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# **Review Article**

# Abnormal uterine bleeding in adolescence

# Sunita Samal<sup>1\*</sup>, Ashwini Vishalakshi<sup>2</sup>

<sup>1</sup>Department of Obstetrics and Gynecology, SRM MCH and RC, Kattankullathur, Chennai, Tamil Nadu, India

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# \*Correspondence: Dr. Sunita Samal,

E-mail: sunitasonesh@gmail.com

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### **ABSTRACT**

Abnormal uterine bleeding (AUB), which is defined as excessively heavy, prolonged and/or frequent bleeding of uterine origin, is a frequent cause of visits to the Emergency Department and/or health care provider. While there are many etiologies of AUB, the one most likely among otherwise healthy adolescents is dysfunctional uterine bleeding (DUB), which is characterizing any AUB when all possible underlying pathologic causes have been previously excluded. The most common cause of DUB in adolescence is anovulation, which is very frequent in the first 2-3 post-menarchal years and is associated with immaturity of the hypothalamic-pituitary-ovarian axis. Management of AUB is based on the underlying etiology and the severity of the bleeding and primary goals are prevention of complications, such as anemia and reestablishment of regular cyclical bleeding, while the management of DUB can in part be directed by the amount of flow, the degree of associated anemia, as well as patient and family comfort with different treatment modalities. Treatment options for DUB are: combined oral contraceptives (COCs), progestogens, non-steroidal anti-inflammatory drugs (NSAIDs), tranexamic acid (anti-fibrinolytic), GnRH analogues, Danazol and Levonorgestrel releasing intra uterine system (LNG IUS).

Keywords: Adolescence, AUB

### INTRODUCTION

World health organization (WHO) defines adolescence as the age between 10 and 19 years and is a transitional stage between childhood and adulthood during which significant physical and mental changes occur. Menstruation is a normal part of adolescence, but when there is excessive uterine bleeding, it can be associated with significant morbidity. These menstrual disorders are among the most frequent gynaecologic complaints in adolescents. The American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Pediatrics (AAP) strongly recommend for routine assessment of patterns of menstrual bleeding in all adolescent girls in order to identify possible pathology and to improve their quality of life.<sup>1</sup>

### Definition

Abnormal uterine bleeding (AUB) is defined as a significant alteration in the pattern or volume of menstrual blood flow, may be caused by a number of genital and non-genital tract diseases, systemic disorders, and some medications. Heavy menstrual bleeding (HMB) and heavy and prolonged menstrual bleeding are now the more accepted terminology for excessive menstrual blood loss; intermenstrual bleeding is the preferred term for bleeding in between periods. These terms are better understood by patients and may be used in place of the more ambiguous menorrhagia and menometrorrhagia, respectively.<sup>2</sup> HMB is used to refer to both heavy and prolonged menstrual bleeding.

<sup>&</sup>lt;sup>2</sup>Department of Obstetrics and Gynecology, MGMC and RI, Puducherry, India

Menarche typically occurs 2-3 years after thelarche at tanner four stage of breast development. During the first gynaecologic year mean cycle interval is 32-34 days, varying typically from 21-45 days. Early menstrual life is characterized by anovulatory cycles and is associated with immaturity of the hypothalamic-pituitary-ovarian axis. Moreover, the frequency of ovulation is related to both time since menarche and age at menarche. Early menarche is associated with early onset of ovulatory cycles. Long anovulatory cycles occur most often in the first 3 years following menarche. By the third year after menarche, 60-80% of menstrual cycles are 21-34days long, like adults. An individual's normal cycle length is established around the sixth gynaecologic year, at chronologic age of approximately 19-20 years.<sup>3</sup> A joint AAP-ACOG committee, after reviewing epidemiologic studies of menstrual cycles in adolescents, has defined the normal parameters of menstrual cycles in young females (Table 1).

Table 1: Normal menstrual cycles in adolescent girls.

Menarche (median age)	12.43 years
Mean cycle interval	32.2d in first gynaecologic years
Menstrual cycle interval	Typically, 21-45 days
Menstrual flow length	<7 days
Menstrual product use	3-6 pads or tampons/day

#### REVIEW OF MENSTRUAL PHYSIOLOGY

The normal menstrual cycle, characterized by sequential growth, maturation, and eventual shedding of the endometrium, is produced by the cyclic release of estrogen and progesterone from the ovary. An understanding of the normal cyclic fluctuations of the two gonadotropins (ie, luteinizing hormone [LH] and folliclestimulating hormone [FSH]) and the primary female reproductive hormones (i.e., estrogen and progesterone) helps in clarifying the derangements associated with anovulation. The ovaries produce estrogen under the influence of follicle-stimulating hormone (FSH) secreted by the anterior pituitary gland, which, in turn, stimulates endometrial growth and also stimulates follicular development in the ovary, and ultimately resulting in a dominant follicle. The mid cycle surge of luteinizing hormone (LH) triggers ovulation, following which the remnant follicle becomes the corpus luteum. Progesterone, secreted by the corpus luteum, has combined immunologic, anatomic, and haemostatic effects on the endometrium. Degeneration of the corpus luteum leads to fall in progesterone levels, and this progesterone withdrawal triggers the next menstrual cycle, typically 14 days after ovulation.

Within the hypothalamic-pituitary-ovarian (HPO) axis, complex feedback mechanisms influence and control these processes. Until the HPO axis matures, anovulatory

cycles persist. Anovulation results in chronic exposure of the endometrium to unopposed action of estrogen without the benefit of cyclic exposure to progesterone. Endometrium thus becomes abnormally thickened and structurally incompetent resulting in asynchronous shedding unaccompanied by vasoconstriction. These vessels are also fragile and permeable and become unstable resulting in the classic anovulatory uterine bleeding seen in the early adolescence. Bleeding is heavy as blood has not been lysed by the endometrial enzymes, blood clots are often passed resulting in menstrual cramps. This anovulation, caused by immaturity of the HPO axis, is the most common cause of AUB in adolescents. The transition from anovulatory cycles to ovulatory cycles takes place when there is gradual maturation of the hypothalamic-pituitary-ovarian axis characterized by positive feedback mechanisms in which a rising estrogen level triggers a surge of luteinising hormone from the anterior pituitary and this LH surge results in ovulation.

# CAUSES FOR ABNORMAL UTERINE BLEEDING IN ADOLESCENTS

Once the bleeding is defined as being abnormal, the acronym PALM-COEIN is popularly used now a days to categorize the causes; Polyp, Adenomyosis, Leiomyoma, Malignancy, Coagulopathy, Ovulatory dysfunction, Endometrial, Iatrogenic, not otherwise classified (Table 2). The PALM causes are usually structural but COEIN are non-structural. While there are numerous etiologies for abnormal bleeding in the adolescent, anovulatory bleeding is the most common cause due to immaturity of the HPO axis in the absence of any organic pathology or persistent hormonal aberration. Moreover, AUB due to anovulation and coagulation defects occurs at disproportionately higher rates in adolescence as compared with older women. Even though rare, pregnancy and sexually transmitted diseases and sexual abuse should not be ignored in this population and also should be considered in any sexually active adolescent, particularly when pain is a presenting feature, because anovulatory bleeding is usually painless.

Polycystic ovary syndrome (PCOS), a common cause of anovulatory bleeding, may be suggested by the presence of obesity, hirsutism, acne. Common medications, including hormonal contraceptive pills and selective serotonin reuptake inhibitors, may cause alterations in menstrual bleeding. HPO axis may get affected by systemic illnesses such as eating disorders (anorexia nervosa or bullemia) or inflammatory bowel disease, causing anovulatory bleeding. Structural causes of HMB such as polyps, leiomyoma or vascular malformations occur rarely in adolescents, but may be considered in those who are refractory to treatment as anticipated.

Severe bleeding disorders may manifest in early childhood in the form of HMB as the presenting symptom. Von Willebrand disease, platelet storage pool

deficiencies and other platelet function disorders, connective tissue disorders such as Ehlers-Danlos syndrome (EDS), thrombocytopenia, haemophilia carrier, and clotting factor deficiencies each may lead to HMB., The prevalence of Von Willebrand disease, and platelet

dysfunction may be as high as 36% and 44% respectively among adolescents with HMB.<sup>5</sup> A positive response to screening questions is highly indicative of the presence of a bleeding disorder in adult women with HMB (Table 3).<sup>6</sup>

Table 2: Causes for abnormal uterine bleeding in adolescents.

Anovulation	Physiologic		
	Androgen excess	PCOS, hyperandrogenic state, congenital adrenal hyperplasia, Cushing's syndrome, ovarian adrenal tumors	
	Systemic diseases	Hypothyroidism, hyperprolactinemia, renal disease, liver disease, diabetes mellitus, chronic illness	
	Eating disorders	Anorexia nervosa, bullemia	
	Primary ovarian	Ovarian insufficiency, premature ovarian failure, ovarian tumors	
	Drugs	Glucocorticoids, reserpine, antipsychotic drugs	
	Others	Stress, excessive physical exercise	
Bleeding disorders		Coagulopathy, hereditary bleeding disorders, von willibrand's disease, disorders of platelet function, disorders of fibrinolysis, acquired bleeding abnormalities, ITTP, leukemia, aplastic anemia, anticoagulation therapy	
Pregnancy related complications			
Iatrogenic I		Hormonal contraceptives, exogenous progestins	

Table 3: History suggestive of bleeding disorder.

Whom to screen?		
1-	Duration of bleeding >7days or impairment of	
	daily activities in most of the cycle	
2-	History of treatment of anaemia	
3-	Family history of bleeding disorder	
4-	Excessive bleeding with tooth extraction, surgery,	
	or child birth/miscarriage	

### **EVALUATION**

# History

When an adolescent present with the complaint of AUB, she should be asked detailed questions about her menstrual history, including the age of menarche and the menstrual frequency, regularity, duration and volume of flow. The presence of cramping and/or clots can be useful information as well. A menstrual calendar can be useful for documenting the bleeding pattern and response to treatment. Symptoms of anemia suggest significant bleeding. Sexual history is a must. Associated symptoms abdominal pain, bladder symptoms, bowel symptoms, weight gain/ loss should be noted. Drug history must be taken. Quantifying blood loss is challenging because adolescents have a limited frame of reference for "normal" menstrual flow, and menstrual product use reflects both amount of flow and personal preference for frequency of pad or tampon changes.

In girls reporting heavy periods, one should assess for other evidence of abnormal mucocutaneous bleeding, such as easy bruising, prolonged bleeding after minor injuries, epistaxis that is frequent or difficult to control, or excessive bleeding after surgical procedures, like tonsillectomy or a tooth extraction.<sup>5</sup>

A careful family history of both gynaecologic bleeding (including postpartum bleeding) and non-gynaecologic bleeding is important when assessing for a inheritable bleeding disorder. A history of joint dislocation or subluxation may suggest EDS. Further history should include an history of medication use, including recent history of hormone contraceptive pills. A history of genital trauma or surgery, including pregnancy termination, should be obtained. A sexual history is critical, with an assessment of current pregnancy risk and STI risk.

# Physical examination

A comprehensive physical examination should be performed, which in most cases will be normal. Tachycardia and hypotension may signal acute hemodynamic instability and the need for rapid intervention. The presence of tachycardia, pallor, or a heart murmur suggests anemia. Petechiae or excessive bruising may suggest a platelet defect or another bleeding disorder. Girls with PCOS may have obesity, acne, hirsutism, and acanthosis nigricans. Any palpable pelvic mass should be further evaluated, and ultrasound may be sufficient to evaluate the pelvic pathology. A musculoskeletal examination should be performed, with specific attention to joint hypermobility, suggesting EDS. Visual inspection of the genitalia is necessary for diagnosis in most patients. A sexually active patient may

need a complete pelvic examination (speculum and bimanual exams), particularly if it is associated with pain, if her heavy bleeding represents an acute change from her previous pattern, or if she fails to respond to treatment.

# Investigations

The adolescents with abnormal vaginal bleeding should be evaluated initially with basic blood investigations and ultrasonography. A screening haemoglobin may be sufficient to rule out anemia. A complete blood count with white blood cell differential and platelet count should be obtained in patients whose history and physical findings suggest HMB and anemia.

Further evaluation should be guided by the history and examination findings. Pregnancy complications should be ruled out by pregnancy test. ACOG recommends that all patients younger than 18 years who present with abnormal uterine bleeding be screened for coagulation disorders, particularly Von Willebrand disease, as this disorder has a prevalence of 1% and is one of the common disorder that causes menorrhagia at menarche.<sup>1,7</sup>

Screening for such disorders should include a partial thromboplastin time, prothrombin time, and assessment of platelet function, plasma von Willebrand factor (VWF) antigen, and plasma VWF activity (ristocetin cofactor activity). Exogenous estrogen has been shown to increase VWF levels.<sup>8</sup> Patients with a partial VWF deficiency who are already on estrogen therapies (such as a combination oral contraceptive pill) may therefore have normal VWF activity measurements. It may be reasonable, if clinical suspicion is high, to discontinue estrogen therapy for several weeks and repeat VWF levels.

Sexually active adolescents should be tested for pregnancy and STIs, including gonorrhoea and chlamydia, which can cause endometritis, cervical friability, and bleeding. As well, in any patient with abnormal uterine bleeding, thyroid function tests should be considered, as this can be a common cause of abnormal uterine bleeding.

In patients with headaches or nipple discharge, prolactin testing is mandatory. In those with signs of polycystic ovary syndrome or insulin resistance, laboratory testing including testosterone, insulin, and glucose levels should be done. Evaluating the adrenal glands to look for abnormalities in suspected cases may be done as well.

#### **MANAGEMENT**

Most of the adolescents with AUB have anovulatory bleeding because of the HPO-axis immaturity which is self-limited and resolves once the HPO axis matures. Therefore, they are managed supportively till then. Supportive management should include anemia prevention and psychological counselling. After other diagnoses have been ruled out, the management of HMB

can occur as an outpatient in the majority of cases. Occasionally, however, hospitalization is required due to hemodynamic instability. The primary measure is to decrease the flow and improve the regularity of cycles. This can be accomplished by hormonal or non-hormonal treatment. The goal is to achieve synchronous endometrial shedding at regular intervals. Non-hormonal treatment can be used as first line management to reduce the amount of bleeding. Regularity of the cycles is achieved by hormonal treatment.

#### Non-hormonal treatment

It includes, prostaglandin syntheses inhibitors, antifibrinolytics, ethamsylate.

#### 1-Prostaglandin syntheses inhibitors

Fenamates are used most commonly as compared to other prostaglandin syntheses inhibitors as in addition to inhibition of prostaglandin synthases enzyme they also bind and inhibit the prostaglandin receptors and improve endometrial hemostasis. Hence, they are more effective in reducing blood loss (more than 25-40%) and these beneficial effects of mefenamic acid on menstrual blood loss and pain relief persists for several months (Table 4).

Table 4: 1-Prostaglandin syntheses inhibitors.

Mefenamic acid	500mg TID fro 5 days	
Naproxen	550mg on first day, then 275mg daily	
Ibuprofen	600mg daily throughout menses	
Flurbiprofen	ofen 100mg BD for 5 days	
Meclofenamate	100mg TID for 3 days	

# 2-Tranexamic acid

It acts by reversibly blocking lysine binding sites on plasminogen. The resulting decreased plasmin levels diminish fibrinolytic activity within endometrial vessels to prevent bleeding. It has no effect on other blood coagulation parameters such as platelet count, aPTT, and PT.<sup>9</sup> It is a used as first line drug as it is effective and reduces the mean blood loss by40-50%. It requires to be administered only during the menstrual cycle and has minor side effects, predominantly gastrointestinal which is dose dependant. A known complication that has limited its use is from increased systemic thrombotic activity. It is given as 500mg -1gm 6<sup>th</sup> hrly for 5 days beginning with menses.

#### 3-Ethamsylate

The mechanism of action of this drug is by increasing platelet adhesiveness and aggregation and improving the vascular stability. It had not been widely used because of its inconsistent efficacy.

#### Hormonal treatment

Abnormal bleeding in adolescents can present in various different ways as listed below.<sup>10</sup>

- Frequent cycles
- Anovulatory cycles with prolonged period of amenorrhea
- Ovulatory AUB with excessive bleeding
- Anovulatory AUB
- Acute severe bleeding

Treatment of AUB is based on the severity and duration of bleeding. If haemoglobin is normal and the periods are only slightly varying from normal she can be reassured and seen every 3 months. She has to keep a menstrual diary which can be reviewed at each visit. Most will achieve regular periods by 2-3 years.

Adolescents in whom bleeding occurs frequently (every 2-3 weeks) and the haemoglobin is normal or slightly below normal have to be treated with medroxyprogesterone acetate 10mg for 14 days starting from day 16 to day 28. Progestogens have an endometrial suppressive effect resulting in small depleted glands lined with a thin epithelium and decidualised transformation of the stroma. Organized sloughing occurs on withdrawal of the drug.

Patients with prolonged amenorrhea or oligomenorrhea followed by episodes of abnormally heavy bleeding may be given medroxyprogesterone acetate 10mg once daily for 5-7days once in 2-3 months to initiate bleeding and prevent abnormal endometrial shedding. It also acts as an excellent cycle regulator since it allows spontaneous menses to occur in between treatment. Iron supplements should be prescribed.

Ovulatory AUB respond well to NSAIDs but low dose short duration therapy with progestogens during the luteal phase is ineffective in reducing the menstrual loss in ovulatory AUB. These group of patients responds to treatment when progestogens are given from day 5-26 each cycle.

Anovulatory AUB can be treated with progestogens alone or oral contraceptive pills (OCPs). There is a paucity of data from randomized trials regarding the treatment of HMB in adolescents. Nonetheless, there are a variety of regimens that appear to be equally effective. Patients who have complaints of heavier bleeding may have a better response to OCPs that have a combination of estrogen and progestin rather than to progestin-only preparations, as estrogen provides hemostasis and promotes rapid endometrial growth to cover the denuded surfaces. They also cause endometrial atrophy thereby reducing the amount of endometrial prostaglandin synthesis and fibrinolysis. Thus, one option is to use monophasic contraceptive pills in the traditional fashion of 1tab per day. Another regimen states that OC pills can be taken 3

times per day until the bleeding ceases (usually within 48 hours), then tapered to twice daily for 5 days, and then decreased to once daily to complete 21 days of hormone therapy.<sup>11</sup> They decrease blood loss by up to 50%. OCP should be given for 3-6 cycles before re-evaluation. Alternatively, extended regimen may be prescribed, such as levonorgestrel 0.15mg/ethinyl estradiol 30µg 84/7ee, in which 84 days of combination hormone pills are followed by 7 days of low-dose estrogen. Although extended regimen may lead to fewer scheduled bleeds and faster recovery from anemia, breakthrough bleeding is a common adverse effect during the first several months of use and which may not often have tolerated by adolescents, particularly those who are using the medication exclusively for cycle control as opposed to contraception. Progestin-only therapy is an alternative for girls with moderate bleeding who cannot tolerate or have contraindication estrogen therapy. to medroxyprogesterone 10mg may be used daily in a continuous fashion or in a cyclic pattern of 10 to 12 days monthly. Depot medroxyprogesterone acetate (DMPA) 150mg, given as an intramuscular injection every 3months, may be more appropriate for patients needing pregnancy prevention. Although amenorrhea is a common adverse effect of DMPA, in some adolescents it causes prolonged or erratic bleeding, limiting its use in this population. The levonorgestrel intrauterine system (LNG-IUS), however, is generally associated with a significant reduction in menstrual blood flow for most users (many of whom become completely amenorrhoeic), including women with bleeding disorders. 12 But its use in nulliparous adolescents who do not need contraception is off label, but it can be effective in the mature adolescent who can tolerate the insertion procedure.<sup>13</sup>

Adolescents who are actively and heavily bleeding must be admitted. Hemodynamic stabilization should be done with administration of intravenous fluids and blood transfusion. 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. For patients who can tolerate oral intake, therapy typically includes a monophasic combination OC pill with 50µg estradiol and 0.5mg norgestrel (eg, Ovral, Ogestrel) or 50µg estradiol and 1mg norethindrone (eg, Ovcon 50), administered according to various schedules. A common schedule is to take it 4 times a day until bleeding is controlled, then taper to 3 times daily for 3 days, and then to twice daily to complete a 21day course of pills.<sup>14</sup> Then the patient starts a new pack of pills (without using the placebo pills). For patients who can take oral medications but in whom estrogen is contraindicated (eg. those with thromboembolic disease, estrogen-dependent tumours, or hepatic disease), a progestin such as norethindrone acetate (5 to 10mg daily) or micronized progesterone (200mg before bedtime) can be used. In patients who need intravenous treatment, conjugated equine estrogen (Premarin) may be used. In cases of severe bleeding unresponsive to 24 hours of hormonal therapy or in those with platelet dysfunction, nonhormonal haemostatic drugs may be used. These include the antifibrinolytic compounds, tranexamic acid or aminocaproic acid, or desmopressin, which is classically used for the treatment of von Willebrand disease. Treatment is continued for approximately 8 hours or until the bleeding has been controlled. Once the bleeding has been controlled and the patient can tolerate

oral intake, she should be changed to oral hormonal therapy for maintenance of any regimen.

Other agents that can be used for adolescent AUB as second line are danazole, gestrinone and GnRH analogues. They are used sparingly only when other options have failed or when estrogen-progesterone hormonal therapy is contraindicated.

<b>Table 5: Treatment summary</b>
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Group	Hb	Management		
1	>12g/dl	Reassurance, Menstrual calendar, Iron supplement, Periodic re-evaluation		
2	10-12g/dl	Reassurance, Menstrual calendar, Iron supplement, Cyclic progestin therapy/ OCP Re-evaluation in 6 months		
	<10g/dl	No active bleeding A	ctive bleeding	
3		<ul><li>Explanation</li><li>Transfusion</li><li>Iron supplement</li><li>OCP</li></ul>	<ul> <li>Transfusion</li> <li>Fluid replacement</li> <li>Hormonal hemostasis- OCP/ intensive progesterone therapy</li> </ul>	
		• Re-evaluation at 6-12 months	• OCP for 6-12 months.	

# 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.

### CONCLUSION

Abnormal uterine bleeding is common but may significantly impair an adolescent's quality of life. Although it is often simply a reflection of HPO axis immaturity, a careful history and high index of suspicion may reveal an underlying bleeding disorder. In either case, many effective treatments are available.

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