrombosis and so routine evaluation does not appear to be justified.

Keywords: Abnormal uterine bleeding, adolescents, anovulatory bleeding, heavy menstrual bleeding

Introduction

Abnormal uterine bleeding (AUB) is defined as bleeding from the uterine corpus that is abnormal in duration, volume,

frequency and/or regularity. AUB affects 3-20% of women of reproductive age and is more common in adolescence (1). Thus, AUB is one of the most common gynecological presentations encountered in the adolescent age group



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Conflict of interest: None declared
Received: 02.11.2022
Accepted: 04.02.2023



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(2,3,4). In 2011, the International Federation of Obstetrics and Gynecology (FIGO) defined AUB as menstrual bleedings that has a uterine origin, is unrelated to pregnancy, has been abnormal in the last six months in terms of amount, frequency, and/or duration), and is either irregular or regular but persists for more than eight days (3). The term “dysfunctional uterine bleeding” has been removed because the different terminologies were considered confusing and FIGO suggests only using the label AUB (5,6).

Each menstrual cycle of healthy adolescents usually has a bleeding duration every 21-45 days, lasting from 2-7 days, and the volume 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 every 21-34 days by the third year after menarche, and is similar to adults in 60-80% of adolescents (2). A 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 has suggested the mnemonic 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). It should be noted that structural causes are very rare in adolescence, reported to account for around 1.3-1.7% of AUB (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 and they may be unaware of their own personal regular cycle pattern. However, AUB and the factors that cause it can cause long-term health problems. AUB may affect physical, emotional, and social wellbeing and quality of life. It has been reported that AUB may possibly lead to absenteeism from full-time education and thus cause a decrease in academic achievement (13).

AUB is the most common cause of gynecological problems in adolescents and is a major source of stress for affected 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 important. Since the adolescent age group is transitional, both obstetricians and pediatricians are often involved in clinical management. However, there is no standard guideline for optimal clinical management. The aim of the present study was to determine the differences in diagnosis and management between those with and without heavy menstrual bleeding by evaluating AUB in a large case series of adolescent girls.

Methods

Study Population

This retrospective case series included all adolescents aged 10-19 years and diagnosed with AUB at our institution between 2016 and 2021. The study was approved by the Ethical Committee of the study Ankara University (approval number: 15-378-21, date: 25.06.2021).

The following data were retrospectively evaluated: demography, family history, complaints at presentation, characteristics of AUB, findings of examination at diagnosis and during follow-up, results of laboratory and radiological evaluation, treatment regimen, and responses to treatments. Adolescents with typical menstrual characteristics (frequency, duration, and bleeding intensity) and with previously diagnosed bleeding disorders were excluded.

Criteria for AUB are cycles which are: frequent (interval shorter than 21 days); or rare (longer than 45 days); or prolonged (longer than seven days); or heavy (more than 80 mL bleed). Heavy bleeding was defined as using more than six pads per day for more than seven days or bleeding that affected daily activity (1). We used the parameters shown in Table 1 to define AUB.

The initial evaluation was standardized since the approach used at the single management center follows a single 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, activated partial thromboplastin time, and fibrinogen values. Based on the family history and the results of the initial tests, other factor levels were investigated with priority.

In cases with small amounts of prolonged bleeding, human chorionic gonadotropin and pelvic ultrasound (USG) were performed to exclude pregnancy.

Findings of anemia were investigated, together with the duration of anemia by enquiring about history and through physical examination, hemogram, peripheral smear, and patients' previous blood examination results. 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 using 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 and/or 3) exclusion of other known causes of AUB. All subjects were also classified in terms of the degree of anemia. Group 1 consisted of adolescents with heavy and severe bleeding [hemoglobin (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 performed by following the the standard protocol. According to this protocol, the main clinical aim of management was to provide hemodynamic stability by correcting anemia until the etiology was identified. Anemia was classified as: 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 treated with non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and sodium naproxen, to decrease bleeding flow. If the Hb 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) and severe bleeding (Hb <8 g/dL), which means active bleeding, combined oral contraceptives (COCs) containing at least 30 mcg of ethinyl estradiol (E2) were given, starting with one pill every 8-12 hours until the menstrual bleeding ceased. Then COCs were continued, giving one pill daily until the Hb level increased to more than 10 g/dL for 3-6 months. Patients with Hb <7 g/dL and patients with Hb <10 g/dL who had active heavy bleeding and hemodynamic instability were consistently hospitalized. Treatment for this group consisted of erythrocyte suspension transfusion and 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 at 10 mg/day) was given any patient with a contraindication for estrogen therapy, such as thromboembolic disease, migraine with aura, or hepatic dysfunction. Additional antiemetic treatment was used when necessary. After initial management, patients were treated according to the underlying etiology of AUB.

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
Amount of flow	
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 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).
Hb: hemoglobin

Statistical Analysis

All statistical analyses were performed using Statistical Package for the Social Sciences, version 21.0 (IBM Corp., Armonk, NY, USA). Data were expressed as the mean \pm standard deviation (SD), median (minimum; maximum). The Kolmogorov-Smirnov test was used to evaluate the normality of variables. Descriptive analyses are presented using means \pm SD 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 nonparametric measurements. A p value <0.05 was assumed to indicate statistically significant result in all analyses.

Results

This study included 79 adolescents. The overall mean age was 14.3 ± 1.8 (10.7-17.9) years, and the age at menarche was 11.9 ± 1.4 (9.5-15.9) years. Group 1 was older than group 2 ($p=0.02$). While 64.6% had normal weight, 22.8% were obese, and 11.4% were underweight. Menstrual irregularity in the first two years after menarche was reported by 85%, while this proportion increased to 95% in 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 girl. In terms of severity of bleeding based on systemic Hb concentration, 32 % had dense bleeding, and all had Hb < 10 g/dL. While 48 % had frequent bleeding of whom 32 % were in group 1, and the rest were in group 2. Taking both groups together, anovulation (80 %) was the main reason for AUB. While 13 girls (16 %) were diagnosed with polycystic ovary syndrome (PCOS), two adolescents (2 %) had structural anomalies (uterus didelphys). No adolescents had hypothyroidism or hyperprolactinemia. Two girls were taking antiepileptics, and eight were on vitamin supplements (iron, vitamin D, vitamin B12). None caused bleeding.

In group 1, 25 (33 %) had frequent bleeding, and 25 (33 %) had dense bleeding, which caused low Hb (< 10 g/dL). Anovulation was the most common etiology. Other etiologies were PCOS (16 %), and factor VII deficiency (5 %) while 34 % had a family history of PCOS and 6 % had a family history of AUB (Table 2).

Overall, 28 girls were under close follow-up and assessment for hematological diseases. Three (10.7 %) were diagnosed with factor VII deficiency and two of these were in group 1 with the other in group 2. None had von Willebrand disease (vWD), other factor deficiency or platelet structural/functional disorders. Thirty-four subjects with a suspected family history of thrombosis (history of immobilization,

Table 2. Clinical and laboratory features of cases with abnormal uterine bleeding

		All subjects (n = 79)	Group 1 (n = 43)	Group 2 (n = 36)	p (Group 1 vs Group 2)
	Age (year)	14.3 ± 1.8	14.7 ± 1.7	13.8 ± 1.7	0.02*
	Menarche age (year)	11.9 ± 1.4	12.3 ± 1.4	11.5 ± 1.2	0.01
	BMI (%)	109.3 ± 25.6	106.3 ± 21.7	112.5 ± 28.2	0.27
	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, %)				
	< 2 years	67	41	26	< 0.01
	> 2 years	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 VII deficiency (n)	3/28	2/16	1/12	0.72
	vWD or 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	-

Student's t-test.

BMI: body mass index, PCOS: polycystic ovary syndrome, vWD: von Willebrand disease, Hb: hemoglobin

pregnancy, hormone therapy) and two with a proven thrombosis history (history of hospitalization due to venous thromboembolism), underwent genetic examination. Of these, 50% had an *MTHFR* mutation (homozygous $n=4$, heterozygous $n=15$) with no hyperhomocysteinemia. Prothrombin mutation or factor V Leiden mutation was not detected. None had venous thromboembolism during at least six months of follow-up.

In terms of a treatment procedures, since group 1 had patients with $Hb < 10$ g/dL, they were on 3-4 tablets of COC daily until the bleeding ceased. In group 1, 18 (22.8%) needed erythrocyte transfusion. Half of the patients had heavy bleeding during every menstrual period since menarche. The most longest 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 ceased at a mean of 2.77 ± 0.86 (range 1-5) days, following start of treatment with COCs. In the first month and a half, Hb increased above 10 g/dL in all groups. Oral iron supplementation was initiated in all patients. Four (5%) required rehospitalization and all four had a history of maternal AUB, but none had a family history of bleeding disorders.

In group 2, NSAIDs decreased the duration and amount of bleeding in subjects with mild uterine bleeding ($n=22$) and subjects with normal Hb. In adolescents with moderate uterine bleeding ($n=14$), iron supplementation with 60 mg of elemental iron per day and additional COCs were begun. In addition, 5 mg medroxyprogesterone acetate was started in two girls due to a proven family history of thromboembolism. Other patients were on 1-2 COC tablets with 0.15 mg desogestrel and 30 mcg ethinyl E2 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 follow-up, 20 of 79 (25.3%) did not comply with the recommended treatment. Non-compliance was observed in all patients ($n=7$, 8%) who presented with rebleeding. Six of these patients required rehospitalization. Three of them had bleeding disorders. The clinical and laboratory characteristics of the whole cohort and both groups are 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 female adolescent health. During the first two years of menarche, approximately half of the menstrual cycle is anovulatory but by the fifth year after menarche 75% of the cycles will be ovulatory (2). A deficiency in progesterone secretion from the ovarian follicles and excessive E2 production causes this early anovulation. Endometrial proliferation is also a cause of unpredictable menstrual bleeding (2). The results of the present study were in keeping with the published evidence that the most common cause of AUB in adolescents is anovulation (14,15,16). There was no history of excessive exercise in any of the cases included in the present study. It has been reported that obesity, anorexia, weight loss, PCOS, hyperprolactinemia, drugs such as steroids, phenothiazines, tricyclic antidepressants (3), and hypothyroidism can all cause AUB (17,18,19). All girls in the present study were evaluated for endocrinopathies and no endocrinopathies, except PCOS, were detected. Due to the study's retrospective nature, we could not assess the psychological status of girls at presentation.

The second most common cause of AUB is reported to be coagulopathies, with a 5-28% frequency (11,20,21,22). Studies have reported that vWD was the most common etiology of coagulopathy in women, with a frequency of 5-48%. Other causes of coagulopathy in descending order of reported prevalence are: platelet dysfunction (2-44%); thrombocytopenia (13-20%); coagulation factor deficiencies (8-9%); and then smaller proportions of leukemia, hypersplenism, and hereditary bleeding disorder (11,20,21,22). Earlier studies in this field have included cases previously diagnosed with a bleeding disorder. Since we did not include them, the proportion of patients diagnosed with a bleeding disorders was low. However, three girls had previously undiagnosed factor VII deficiency, and their first presenting symptom was AUB. In addition, two were in group 1 while one was in group 2, showing a phenotypical variability in this bleeding disorder. Given that this amounted to nearly 4% of our cohort, we caution colleagues that undiagnosed bleeding disorder should be considered in adolescents presenting with any degree of AUB, especially after exclusion of either, more common etiologies.

No pregnancy was observed in this cohort. Invasive imaging methods were not needed because a structural abnormality as an etiology is not common in adolescents. Incidental structural anomaly (uterus didelphys) was detected by pelvic

USG in only two girls. We could not explain the relationship between this anomaly and AUB. These cases were also anovulatory.

Severe AUB affects 10-20% of adult women and 37% of adolescents. A study of approximately 1,000 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, resolution of anemia, and maintaining regular cycles in all patients were our main goals in managing severe AUB. Three patients in the severe group required intensive care unit follow-up. All girls with heavy bleeding were admitted to the inpatient unit. Earlier studies have emphasized that the basic approach in treatment is to stop the bleeding, treat the anemia, ensure a regular menstrual cycle, and increase the quality of life of the adolescent (25,26).

Treatment options include iron supplementation, COCs, progesterone, NSAIDs, antifibrinolytics, desmopressin, and gonadotropin releasing hormone (GnRH) analogs (27). Supportive treatment options include antiemetics, iron, NSAIDs, antifibrinolytic (tranexamic acid, aminocaproic acid), and a range of other drugs such as danazol, ulipristal acetate, and desmopressin acetate (28). The management is mainly based on the severity of bleeding and anemia. All were on COCs, NSAIDs, and iron supplementation in our follow-up. A side-effect associated with COCs was nausea. As girls who were previously diagnosed with bleeding disorders and malignancies were excluded, there is no description of our experience with GnRH analogs and antifibrinolytic treatments in this report.

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 (50%) to be consistent with the reported frequency for a Turkish population. However, as previously suggested, this mutation did not increase the risk of bleeding/thrombosis, and we suggest that routine evaluation is unnecessary.

Menstrual problems are significant in the adolescent age group and may disrupt many aspects of daily life. A study from 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 were unable to directly investigate quality of life in the present study but more than half of the patients were hospitalized, and this indirectly confirms a disruption of normal living. Some of the patients had also reported that AUB caused them to avoid a range of daily activities when medical history was being investigated during diagnosis.

Study Limitations

The limitations of our study include the retrospective nature of the study and that participants were all from a single center, notwithstanding that all patients diagnosed in our center over five years were eligible for inclusion. Multicenter national studies would yield more generalizable results.

Conclusion

Most adolescent girls with AUB were anovulatory in the first two years. A third had intense bleeding, and nearly a quarter needed erythrocyte transfusion. In addition, in the girls with suspected hematological disease, making up more than a third of the cohort, the frequency of undiagnosed hematological disease, in this case factor VII deficiency was 10.7%. Although *MTHFR* mutation frequency was 50%, this was consistent with frequency in the general population, did not increase the risk of bleeding/thrombosis, and thus we recommend that routine evaluation is unnecessary in Turkish adolescents with AUB.

Acknowledgement

We thank all adolescents who participated in the study.

Ethics

Ethics Committee Approval: The study was approved by the Ankara University of Local Ethics Committee (decision no: 15-378-21, date: 25.06.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Sirmen Kızılcan Çetin, Zehra Aycan, Elif Özsu, Zeynep Şıklar, Ayşegül Ceran, Seda Erişen Karaca, Gizem Şenyazar, Merih Berberoğlu, Concept: Sirmen Kızılcan Çetin, Zehra Aycan, Merih Berberoğlu, Design: Zehra Aycan, Elif Özsu, Merih Berberoğlu, Data Collection or Processing: Sirmen Kızılcan Çetin, Zeynep Şıklar, Ayşegül Ceran, Seda Erişen Karaca, Gizem Şenyazar, Analysis or Interpretation: Sirmen Kızılcan Çetin, Zeynep Şıklar, Ayşegül Ceran, Literature Search: Sirmen Kızılcan Çetin, Elif Özsu, Seda Erişen Karaca, Gizem Şenyazar, Writing: Sirmen Kızılcan Çetin, Zehra Aycan, Merih Berberoğlu.

Financial Disclosure: The authors declared that this study received no financial support.

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