

## Abnormal Uterine Bleeding in Adolescent

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### Abstract

Abnormal uterine bleeding (AUB) is a frequent cause of visits to health care provider during adolescent period. Heavy menstrual bleeding is the most frequent clinical presentation of AUB. This condition particularly worrisome in this group not only when it occurs at menarche, but also anytime afterward when bleeding lasts longer than 7 days, blood loss is greater than 80 mL per cycle, or other warning signs that indicate a history of heavy bleeding such as anemia. Careful history and examination can help elucidate the best next steps for workup and management. The primary goal of treatment is prevention of hemodynamic instability. Therefore, assessing the severity and cause of bleeding is important. Therapeutic approach in the acute period should be established according to the degree of anemia and amount of flow. Treatment options for medical care of AUB generally include hormonal, nonhormonal and surgery. Additionally, long-term management with hormonal therapy in patients with severe uterine bleeding is known to be safe for developing HPO axis.

**Keyword:** Abnormal uterine bleeding, adolescents, heavy menstrual bleeding

## Perdarahan Uterus Abnormal pada Remaja

### Abstrak

Perdarahan uterus abnormal (PUA) sering menjadi penyebab kunjungan ke penyedia layanan kesehatan selama masa remaja. Perdarahan menstruasi yang berat adalah gambaran klinis yang paling sering dari AUB. Kondisi ini sangat mengkhawatirkan para remaja yang terjadi bukan hanya saat menarche, tetapi juga bila perdarahan berlangsung lebih dari 7 hari, kehilangan darah lebih dari 80 mL per siklus, atau gejala lain yang menunjukkan riwayat perdarahan berat seperti anemia. Anamnesa dan pemeriksaan yang cermat dapat membantu menentukan langkah selanjutnya untuk pemeriksaan lanjutan dan penatalaksanaan. Tujuan utama penatalaksanaan adalah untuk mencegah ketidakstabilan hemodinamik. Oleh karena itu, menilai tingkat keparahan dan penyebab perdarahan sangat penting. Pendekatan terapeutik pada periode akut harus disesuaikan dengan derajat anemia dan jumlah perdarahan. Pilihan pengobatan untuk perawatan medis pada PUA umumnya termasuk hormonal, nonhormonal dan pembedahan. Selain itu, manajemen jangka panjang dengan terapi hormonal pada pasien dengan perdarahan uterus yang parah diketahui aman untuk perkembangan aksis HPO.

**Kata kunci:** Perdarahan uterus abnormal, remaja, menstruasi berat

## Introduction

Adolescents have frequent menstrual problems such as irregular menses, painful cycles and prolonged or heavy menstrual bleeding (HMB).<sup>1</sup> Menstrual disorders are among the most common complaints of adolescents. This is in part because adolescents and their families often have difficulty understanding what normal cycles or patterns of bleeding are and in part because there is considerable menstrual cycle variability in the adolescent years.<sup>2</sup> Also, some adolescents maybe unaware that their bleedings patterns are abnormal, as menstrual cycles are known to often be irregular during adolescence.<sup>3</sup>

Abnormal uterine bleeding (AUB) is defined as bleeding from uterine corpus that is abnormal in duration, volume, frequency and/or regularity. Due to immaturity of the hypothalamic-pituitary-ovarian (HPO) axis, AUB is common in adolescents.<sup>3</sup> It may impact physical, emotional sexual and professional aspects of the lives of adolescents, impairing their quality of life. In cases of acute and severe bleeding, adolescents may need urgent treatment with volumetric replacement and prescription of hemostatic substances. In some specific cases with more intense and prolonged bleeding, surgical treatment may be necessary.<sup>2,3</sup>

Although the management of this problem has evolved over time, the most important goal remains to alleviate the anxiety of both affected girls and their families and to identify the underlying medical conditions that may have chronic health effects for these girls. In this paper, the most common causes of AUB will be discussed and current management will be reviewed.<sup>1</sup>

## Normal Menstrual Cycle in Adolescents

Menarche, which is a major landmark of female puberty, usually occurs within 2 to 3 years of the first appearance of breast budding

or pubic hair.<sup>4</sup> However, this period can feature individual and racial variances related to genetic and socio-economic factors.<sup>5</sup>

The average age of menarche has remained stable at approximately 12–13 years over the past 80 years in well-nourished populations in developed countries. Irregular cycles occur most frequently within the first 2–3 years after menarche.<sup>6</sup>

The time required for HPO axis maturation following menarche, which is thought to result in ovulatory cycles and subsequent regular bleeding, varies between six months and three years. Due to ovulatory dysfunction, in the following months after menarche, irregular and unpredictable, heavy and prolonged, and, rarely, skipped menses for less than three months may occur. Thus perception of “normal” menstrual cycle may vary in these girls and their families. As in adults, menstrual cycles are between 21 and 34 days, last for seven days or fewer, with an average blood loss of 30–40 mL, requiring the use of 3 to 6 pads or tampons per day or 10 to 15 soaked pads or tampons per cycle.<sup>1,3</sup>

## Abnomal Uterine Bleeding

The International Federation of Gynecology and Obstetrics (FIGO) recommends the use of the term AUB to describe any aberration of menstrual volume, regulation, duration and/or frequency in a woman who is not pregnant. FIGO also proposes to discard some definitions from accepted terminology, such as “menorrhagia”, “metrorrhagia”, “hyper/hypomenorrhea”, “polymenorrhea” and “dysfunctional uterine bleeding” as they are controversial, confusing and poorly defined.<sup>3,7</sup>

The system further separates the causes of AUB into structural and nonstructural etiologies. Structural causes (polyps, adenomyosis, leiomyomas, malignancies [PALM]) are rare in adolescents, constituting only about 1.3% of AUB in this population.<sup>8</sup>

Nonstructural causes (coagulopathies, ovulatory disorders, endometrial disorders, iatrogenic, not yet classified [COEIN]) are more prevalent in the adolescent population, with ovulatory dysfunction being the most prevalent. Ovulatory dysfunction due to an immature hypothalamic-pituitary-ovarian axis occurs in up to 95% of adolescents with AUB.<sup>6</sup>

Abnormal Uterine Bleeding might also be classified as acute or chronic. Acute AUB refers to an episode of heavy bleeding which is sufficient in quantity to require immediate intervention to prevent further blood loss. Abnormalities in quantity, regularity and/or timing in the last six months may all be defined as chronic AUB.<sup>1</sup>

### **Incidence**

Abnormal uterine bleeding affects 3–20% of reproductive-aged females, with a higher incidence in adolescence.<sup>7</sup> Heavy menstrual bleeding is the most frequent symptom. In a population-based study of 1,000 healthy Swedish adolescents, 73% reported menstrual problems and 37% reported heavy menstrual bleeding. Other population-based studies have reported that 12.1% and 17.9% of adolescents experienced heavy menstrual bleeding in Nigeria and Hong Kong, respectively.<sup>6,9</sup>

### **Diagnosis**

Abnormal Uterine Bleeding in adolescents is a challenging and often neglected problem. Cycle to cycle variability, differences in menstrual hygiene, the wide variety of menstrual hygiene pads or tampons available, inconsistency in giving information about menstrual regularity and bleeding amounts make initial assessment of AUB even more difficult in these girls. The focus of initial evaluation of a patient with HMB is to determine whether the bleeding is acute and

causing hemodynamic instability, through careful history taking, physical examination, laboratory testing and radiologic imaging.<sup>1,3</sup>

History taking should be taken both with and without the parents being present because some of the questions asked would be difficult for patients to answer candidly in the presence of their parents, especially those relating to sexual activity, while asking with the parents present may help to clarify the details in some cases.<sup>3</sup> An accurate history of patient's cycles is the main issue for diagnosis, to determine if her experiences are normal or abnormal. Questions about cycle characteristics, such as cycle length, duration between cycles, pain and premenstrual symptoms (e.g. abdominal swelling and breast tenderness), should be asked, and, to ensure a clear interpretation of symptoms, the patient should keep a menstrual diary. The amount of bleeding can be evaluated by asking the patient about the number of pads used daily and the duration of bleeding.<sup>3</sup> After providing a suitable conversation environment, sexual activity should be questioned. Pregnancy and its related complications should also be part of the initial investigation in girls presenting with AUB.<sup>1,3</sup>

Bleeding disorders, which cause 20-33% of cases of prolonged and/or severe bleeding, should always be taken into consideration. Family history of bleeding disorders should be obtained, in addition to assessing for easy bruising or gum bleeding. Up to 20% of adolescents with heavy menstrual bleeding have subsequently been found to have a bleeding disorder.<sup>6</sup> Excessive bleeding during menarche can usually indicate an underlying bleeding disorder, while regular but excessive bleeding may also be indicative of bleeding disorders. Additionally, patients should be queried as to whether they have a history of recurrent nasal bleeding, easy bruising, symptomatic anaemia or prolonged bleeding after surgery or tooth extraction. Von Willebrand disease, platelet function

defects, thrombocytopenia and clotting factor deficiencies are the most common bleeding disorders in adolescent girls that present with heavy menstrual bleeding.<sup>1,5</sup>

The physical examination should start with an evaluation of haemodynamics and anaemia signs, it should focus on signs of acute blood loss and the etiology of bleeding. While tachycardia and orthostatic hypotension may be the only signs of severe anemia. Young patients will not present with clinical signs, despite severe anemia.<sup>1,5</sup>

A vaginal/cervical examination may be required to determine the source of the bleeding in certain patients. However, since adolescents do not tolerate this examination well, its necessity should therefore be evaluated carefully in cases of patients who are not sexually active, are at the beginning of the gynaecological maturation process, have no pelvic pain and whose history does not suggest genital-tract trauma, the presence of a foreign body, or sexual abuse.<sup>5</sup> While the presence of bruises and petechiae on the skin may indicate an underlying coagulation disorders, pallor may be seen due to anemia. In adolescents who are sexually active, trauma, foreign body, structural causes and pelvic inflammatory diseases can be investigated by pelvic and bimanual examination.<sup>3</sup>

Initial evaluation of adolescents presenting with acute AUB should include screening for pregnancy, anemia, bleeding disorders, iron deficiency and thyroid disease. Complete blood count, blood type, cross match and pregnancy test should be first line tests. In addition, partial thromboplastin time, prothrombin time, activated partial thromboplastin time and fibrinogen level are the initial evaluation for disorders of hemostasis. All adolescents with abnormal initial test or positive screening results for disorders of hemostasis should be evaluated by assessment of von Willebrand-ristocetin cofactor activity, von Willebrand antigen and factor VIII for diagnosis of von Willebrand

disease and other coagulopathies.<sup>10,11</sup>

If patient's history or physical examination findings are suggestive of PCOS, testosterone (free/total), DHEAS and prolactin should be evaluated. Sexually active adolescents should be screened for *Neisseria gonorrhoea* and *Chlamydia trachomatis* infections with nucleic acid amplification tests.<sup>1</sup>

Routine pelvic imaging is considered unnecessary since structural etiologies are rarely seen in this group. However, in the girls who do not respond to initial treatment, transabdominal ultrasonography may be more appropriate than transvaginal ultrasonography. An examination of the structure of the uterine cavity, ovaries and endometrial thickness can be seen via pelvic ultrasonography (USG).<sup>1</sup>

## Management

Most adolescents need outpatient management and reassurance that their menstrual cycles would become cyclic and ovulatory over time. However, treatment is required when AUB causes anemia or impairs quality of life. In these girls, the first line treatment is generally medical. Surgical options should be reserved for girls who can't be managed by medical treatment.<sup>1</sup> In the acute management of patients with AUB, the primary aim is to ensure haemodynamic stability and, if possible, to stop the bleeding.<sup>5</sup>

A clinical decision should be made regarding intravenous crystalloid and blood or blood product transfusions, hormone treatment, and iron replacement, according to the severity of bleeding, clinical condition of the patient, hemodynamic stability and the underlying medical problem. If an underlying cause can be identified, appropriate specific treatment should be given.<sup>1,5</sup>

Four main categories of treatment are administered based on bleeding severity, haemodynamic status and the patient's

haemoglobin level.<sup>5</sup>

### **Mild/Moderate Bleeding (Hb > 12 g/dL)**

Girls with light or mild bleeding, indicated by normal Hb concentrations, should be reassured that observation is sufficient, unless there is an impairment of quality of life. NSAIDs can be used to reduce the amount of bleeding.<sup>1</sup> If bleeding persists or becomes more severe, re-evaluation of the patient is required. The patient should be followed up at 3-month intervals and should be instructed to keep a menstrual-cycle diary.<sup>5</sup>

### **Moderate Bleeding (Hb 10–12 g/dL)**

Oral contraceptives or oral progesterone can be prescribed for treatment. Monophasic oral contraceptive pills (OCPs) containing 30–35 µg ethinyl oestradiol should be prescribed; for the first 5 days, the patient should take two pills a day. When the bleeding stops, the dose should be tapered to single pill daily over the course of a few days, and this regimen should be continued for 3–6 months. Progesterone-only pills can also be used for treatment and are preferred in cases where oestrogen use is contraindicated.<sup>1,12</sup>

Available progesterone therapies are oral medroxyprogesterone acetate (10 mg/day), micronized oral progesterone (200 mg/day) or norethindrone acetate (2.5–5 mg/day), which should be given for 12 days in every cycle. To replenish iron stores, iron supplements should be prescribed for at least 6 months. NSAIDs can be added to the treatment.<sup>5</sup>

### **Severe Bleeding, Haemodynamically Stable (Hb = 8–10 g/dL)**

The use of OCPs, an approach that is similar to that for patients with moderate bleeding, is indicated if the family and the patient can comply with the treatment plan and follow-

up. If there is no decrease in the severity of the bleeding following the first two doses of OCP treatment, the dose should be increased to three to 4 pills per day for 2 days; this dosage should be continued as needed until the bleeding stops. The OCP treatment is continued at a dose of 4 pills per day for 4 days and then one pill per day for a minimum of 3–6 months. Close monitoring is important, and iron supplements should be prescribed.<sup>5</sup>

### **Severe Bleeding (Hb ≤ 7 g/dL) or Haemodynamically Unstable**

Hospitalization is necessary for patients who are hemodynamically unstable with low Hb concentration (<7 mg/dL), or who have symptomatic anemia.<sup>2,5</sup> The need for blood transfusion should be individualized, and it should be administered as deemed necessary by the clinician based on the patient's initial blood count, amount of bleeding, and any other comorbidities. Bleeding disorders must be eliminated before starting hormonal treatment.<sup>2</sup>

The first treatment of choice is to prescribe OCPs containing high doses of oestrogen (35–50 µg ethinyl oestradiol) because OCPs promote rapid endometrial regrowth to cover denuded epithelial surfaces.

The treatment with high-dose oestrogen is continued at 6-hour intervals until the severity of the bleeding decreases. The dose is then decreased within 1 week as follows: one pill every 6 hours for 2 days, then every 8 hours for 2 days, then every 12 hours for 2 days and finally 1 pill daily for a minimum of 6 months. However, in cases where the bleeding is controlled with 50 µg high-dose ethinyl oestradiol-containing pills, these are continued for about one or two cycles at the same dose (50 µg ethinyl oestradiol); the treatment is then continued for three to six months with 35 µg ethinyl oestradiol-containing pills.<sup>3</sup>

Intravenous (IV) conjugated oestrogen

treatment (25 mg at intervals of 4-6 hours) may be considered for patients who cannot tolerate high-dose oral oestrogen therapy, if oral treatment is not possible due to a loss of consciousness or if the severity of bleeding does not decrease within 6-12 hours despite high-dose oral oestrogen.<sup>3,5</sup>

The use of conjugated oestrogen treatment for more than 24 hours is not recommended due to potential side-effects (e.g. pulmonary embolism); the treatment is therefore continued with high doses of OCPs.<sup>3,5</sup>

The bleeding is usually controlled within 24 hours with OCP treatment. If the bleeding continues for more than 24-48 hours without any decrease in severity, the addition of haemostatic agents and surgery should be considered.<sup>3,5</sup>

High-dose progesterone is an alternative treatment choice in patients with severe bleeding, especially when the use of oestrogen is contraindicated. The progesterone reverses endometrial proliferation related to long-term estrogen exposure and induces endometrial maturation. Medroxyprogesterone acetate (MPA, 20-40 mg) or norethindrone acetate (NETA, 5-10 mg) are administered three times per day for 7 days (7). For patients who have been given high doses of oral MPA, the median time before the cessation of bleeding has been shown to be 3 days.<sup>3</sup>

Another recommended treatment for acute HMB is depot-MPA (150 mg), administered intramuscularly and followed by MPA (20 mg) orally, every 8 hours for 9 doses. When the bleeding stops, the progesterone dose is decreased to every 12 hours for 2 weeks. Thereafter, therapy is maintained with the cyclic use of MPA (10 mg/d) and NETA (5 mg/d) for 12 days per month and between the same dates in every month.<sup>1</sup>

Since daily, monthly and quarterly use of some formulas can be difficult for adolescents the LNG-IUD may be preferred. The LNG-

IUD releases 20 mcg of levonorgestrel daily, resulting, through several mechanisms, in endometrial atrophy with reduced bleeding.<sup>1</sup> The LNG-IUD is active for up to five years after being placed in the uterine cavity.

Additional benefits of the LNG-IUD are highly effective contraception, higher continuation rates and higher satisfaction rates when used for bleeding control compared with OCP in an adolescent population. In adolescents with bleeding disorders, the LNG-IUD has been demonstrated to be effective in controlling menstrual bleeding.<sup>1,5</sup>

### **Non-hormonal Treatments**

The non-hormonal treatment of AUB includes the use of antifibrinolytics or non-steroidal anti-inflammatory drugs (NSAIDs). It is particularly indicated for those who do not wish to use hormones or who have contraindications to use them, and those who want to get pregnant.<sup>1</sup>

### **Tranexamic Acid**

Tranexamic acid, a lysine derivative, is bound to lysine in its fibrinogen structure. Tranexamic acid prevents the destruction of fibrin and decreases bleeding by 30-55%. The recommended dose and duration are 3-4 doses of 1-1.5 g/d orally or 10 mg/kg intravenously (maximum 600 mg/dose) per day for 5 days.<sup>5,13</sup>

### **Non-steroidal Anti-inflammatory Drugs**

Non-steroidal Anti-inflammatory Drugs decrease bleeding by preventing prostacyclin formation. It has been reported that the circulating total prostaglandin levels of females with menorrhagia are high and that bleeding can be decreased only with NSAIDs in these patients.<sup>13</sup> However, until a work-up has been completed, adolescents with HMB and a possible history of bleeding disorders

should be instructed to avoid NSAIDs due to decreased platelet aggregation by inhibiting thromboxane A2 synthesis.<sup>14</sup>

The recommended usage for mefenamic acid is 500 mg/dose at intervals of 3-5 hours on the first day and a 250mg or 500mg dose 3 to 4 times per day thereafter. The recommended dose for naproxen is 500-550 mg at intervals of 3-5 hours on the first day and 250-275 mg 4 times per day, while ibuprofen is recommended at 600-1200 mg/d following the start of menstrual bleeding.<sup>5</sup>

### **Desmopressin**

Desmopressin is a synthetic analogue of arginine-vasopressin. It is used to control and to prevent bleeding episodes in patients with a coagulation disorder. Desmopressin increases the vWF and FVIII levels, as well as platelet adhesion, and its effects last for about 6 hours.<sup>5</sup> The literature contains various recommendations regarding dose and duration of desmopressin use. However, bleeding control is generally ensured in 80-92% of patients who take desmopressin nasally, 300 µg/d, divided into 2 or 3 doses in the first 2-3 days of the cycle.<sup>5</sup>

Desmopressin combined with tranexamic acid is recommended as a good treatment option for adolescents who do not want hormone treatment. Possible side effects due to the vasomotor and antidiuretic effects are headache, mild tachycardia, hyponatremia and, rarely, water intoxication.<sup>3,5</sup>

### **Surgical Treatment**

Medical therapy is, no question, the first line in the adolescent population, because maintaining fertility is paramount.<sup>6</sup> More than 90% of the severe bleeding that occurs in adolescents is controlled with medical treatment. However, surgery is required in the event of life-threatening bleeding, when medical treatment is unsuccessful and in

situations where a histopathology evaluation is needed. Dilatation and curettage, uterine artery embolization, endometrial ablation and hysterectomy are surgical treatment options. The decision to proceed with surgical treatment should be made after taking into account the fertility desire of the patient. Mechanical methods, such as the use of Foley catheter balloons, have also been shown to be useful for bleeding control.<sup>5,13</sup>

### **Follow-up and long-term care**

After treatment is initiated, patients should be seen at regular intervals to ensure that their bleeding profile has improved to their satisfaction and that they are tolerating any medicines that may have been started. Long-term management depends on the anemia and the desire for contraception. Most experts recommend continuing hormonal therapy for at least 6 months. After therapy is discontinued, the patient should still be followed to ensure regulation of menstruation.<sup>2</sup>

### **Conclusion**

In conclusion, AUB is an important clinical condition commonly encountered in the adolescent age group. It decreases the quality of life and is worrisome for both the patient and family. Girls with AUB should be evaluated with care and a wide differential diagnosis should be borne in mind. During the acute period of bleeding management, the treatment should be determined while considering the cause and severity of the bleeding. While evaluations to determine the cause should be completed, treatments that will rapidly restore haemodynamic stability should be administered via an algorithm for patients with severe bleeding. Medical therapy is usually an effective and sufficient treatment. With respect to long-term treatment and/or follow-up, hormonal treatments can be

safely used with adolescents; moreover, they have positive effects on school performance and on the social activities of this group by decreasing the number and severity of bleeding episodes without damaging the hormonal axis during the maturation process. Generally, adolescents respond well to therapy. Hematology consultation, imaging methods and clinical intervention should be considered in patients who do not respond to treatment.

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