

Abnormal Uterine Bleeding in Adolescents: Diagnosis and Management

Adolesanlarda Anormal Uterin Kanama: Tanı ve Yönetim

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ÖZET

Anormal uterin kanama (AUK) adolesan dönemde sağlık kuruluşlarına başvurunun sık görülen nedenlerinden biridir. AUK etyolojisinde birçok neden görülebilir, adolesanlar arasında en sık rastlanılan sebep disfonksiyonel uterin kanamadır (DUK). Bütün nedenler dışlandığında görülen kanama DUK olarak isimlendirilmektedir. Hipotalamo-pitüiter-ovaryan aksın immatüresine bağlı anovulasyon, perimenarşal yıllarda en sık görülen nedendir. Menoraji nedeni ile başvuran adolesanda, kanama diatezleri, özellikle de von Willebrand hastalığı daima akılda tutulmalıdır. Hastanın değerlendirilmesi ilk olarak detaylı bir anamnez, tam fizik muayene ve tam kan sayımı, koagülasyon parametreleri, serum gebelik testi ve hormon profilini içeren laboratuvar testleri ile başlamalıdır. Tedavi kanamanın şiddetine göre değişmektedir. Hafif kanamalarda hasta ve ailesinin bilgilendirilmesi yeterli olurken, orta ve şiddetli kanamalarda medikal tedavi gerekmektedir. Kombine oral kontraseptifler, progestojenler, non-steroidal anti-inflamatuar ajanlar, anti-fibrinolitik ajanlar ve GnRH analogları tedavide kullanılan ajanlardır. Anemi varlığında demir replasmanı da gerekmektedir.

Anahtar Kelimeler: Anormal uterin kanama, kanama diatezi, adolesan

ABSTRACT

Abnormal uterine bleeding (AUB) is a frequent cause of visits to health care provider during adolescent period. Although many etiologies cause AUB, the most likely cause among adolescents are dysfunctional uterine bleeding (DUB). Any kind of bleeding when all possible causes are excluded is termed as DUB. Anovulation due to immaturity of the hypothalamic-pituitary-ovarian axis is the leading cause during perimenarchal years. Bleeding disorders especially von Willebrand disease should always be kept in mind while evaluating an adolescent presenting with menorrhagia. Initial evaluation of the patient starts with detailed clinical history, complete physical examination and followed by laboratory tests which includes complete blood count, coagulation profile, serum pregnancy test and hormonal evaluation if indicated. Treatment depends on the severity of bleeding. Management in mild cases consist of reassurance of adolescent and her parents. Moderate and severe cases of DUB usually require medical treatment. Treatment options are combined oral contraceptives (COCs), progestogens, non-steroidal anti-inflammatory drugs (NSAIDs), anti-fibrinolytic agents and GnRH analogues. Iron supplementation is usually required in case of anemia.

Keywords: Abnormal uterine bleeding, bleeding disorder, adolescent.

Introduction

Adolescence is defined by World Health Organization as a transitional stage between childhood and adulthood from the age of 10 to 19 years. It represents a critical developmental period in the life span that tremendous growth and changes occur. It is one of the most dynamic stages of human growth and is second only to infancy in the rate of developmental changes that take place which both the physiological changes and developmental disorders represents a great challenge to teens and their families. Abnormal uterine bleeding (AUB) is one of

the most frequent gynecologic complaints of adolescents as well as a frequent cause of visits to health care providers in the course of this time period(1,2). AUB refers to cases of irregular, heavy bleeding or bleeding occurs outside of normal cyclic menstruation. It is caused by a number of genital and nongenital tract diseases, medical illnesses or medications (Table I). But the most common cause of AUB among otherwise healthy adolescents is dysfunctional uterine bleeding (DUB). DUB describes any kind of abnormal bleeding pattern that is not attributable to any structural or systemic disease. It is a diagnosis of exclusion and is due to the immaturity of hypothalamic-pituitary-ovarian (HPO) axis which results in anovulatory and unpredictable bleeding.

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In the USA, the definition of DUB refers to anovulatory bleeding (4), while the European Society of Human Reproduction and Embryology (ESHRE) defined DUB as excessive bleeding (heavy, frequent or prolonged) of uterine origin, which is not due to demonstrable pelvic disease, complication of pregnancy or systemic disease (3). According to this definition DUB can be either ovulatory or anovulatory.

Table I. Causes of abnormal uterine bleeding in adolescents.

Endocrine
<ul style="list-style-type: none"> • Thyroid disorder • Hyperprolactinemi • Polycystic ovary syndrome • Adrenal disease • Ovarian failure
Coagulopathies
<ul style="list-style-type: none"> • Von Willebrand disease • Thrombocytopenia • Platelet dysfunction • Factor deficiencies
Genital tract pathologies
<ul style="list-style-type: none"> • Ovarian cysts or tumors • Endometriosis • Endometritis • Pelvic inflammatory disease • Submucous myoma • Endometrial polyp • Congenital anomalies • Cervical polyps • Cervicitis • Vaginitis
Pregnancy related conditions
<ul style="list-style-type: none"> • Threatened, spontaneous, incomplete or missed abortion • Ectopic pregnancy • Retained products of conception
Trauma
<ul style="list-style-type: none"> • Sexual abuse • Laseration • Foreign body
Systemic disease
<ul style="list-style-type: none"> • Diabetes mellitus • Renal disease • Systemic lupus erythematosus
Medications
<ul style="list-style-type: none"> • Anticoagulants • Hormones • Antipsychotics • Platelet inhibitors

Other

- Excessive exercise
- Eating disorders
- Stress

Menarche, which is the major landmark of puberty, usually occurs between 12 and 13 years across well-nourished populations in developed countries (4). The average length of normal cycle varies between 21 to 35 days, usually lasting three to seven days. The median blood loss at each menstrual cycle is estimated to be 35 ml, ranging from 10 to 80 ml (2). Early menstrual life is characterized by anovulatory cycles due to immaturity of HPO axis (5,6). Many adolescents report irregular cycles for 2 to 3 years after menarche. The time required to establish regular ovulatory cycles is related to time since menarche and age at menarche (7,8). Early menarche was associated with early onset of ovulatory cycles. In girls who begin to menstruate at less than 12.0, between 12.0 and 12.9, and more than or equal to 13.0 years, 50% of the cycles become ovulatory by 1, 3, and 4.5 year from menarche respectively (7).

In normal menstrual cycles, endometrial glands and spiral arteries respond to rising estradiol (E2) from growing follicles and the process of endometrial healing and growth begins. The positive feedback effect of E2 on luteinizing hormone (LH) results in LH surge and ovulation. This feedback mechanism in anovulatory DUB is not working properly due to the absence of midcycle LH surge. Only estrogen is produced by follicles but not progesterone. As a result, in an estrogen primed endometrium, lack of progesterone stabilization causes disorderly endometrial shedding (2,6). In ovulatory bleeding, disruption of balance between vasoconstrictor (PGF_{2α}) and vasodilatory (PGE₂, PGI₂) prostoglandins was also demonstrated (9).

Besides DUB, it should always be kept in mind that bleeding disorders come to the attention of a gynecologist when menarche is anticipated. Inherited bleeding disorders should be considered in differential diagnosis of all adolescent girls presenting with menorrhagia. It is difficult to estimate the prevalence of bleeding disorders in young population as most studies have focused on severe cases. The prevalence of menorrhagia in women who have von Willebrand disease (VWD) ranges from 32% to 100% in reports (10). With respect to the other bleeding disorders, the prevalence in women with severe platelet dysfunction as Bernard-Soulier syndrome and Glanzmann's thrombasthenia has been reported to be 51% and 98% respectively (11,12).

Evaluation

Initial evaluation of adolescent with abnormal uterine bleeding should start with history and physical examination. The history should be taken with and without a parent. Adolescent girl may prefer to be alone especially if they're sexually active. The history should focus on menstrual history including menarche, timing, duration and quantity of bleeding and the pattern of abnormal bleeding episodes. Sexual history regarding contraception, number of partners, sexually transmitted infections, previous pregnancy or abortion or whether the adolescent has a history of sexual abuse should also be discussed with her. Also systemic diseases, recent or past medications and family history should also be taken into consideration.

Abnormal bleeding patterns in adolescents may be classified as excessive menstrual bleeding, irregular bleeding, amenorrhea or acute bleeding episode due to anatomic defects or medicines (13). Recognition of bleeding pattern may help to determine the etiology. Cyclic excessive bleeding, menorrhagia, which is defined as bleeding lasts more than 7 days and more than 80 ml blood loss, is usually a sign of bleeding disorders, mostly von Willebrand disease (VWD) or may suggest an uterine pathology (14). Intercycle bleeding may raise the suspicion of cervical disease or endometrial/cervical infection with Chlamydia trachomatis and Neisseria gonorrhoeae especially in sexually active teenagers. Noncyclic bleeding is mostly caused by anovulation, which may be due to strenuous exercise, eating disorders, stress or endocrinopathies like diabetes mellitus, hypo or hyperthyroidism, polycystic ovary syndrome.

It should always be kept in mind that pregnancy and its complications may present with any abnormal bleeding pattern. So it's very important to rule out pregnancy first in adolescent girls with unexplained bleeding who had regular cycles previously.

General and pelvic examination may give important clues about the etiology. Clinical examination should begin with vital signs. The signs of hemodynamic instability should be assessed especially in patients with prolonged and heavy bleeding. Measurement of weight, height, assessment of thyroid gland for enlargement and other pathologies, evaluation for androgen excess (hirsutism, acne, balding), examination of breast development, examination of skin for acanthosis nigricans, petechia, bruising should be included. External genital examination should focus on the detection of conditions in differential diagnosis of abnormal bleeding like clitoromegaly, pubertal hair development, signs of perineal or vulvar trauma or lesions. Pelvic examination is important in assessment of genital organs especially in patients with severe bleeding. But this examination may be traumatic in girls who are not sexually active. When digital pelvic examination is uncomfortable, rectoabdominal examination may be helpful (15). Pelvic examination may be deferred until after a medical therapy trial. Examination under general anesthesia is rarely indicated if medical treatment is ineffective or appropriate diagnosis cannot be established despite pelvic imaging.

Pelvic ultrasonography is indicated when pelvic examination is limited or structural abnormalities are suspected.

Laboratory studies should start with a pregnancy test, complete blood count including hemoglobin, and hematocrit with platelet count. If a bleeding diathesis is suspected or in case of severe bleeding, prothrombin time, partial thromboplastin time, bleeding time, screening tests for platelet function should be added. Blood samples for von Willebrand panel should be drawn before hormonal therapy is started as estrogen increases the concentration of von Willebrand factor (16). If an endocrine disorder is suspected, measurement of thyroid stimulating hormone (TSH), prolactin (PRL), total and free testosterone, dehydroepiandrosterone sulphate (DHEA-S), follicle stimulating hormone (FSH) and luteinizing hormone (LH) may help to determine the etiology. If bleeding is so severe to cause volume depletion in adolescent, blood should be obtained for cross-matching. Cultures from vaginal discharge and urethral meatus should be taken if pelvic infection is suspected (2).

Management

Treatment of AUB in adolescents depends on underlying etiology and severity of the bleeding episode. The aim of treatment should be the restoration of hemodynamic stability with correction of anemia initially,

than restoration of normal menstrual cycle and prevention of long term consequences. Additional evaluation and consultation should be obtained in protracted bleeding cases. (17).

In all adolescent girls presenting with AUB, pregnancy should be excluded before any treatment is started. Hemodynamic instability and iron deficiency anemia should be corrected immediately. If underlying etiology is defined, appropriate treatment permits the return of normal menstrual cycles usually. When all etiologic causes are excluded, diagnosis of DUB is made and hormonal treatment for anovulatory bleeding is started. The goal of the hormonal treatment is to stabilize the endometrial proliferation and maintain a synchronized shedding. More than 90 % of patients with DUB will respond to hormonal treatment, if not alternative diagnosis like bleeding diathesis or uterine pathologies should be considered (18).

Management of the patients with DUB falls into three categories.

Mild dysfunctional uterine bleeding (DUB): Menstrual period is longer or intervals between cycles are shorter than normal. Observation and reassurance of the adolescent girl and her family is usually sufficient (6,15). Keeping a menstrual calendar, and a reevaluation after three to six months is enough. Hemoglobin concentrations are usually higher than 12 g/dL in mild DUB, but iron supplementation (60 mg/day elemental iron) can be given to treat mild anemia cases. NSAID's may help to decrease menstrual flow (2,19).

Moderate DUB: Menses are prolonged and menstrual intervals are shortened. A mild anemia (hemoglobin 10 to 12 g/dL) is usually present (6,20). Hormonal treatment to stabilize endometrium and iron supplementation for anemia is needed for treatment if the patient is not actively bleeding at present. Low dose oral contraceptives (OCPs) or cyclic progestogen are the treatment of choice for these patients. Medroxyprogesterone acetate 10 mg/day or norethindrone acetate 5 mg/day for 10 to 12 days for each month will stabilize the endometrium and prevent the action of unopposed estrogen (6,21). Micronised oral progesterone 200 mg is another option in women susceptible to pregnancy, but the patient should be warned against drowsiness as a side effect.

If patient has a complaint of active bleeding, monophasic oral contraceptive pills containing a minimum of 30 mcg ethinyl estradiol should be used to prevent breakthrough bleeding. OCPs 3 or 4 times daily is taken until bleeding stops (usually within 48 hours), then tapered to two pills daily for 4 days and then one pill daily to complete 21 days (2,17). As high doses of estrogen may cause nausea, antiemetic therapy is required before each dose (2, 5). Hormonal therapy is continued for three to six months and the adolescent will be evaluated at the end of this period. If the regular menstrual pattern is established, hormonal therapy can be discontinued (18). If not, a detailed endocrine evaluation is needed.

Severe DUB: Heavy bleeding that causes a decrease in hemoglobin level below 10 g/dL is usually considered as severe DUB. If the patient is presented with hemodynamic instability, low hemoglobin concentrations (below 7 g/dL) or symptomatic anemia, hospitalization is required (22, 23). Need for blood transfusion should be assessed on a case-by-case basis (20). Blood samples must be taken from these patients to exclude underlying bleeding disorder before starting hormone therapy.

OCPs containing high dose estrogen is the first-line therapy in severe DUB. OCPs with 50 mcg estradiol and 0,5 mg norgestrel or 50 mcg estradiol and 1 mg norethindrone administered every four hour until the bleeding slows. The dose is tapered and the pills are administered four

times per day for four days, three times per day for three days, then two times per day for two weeks. Antiemetics therapy may be required as high dose estrogen is administered. When high dose estrogen is contraindicated, alternative progesterone treatment may be tried. High dose progestin therapy may be used in the treatment of acute severe DUB if the endometrial thickness is normal. It should be kept in mind that prolonged uterine bleeding results in thin endometrial lining in which estrogen will rapidly initiate endometrial proliferation while progesterone is unlikely to control bleeding in this circumstances. Norethindrone acetate (5-10 mg) or micronized progesterone (200 mg) is given every four hours until the bleeding stops. When the bleeding stops the dose was tapered, the progesterone pills are administered four times per day for four days, then three times per day for three days, then two times per day for two weeks. In patients with hemodynamic instability who are unable to take oral medications, intravenous conjugated equine estrogen may be necessary. 25 mg intravenous conjugated equine estrogen is given every four to six hours until the bleeding stops. Due to pulmonary embolism as a potential serious complication, no more than 6 doses should be administered (24). The bleeding is usually controlled in 4 to 24 hours (22). Antiemetics should be administered one hour before each dose. When the bleeding subsides, the patient should switch to high dose OCP treatment. If bleeding persists after 24 to 48 hours, hemostatic therapy should be considered (25). Hemostatic agents are as follows:

- Aminocaproic acid: It is given in doses of 5 gr orally in the first hour followed by 1-1,25 g per hour or 4-5 g intravenous followed by 1 g/hour until the bleeding stops (maximum 8 hours).
- Tranexamic acid: It's a lysergic acid derivative which reversibly block lysine binding sites on plasminogen and prevent fibrin degradation. Administration of 1-1,5 gr tranexamic acid 3-4 times a day reduces menstrual blood loss by 35-60 % (26).
- Desmopressin: It is a synthetic analog of arginine-vasopressin. Treatment results in a rapid increase in von Willebrand factor and factor VIII lasting about 6-12 hours (27).

Dilatation and curettage is reserved for patients who had protracted bleeding despite adequate hormonal treatment (2).

In extreme cases like bone marrow transplantation or anticoagulant therapies with high INR values, gonadotrophin-releasing hormone agonist may be necessary to induce amenorrhea, in which add-back therapy is important in long term therapy to prevent bone loss (5).

Summary

AUB is one of the most frequent gynecological complaints of adolescents that brings them to the physician. DUB is the most frequent cause of AUB which is caused by immaturity of hypothalamic-pituitary-ovarian axis. Continuous production of estrogen results in endometrial proliferation that's not stabilized by progesterone. As a result endometrial shedding occurs in a disordered pattern. In adolescent age group, a special consideration should also be given to bleeding disorders, especially VWD, in patients who present with menorrhagia. Adolescent may come to attention of gynecologist first when the menarche is anticipated. After a detailed history and physical examination, appropriate laboratory tests should be done. Treatment depends on the cause and the severity of the bleeding. Combined oral contraceptive, progestins, NSAID's, antifibrinolytics and GnRH analogs are the most frequent drugs that are used in treatment.

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