ORIGINAL ARTICLE

M. Metin ALTAY

Ali HABERAL

Abnormal Uterine Bleeding in Adolescents: Treatment with Combined Oral Contraceptive Pills is Effective Even in Hospitalized Patients with Bleeding Disorders

Aims: To show the efficacy of oral contraceptive (OC) treatment for hospitalized adolescent patients with abnormal uterine bleeding (AUB).

Materials and Methods: Thirty-one girls with AUB and anemia hospitalized within the last two years were included. The patients' medical records were evaluated retrospectively. All patients were given combined OC containing 0.03 mg ethinyl estradiol plus 0.15 mg desogestrel according to a defined protocol.

Results: Among 31 patients, 8 (25.8%) had bleeding disorders: 3 (9.7%) had factor VII deficiency, 3 (9.7%) thrombocytopenia, 1 (3.2%) factor VIII deficiency and 1 (3.2%) von Willebrand disease. Vaginal bleeding stopped in all patients within a few days with the treatment protocol.

Conclusions: Adolescents are good responders to medical treatment despite the presence of bleeding disorders, probably due to the positive coagulative effect of the estrogen component of OCs on platelets and clotting factors. Continuation of OC will be a problem in adolescent girls, because there are some misconceptions about OC in the Turkish population, such as that OC can cause infertility or hormonal imbalance. Appropriate counselling is necessary to overcome this difficulty. We believe that the presence of an Adolescent Gynecology Unit affected the success of our treatment.

Key Words: Dysfunctional uterine bleeding, adolescence, bleeding disorder, ethinyl estradiol, desogestrel

Department of Gynecology,
Turkish Ministry of Health
Ankara Etlik Maternity and
Women's Health Academic and
Research Hospital,
Ankara - TURKEY

Anormal Uterus Kanamalı Ergenlerde Kombine Oral Kontraseptif Haplarla Tedavi, Hastaneye Yatırılan Kanama Bozukluğu olan Hastalarda bile Etkindir

Amaç: Anormal uterus kanamalı (AUK) hastaneye yatırılan adolesan hastalarda oral kontraseptif (OK) tedavisinin etkinliğini göstermek

Yöntem ve Gereç: Son iki yıl içinde hastaneye yatırılan AUKlı ve anemisi olan 31 genç kız çalışmaya dahil edildi. Hasta kayıtları geriye dönük değerlendirildi. Bütün hastalara 0.03 mg etinil östradiol ve 0.15 mg desogestrel içeren OK belirli bir protokole göre verildi.

Bulgular: Otuz bir hastanın 8'inde (% 25.80) kanama bozukluğu vardı: üçünde (% 9.67) faktör VII eksikliği, üçünde (% 9.67) trombositopeni, birinde (% 3.22) faktör VIII eksikliği ve birinde de (% 3.22) von Willebrand hastalığı mevcuttu. Tedavi ile bütün hastaların kanamaları birkaç günde durdu.

Sonuç: Adolesanlar kanama bozukluğuna sahip olsalar bile tıbbi tedaviye iyi yanıt verirler. Bu, muhtemelen OK nın estrojen bileşeninin trombositler ve pıhtılaşma faktörleri üzerindeki pozitif pıhtılaştırıcı etkisine bağlıdır. Türk toplumunda OK lerin infertiliteye veya hormon dengesizliklerine yol açtığı gibi yanlış inanışlar yüzünden adolesan kızlarda OK tedavisine devam etmek sorun olabilir. Bu güçlüğün üstesinden gelmek için uygun danışmanlık vermek gereklidir. Biz Adolesan Jinekolojisi Birimimizin olmasının tedavi başarımızı etkilediğine inanıyoruz.

Anahtar Sözcükler: Disfonksiyonel uterus kanaması, ergenlik, kanama bozukluğu, etinil östradiol, desogestrel.

Correspondence
M. Metin ALTAY
48. Cadde Yonca Apt.
No.: 12 / 31
06520 Çukurambar,
Ankara - TURKEY

altay_metin@yahoo.com

Introduction

Dysfunctional uterine bleeding (DUB) is defined as abnormal endometrial bleeding in the absence of pelvic pathology and is usually associated with anovulation. DUB commonly presents within two years of menarche, when more than 50% of cycles are anovulatory. The presentation varies from heavy prolonged menses interspersed with long periods of amenorrhea to heavy, frequent bleeding occurring every 1 to 2 weeks. Because the presentation of DUB is similar to that of many pelvic lesions, it should be diagnosed only after other causes of bleeding have been excluded (1).

Abnormal uterine bleeding (AUB) is occasionally the initial presentation of a blood dyscrasia or coagulation defect. Management of AUB depends on the severity of the bleeding and hemoglobin level. In this article, we present adolescent cases with AUB who required hospitalization during the last two-year period and discuss the etiology and management.

Materials and Methods

The prevalence of AUB in 2005 was calculated by examining the medical records of our hospital's Adolescent Gynecology Unit. Percentages of AUB according to age groups were given.

Thirty-one adolescent patients who were hospitalized with the diagnosis of AUB and anemia during the last two years were included in the analysis. This study was in accordance with the Helsinki Declaration. All the patients' medical records were evaluated retrospectively.

All patients were assessed for age, age at menarche, lowest hemoglobin (Hb) level during hospitalization, past history of medical or surgical problems, treatment carried out (including surgical intervention) and the details of hematologic investigation. Transabdominal pelvic ultrasonographic examination was performed in all patients. Their hormonal status, including thyroid function tests, and blood biochemistry were evaluated.

The patients were divided into two groups: the first group was composed of 23 patients with no bleeding disorder and the second group of 8 patients with bleeding disorder. The groups were compared for period of bleeding, Hb level, body mass index (BMI), age, and age at menarche. Statistical analysis was done using Mann-Whitney U test and Statistical Package for Social Sciences (SPSS) 10.0 for Windows, and $P<0.05$ was accepted as indicating statistical significance.

All patients were given combined oral contraceptive pill containing 0.03 mg ethinyl estradiol plus 0.15 mg desogestrel (Desolett ®, Organon Ilaclari A.S., Istanbul – Turkey) as follows: The initial dose was four times a day for 3 days, then three times a day for 3 days, and then twice daily for 3 days. Treatment was then continued as once daily for 12 days to complete the first 21 days of treatment. After 7 days off the hormones, treatment was continued as once daily for 21 days, and then no pills for 7 days. The treatment was continued for at least 3 cycles.

This protocol was routinely given at our hospital for the treatment of AUB in adolescents. The parents of the adolescents were informed about the therapy and provided signed informed consent before hospitalization of the patient.

Results

During 2005, 2171 patients aged 10–19 were followed in the Adolescent Gynecology Unit of our hospital. Of these patients, menstrual disorders were found in 725 (33.4%). While the prevalence of menstrual disorders was about 48% between the ages 12–15, this figure was 40.8% at the age of 16-17, and then declined to 25% at the age of 18-19. One hundred and twenty (16.6%) of 725 were diagnosed as having AUB. Twenty of these 120 (16.7%) required hospitalization because of AUB plus anemia. As a result, 2.8% of adolescents with menstrual disorders had AUB severe enough to require hospitalization in 2005.

A total of 31 adolescent patients were hospitalized for AUB during 2005-2006. The average age of the patients was 15.3 (12–19) years. There were no medical or surgical problems in their history, but 4 (12.9%) patients had bleeding disorders in their family history. The mean period of bleeding was 22.6±20.0 days (4–90 days), systolic blood pressure was 102.3±11.3 mmHg (85–120) and diastolic blood pressure was 65.6±8.1 mmHg (50–80) upon admission. On ultrasonographic examination, the mean endometrial thickness was 5.2±2.4 mm (2-13). Eighteen of the patients (58.1%) had endometrial thickness <4 mm. There were no abnormalities on thyroid function tests or blood biochemistry.

There were 8 patients (25.8%) with bleeding disorders: 3 (9.7%) had factor VII deficiency, 3 (9.7%) thrombocytopenia (with platelet count <100,000/mm^3), 1 (3.2%) factor VIII deficiency, and 1 (3.2%) von Willebrand (vWD) disease.

The comparison of patients with and without bleeding disorders is presented in Table. There were significant differences between the groups in systolic and diastolic blood pressures on admission and Hb levels.

The mean Hb level was 7.9±2.4 (3–10.5) g/dL. Of 21 patients with Hb <10 g/dL, 8 (38.1%) had bleeding disorder, whereas there was no bleeding diathesis among the patients with Hb ≥10 g/dL.

Table. Comparison of the groups with and without bleeding disorders with respect to various parameters.

	Bleeding Disorder		
	Absent N=23 (mean±SD)	Present N=8 (mean±SD)	P
Period of Bleeding (days)	19.95±17.41	30.25±25.91	0.21
Hemoglobin (g/dL)	8.54±2.35	6.23±1.84	0.01*
BMI (kg/m^2)	21.25±1.39	20.69±1.51	0.34
Age (years)	15.43±2.35	14.87±1.64	0.54
Age at Menarche (years)	13.08±0.84	13.12±0.99	0.91
Systolic Blood Pressure (mmHg)	105.43±10.65	93.12±7.98	0.006*
Diastolic Blood Pressure (mmHg)	67.60±7.95	60.00±5.97	0.02*
Endometrial Thickness (mm)	5.30±3.28	4.85±3.53	0.75

* Statistically significant difference (Mann-Whitney U test).

Sixteen patients (51.6%) required blood transfusions. Of these, 7 (43.8%) had bleeding disorder. Of the 15 patients who did not have blood transfusion, only 1 (6.7%) had bleeding disorder.

Vaginal bleeding stopped in all patients within a few days with the treatment regimen. One of the thrombocytopenic patients (3.2%) had the diagnosis of immune thrombocytopenic purpura (ITP) and splenectomy was planned. Only one patient was readmitted for further follow-up of DUB; the rest (96.8%) were followed as outpatients. For the readmitted patient, the same protocol was used by doubling the initial dosage, and the patient responded well.

Discussion

One of the most common gynecologic problems during adolescence is menstrual irregularities. Demir et al. (2) reported the incidence of DUB among adolescents 12-15 years of age as 45.5%. We found that incidence of menstrual irregularities among adolescents of the same age group in the outpatient Adolescent Gynecology Unit of our hospital was about 48% (3).

This is not surprising, however, since 50 to 80% of cycles within the first two years after menarche are anovulatory (4). A regular menstrual pattern is generally not established until 20 months after menarche. Regular ovulatory periods may not occur for four or five years, and 80% of cycles are anovulatory in the first year after menarche (5). Many resolve spontaneously within a few years as the hypothalamic-pituitary-ovarian axis matures. However, if there is severe AUB requiring hospitalization of an adolescent, one should search for a significant medical problem.

Even in those adolescents with bleeding sufficient to require hospitalization, in one study, 74% of cases were secondary to DUB (6). Of the rest, 19% were secondary to primary coagulopathies, and 7% included pregnancy complications, oral contraceptives, trauma, systemic illness, and malignancy.

Systemic bleeding disorders are reported in 7-20% of women of all ages who present with menorrhagia (7). We found this figure as 25.8% in our patient group. It is estimated that there is an underlying coagulopathy in 20% of adolescents who require hospitalization for acute menorrhagia, 25% who experience severe menorrhagia and have Hb levels of <10 g/dL, 33% who require transfusion, and 50% who hemorrhage at menarche (8). In our study, bleeding disorder was present in 38.1% of girls with AUB and with Hb <10 g/dL. Among the patients with blood transfusion, 43.8% had bleeding disorder. Our figures seemed to be slightly higher than in the previously reported articles.

A retrospective review of outpatient and inpatient adolescents seen at a children's hospital for menorrhagia

revealed that 13% had thrombocytopenia, 8% had abnormal platelet function and 11% had inherited coagulation disorders. Among those with thrombocytopenia, the most common diagnoses were ITP (55%) and chemotherapy-induced myelosuppression (22%) (7). The most common dyscrasia in adolescents is primary or secondary thrombocytopenic purpura (9). Hereditary bleeding disorders, such as vWD and Christmas disease (hemophilia B), are usually known to exist in the family and thus are readily recognized. However, about 25% of patients with hereditary coagulation disorders show a negative family history (10). In our study, the most common blood dyscrasias were factor VII deficiency (9.7%) and thrombocytopenia (9.7%).

Treatment of AUB is usually medical with combined oral contraceptives or high- dose estrogen preparations followed by progestin preparations. Hormonal therapy will almost always stop even severe bleeding.

In hospitalized adolescents with heavy bleeding, conjugated estrogens, 25 to 40 mg every 4 hours for 24 hours intravenously, can be used. In addition to estrogen, a progestational agent should be used orally as either norethindrone, 5 mg orally four times a day, or medroxyprogesterone acetate, 5 to 10 mg four times a day, or in the form of a progestational dominant oral contraceptive (11). It is advisable to continue the oral agent four times a day for 4 days, three times a day for 3 days, then twice a day for 2 weeks. Afterwards, the adolescent should be cycled on birth control pills for several months. Therapy usually stops bleeding within 24 hours. If it does not occur within 48 hours, the adolescent should be reevaluated for a bleeding problem or another organic problem.

If hormonal therapy can not control the bleeding, which is an unusual occurrence, a dilatation and curettage is advisable for both diagnostic and therapeutic purposes (11). Dilatation and curettage should be reserved for the few girls who fail with hormonal therapy. In our study, all adolescents responded to high-dose oral contraceptive therapy, and no intravenous hormonal therapy was needed. Dilatation and curettage was not required for our study group. Splenectomy for ITP, as in one of our cases, will be necessary.

Davenas and colleagues (12) reported that the ethinyl estradiol component appears to be responsible for modifications in platelet lipid metabolism during oral contraceptive use. The response appears after a latency period and seems to be irreversible, since the duration of life of platelets is 4-5 days. The increased synthesis occurs mainly in cholesterol and its precursors lanosterol and dihydrolanosterol. Supplemental *in vitro* experiments suggested that lanosterol was responsible for the increased platelet activity (12).

Forty-three percent of the women taking oral contraceptives showed an increased platelet sensitivity to thrombin. The increased sensitivity was correlated with increased lanosterol synthesis, but the relation was only observed in women taking oral contraceptives. The phenomenon is of interest because of its possible relationship to the increased risk of thromboembolic accidents in women taking oral contraceptives (12).

The Society of Obstetricians and Gynecologists of Canada recommends that girls growing up in families with a history of vWD or other inherited bleeding disorders should be tested pre-menarchally to determine whether or not they have inherited the disease to allow both the patient and her family to prepare for her first and subsequent menstrual periods. In adolescents presenting with menorrhagia, an inherited bleeding disorder should be excluded. When possible, investigation should be undertaken before oral contraceptive therapy is instituted, as the hormonally induced increase in factor VIII and vWD may mask the diagnosis (13).

In an interesting 6-month controlled trial, 18 boys with hemophilia were treated with combined estrogens and progesterone. Findings showed a reduction in bleeding of skin and joints, a minor shortening of coagulation time in glass and plastic, a decrease in kaolin-cephalin time, and a significant increase in fibrinogen (P value=0.041), and factor II and VII levels (P value=0.001). However, the treatment did not affect the number of days in bed, hematuria, epistaxis, or muscular bleeding. All patients developed severe side effects (gynecomastia and pubic hair); therefore, this treatment is not recommended in management of hemophilia in boys (14).

Another important factor for the effective treatment of AUB in adolescent girls with oral contraceptive pills is the continuation of the treatment. There are some misconceptions about oral contraceptive pills in the Turkish population, such as that oral contraceptives cause

infertility or hormonal imbalance, and this will cause discontinuation of the treatment. Appropriate counselling is necessary to overcome this difficulty. We established a special gynecological outpatient service for adolescent girls at our hospital in 2005. An obstetrician and gynecologist, general practitioner, clinical psychologist, and a nurse, who have been educated in adolescent reproductive health and counselling, are employed in the Adolescent Gynecology Unit. A dermatologist was added to this team in 2006. Before the establishment of this department, we were unaware of exactly how many girls with DUB applied to our hospital (3). However, in 2005 and 2006, the exact data regarding adolescent girls with AUB was known, and adequate counselling was provided to both the adolescent girls and their parents before initiating a treatment. We believe that presence of this special service for adolescents affected the success of our treatment.

In conclusion, the adolescent patient who presents with severe dysfunctional bleeding may have a significant medical problem like a blood dyscrasia. Medical treatment is highly effective even in those with bleeding disorders, probably due to the positive coagulative effect of the estrogen component of oral contraceptives on platelets and clotting factors. Appropriate clinical evaluation and an individualized approach to treatment are essential for optimal care.

References

1. Muram D. Vaginal bleeding in childhood and adolescence. Obstet Gynecol Clin North Am 1990; 17(2): 389-408.

2. Demir SC, Kadayifci O, Vardar MA, Atay Y. Dysfunctional uterine bleeding and other menstrual problems of secondary school students in Adana, Turkey. J Pediatr Adolesc Gynecol 2000; 13: 171-5.

3. Altay MM, Haberal A. Evaluatıon of adolescent patients' visits at gynecological outpatient clinics of S.S.K. maternity hospital during the year 2001 and suggestions for the establishment of special gynecological services for adolescents. Turk J Fertility 2003; 11(3): 199-207.

4. Greydanus DE, McAnarney ER. Menstruation and its disorders in adolescent menstrual cycles. Curr Probl Pediatr 1982; 12(10): 1-61.

5. Apter D, Viinikka L, Vihko R. Hormonal pattern of adolescent menstrual cycles. J Clin Endocrinol Metab 1978; 47: 944-54.

6. Claessens EA, Cowell CA. Acute adolescent menorrhagia. Am J Gynecol 1981; 139: 277-80.

7. Kouides PA. Obstetric and gynaecological aspects of von Willebrand disease. Best Pract Res Clin Haematol 2001; 14: 381-99.

8. Polaneczky MM, Slap GB. Menstrual disorders in the adolescent: dysmenorrhea and dysfunctional uterine bleeding. Pediatr Rev 1992; 13(3): 83-7.

9. Bevan JA, Maloney KW, Hillery CA, Gill JC, Montgomery RR, Scott JP. Bleeding disorders: a common cause of menorrhagia in adolescents. J Pediatr 2001; 138: 856-61.

10. Gidwani GP. Vaginal bleeding in adolescents. J Reprod Med 1984; 29: 417-20.

11. Smith CB. Dysfunctional uterine bleeding. Am Fam Physician 1987; 36(3): 161-8.

12. Davenas E, Ciavatti M, Poitevin B, Aubin M. Oral contraceptives and blood platelets Homeopath Fr 1985; 73(5): 299-305.

13. Demers C, Derzko C, David M, Douglas J; Society of Obstetricians and Gynecologists of Canada. Gynaecological and obstetric management of women with inherited bleeding disorders. J Obstet Gynaecol Can 2005; 27(7): 707-32.

14. Brandt NJ, Cohn J, Hilden M. Controlled trial of oral contraceptives in haemophilia. Scand J Haematol 1973; 11(3): 225-9.