

Dysfunctional uterine bleeding in adolescent girls and evaluation of their response to treatment

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Dysfunctional uterine bleeding (DUB) is a gynecologic problem that occurs often during adolescence and is the most frequent cause of urgent admission to the hospital. DUB occurs in the adolescent usually because of anovulation, a result of developmental immaturity of the hypothalamic-pituitary-ovarian (HPO) axis. Diagnosis can only be confirmed when there is no other pathology present, so it is important to exclude all the other possibilities. The aim of this study was to evaluate the frequency of coagulation disorders and other underlying situations as a cause of menorrhagia in adolescents with DUB and to assess the response to the treatment(s) given.

Key words: adolescent, metrorrhagia, dysfunctional uterine bleeding.

Dysfunctional uterine bleeding (DUB) is defined as excessive, prolonged, unpatterned bleeding from the endometrium, but not associated with anatomic lesions of the uterus. DUB is seen in almost 10-15% of adults, but it is more frequent in adolescents¹. It is the most frequent gynecologic urgency of adolescence^{2,3}. The most common cause of DUB is anovulation due to the immaturity of the hypothalamic-pituitary-ovarian (HPO) axis, and these anovulatory cycles are especially seen during the first 18 months after menarche¹. DUB is a diagnosis of exclusion. Therefore, organic pathologies of the reproductive system, coagulation disorders and systemic diseases must be excluded first⁴. Previous studies have shown that the second most common cause of abnormal uterine bleeding in adolescence is coagulation disorders, and physicians must investigate an underlying coagulopathy when treating adolescents with menorrhagia^{5,6}.

The aim of this study was to evaluate the causes of DUB in adolescents and their response to medical treatment.

Material and Methods

Participants

The study was conducted at Hacettepe

University İhsan Doğramacı Children's Hospital, Department of Pediatrics, Division of Adolescent Medicine between January 2007 and December 2009. Thirty-six female adolescents between the ages of 11-16 years diagnosed with menorrhagia were enrolled into the study. Menorrhagia was defined as prolonged (>7 days) or excessive (>80 ml) uterine bleeding occurring at regular intervals. All adolescents were queried regarding the age of menarche, pubic hair and breast development, menstrual cycle intervals, bleeding days, and presence or not of dysmenorrhea. All patients underwent a detailed physical examination, and pubertal staging was evaluated according to the Marshall-Tanner classification⁷. A complete blood count, kidney and liver function tests and thrombocyte aggregation tests were performed, and activated partial thromboplastin time, prothrombin time, von Willebrand factor antigen, coagulation factor, follicle stimulating hormone (FSH), luteinizing hormone (LH), progesterone, prolactin, and serum thyroid stimulating hormone (TSH) were measured. If any of the screening tests for bleeding disorders was abnormal, the patients were referred to a clinical hematologist. All patients were evaluated via abdominopelvic ultrasonography that was performed by the same gynecologist. As none of the patients was sexually active,

a pelvic examination was not conducted⁸. If no other pathologies were found, the patients were diagnosed with DUB as a result of developmental immaturity of the HPO axis. After the initial work-up for menorrhagia, the patients were followed for at least six months, and their response to treatment at the sixth-month check-up was re-evaluated. We inform all our patients and their families about the complications of hormonal drugs before starting the therapy. We also recommend that anti-emetic medications be used if needed.

None of our patients experienced any complications. Eight patients (22.2%) received only hormonal therapy (cyclic 0.15 mg levonorgestrel plus 0.03 mg ethinyl estradiol) with no iron replacement. Eleven patients (30.6%) received iron replacement therapy (ferrous glycine sulfate) in addition to the hormonal therapy (cyclic 0.15 mg levonorgestrel plus 0.03 mg ethinyl estradiol). Eight patients (22.2%) received only iron replacement therapy. Nine patients (25.0%) were given no additional therapy.

The study was approved by the Committee of Research Ethics of Hacettepe University, and written informed consents were obtained from the adolescents and their parents who contributed to the study.

Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) 11.5 for Windows. Chi-square and Fisher's exact tests were used to analyze nominal variables for cross tabulations. To evaluate the relations between numerical variables, Pearson correlation coefficient was used. Differences between the means of parametric variables were analyzed by t-test. Wilcoxon signed rank test was used for analyzing non-parametric variables in related samples. A value of $p \leq 0.05$ was considered to be statistically significant.

Results

In this study, 36 female adolescents were evaluated. The mean age of the patients was 13.7 ± 1.4 (11-16) years, and the mean age at menarche was 12.3 ± 1.0 (10-15) years. The mean days of bleeding were 17.3 ± 9.2 (11-60) days (Table I). Twenty-five (69.4%) of the patients had no underlying pathologies, 9 (25%) had hematologic disorders, 1 (2.8%) had hypothyroidism, and 1 (2.8%) had polycystic ovary syndrome (PCOS). From the 9 patients who had hematologic disorders, 2 (22%)

had von Willebrand disease (vWD) type 1, 1 (11%) had acute idiopathic thrombocytopenic purpura (ITP), and 6 (67%) had chronic thrombocytopenic purpura. Of these, 4 (44.4%) of them presented with menorrhagia for the first time, and a primary coagulation disorder (1 vWD type 1, 1 ITP and 2 chronic ITP) was diagnosed during the DUB work-up.

The mean initial and final hemoglobin concentrations of the DUB patients are summarized in Table II.

Two of the patients were diagnosed as vWD type 1 (1 had von Willebrand factor antigen value of 43% and blood group A [54-214%] and the other had von Willebrand factor antigen value of 30% and blood group AB [54-214%]). They were started on desmopressin therapy, and continued taking desmopressin during the menstrual period. Their bleeding periods were controlled with this therapy.

Discussion

Dysfunctional uterine bleeding (DUB) is defined as abnormal uterine bleeding without a structural pathology. Abnormal uterine bleeding can be seen at any age, and is especially frequent in adolescence⁹⁻¹¹. When an adolescent girl is admitted to the clinic for DUB, a detailed medical history is obtained, including gynecologic history, which should review the adolescent female's sexual development milestones, i.e., age of breast development, age of axillary and pubic hair growth, and age of menstrual onset. In the menstrual history, determining the nature of her menses (as patterned or unpatterned) is important. A detailed sexual history is important to identify pregnancy or even sexual abuse. Sexually active patients should undergo a pelvic examination. Contraception usage and history of sexually transmitted infections should also be queried. To exclude the pelvic pathologies, an abdominopelvic ultrasonography should be performed^{12,13}. A review of systems, a menstrual history of the patient's mother or sister, a family history for endocrinopathies and hematologic disorders (hypo-hyperthyroidism, PCOS, vWD), and a history of bleeding after surgery also provide important clues.

Studies report that adolescents presenting with menorrhagia have a 2-33% chance of having an underlying bleeding disorder¹⁴. Claessens and Cowell¹⁵ examined all admissions for menorrhagia (59 patients) at the children's hospital, and reported that 11 of them (19%) had coagulopathy. At Hacettepe University

Table I. Clinical Characteristics of the Patients with Dysfunctional Uterine Bleeding (n=36)

Parameter	
Number of patients with DUB	36
Age (year) of the patients	13.7 ± 1.4
Menarche (year) (mean ± standard deviation)	12.3 ± 1.0
Bleeding days (mean ± standard deviation)	17.3 ± 9.2
Initial hemoglobin (Hb) concentrations (g/dl)	11.0 ± 2.4
Final hemoglobin (Hb) concentrations (g/dl)	12.4 ± 1.1

İhsan Dođramacı Children's Hospital, Kanbur et al.⁵ examined 47 girls admitted for menorrhagia, from May 1999 to April 2002. In that study, a primary coagulation disorder was found in 3 (6%) of 47 patients (2 vWD, 1 factor XI deficiency). Over a 10-year period, Falcone et al.¹⁶ reported 61 patients with the diagnosis of DUB, and only 2 of them (3%) had hematologic disorders. Smith et al.¹⁷ reported a retrospective review of adolescents with menorrhagia (46 girls), and 15 (32.6%) of them had an underlying coagulopathy. Bevan et al.¹⁸ reviewed the medical records of adolescent girls with menorrhagia, aged between 10-19 years, over eight years, and they found that the girls who were admitted for heavy bleeding at menarche had underlying coagulopathies¹⁸. Therefore, girls with prolonged and heavy bleeding at menarche should be investigated for hematologic disorders¹⁹. In our study, 9 (25%) of our patients had a hematologic disorder, similar to the literature. Menorrhagia may be the only symptom of a bleeding disorder and clinicians should be aware of coagulopathy as a cause of abnormal uterine bleeding. Furthermore, the American College of Obstetricians and Gynecologists (ACOG) Committee suggested evaluation of bleeding disorders in girls under 18 years old presenting with abnormal uterine bleeding or menorrhagia^{20,21}.

The most common endocrinological cause of irregular bleeding periods in adolescence is PCOS¹⁰. The irregular bleedings in PCOS may be seen because of chronic anovulation¹¹.

Furthermore, it is known that thyroid hormones affect ovarian receptors and thus affect reproductive functions. Attia et al.²² reported a significant relationship between thyroid dysfunction and menstrual disorders.

In the literature, there are few randomized studies comparing the efficiency of hormonal therapy and other therapy methods in DUB. Fraser et al.²³ studied oral contraceptive pills, mefenamic acid, low-dose danazol, and naproxen in patients with DUB in 1991, but they could not find a significant relationship between groups. Mishell et al.²⁴ reported a significant decrease in bleeding patterns of patients receiving hormonal therapy. In our study, the initial hemoglobin concentrations of the patients were significantly increased with appropriate treatment. In addition, the 19 patients that received hormonal therapy had a statistically significant improvement in hemoglobin concentrations before and after therapy. Administration of iron therapy alone or hormone plus iron therapy revealed no significant hemoglobin concentration increases before or after the therapy. This could be because of the inadequate patient number.

The most common coagulopathy found in adolescents with excessive menstrual bleeding is vWD, and it affects 1% of the population^{3,20}. It is known that high-dose nasal desmopressin preparations can stop excessive and prolonged menstrual bleedings²⁵. Two of our patients were diagnosed with vWD type 1; these patients received intravenous desmopressin

Table II. Initial and Final Hemoglobin Concentrations of DUB Patients

	Number (%)	Initial Hb (g/dl) (mean ± standard deviation)	Final Hb (g/dl) (mean ± standard deviation)	
*Iron therapy only	8 (22.2%)	10.3 ± 3.1	12.0 ± 1.5	p=0.122
*Hormonal therapy only	8 (22.2%)	12.4 ± 1.7	12.6 ± 1.3	p=0.892
Hormonal + iron therapy	11 (30.6%)	9.5 ± 2.2	12.4 ± 1.0	p=0.122
No therapy	9 (25%)	12.2 ± 1.0	12.7 ± 0.8	p=0.122

*One patient who received iron therapy and 1 who received hormonal therapy also received desmopressin therapy.

therapy during their menstrual periods, and their bleeding was controlled with this therapy. Management of DUB in adolescents is based on careful evaluation of underlying conditions and the severity of the anemia. Controlling the hemodynamic instability and regulation of menstrual bleeding are the immediate management goals. Then, to stabilize the endometrium and to replace the iron stores, the clinician should also locate the origin of the bleeding, identify any organic causes, and classify whether the bleeding is ovulatory or not.

Menarche is a milestone in an adolescent's life transiting from childhood to puberty. Excessive and prolonged bleeding is not only a gynecologic but also a social problem in this period. The adolescent with DUB and her family should be informed about this condition and should be given both medical and psychological counseling.

Education of medical staff about menstrual disorders of adolescents and increasing the awareness that coagulopathies must be considered in the differential diagnosis of menorrhagia will help to prevent a delay in diagnosis.

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