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Expert consensus on issues related to abnormal uterine bleeding in adolescence

Xin Yang [1], Huina Su [1], Huiying Zhang,[2] Shan Deng[3]

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[1]Department of Obstetrics and Gynecology, Peking University People's Hospital, Beijing, China
[2]Department of Obstetrics and Gynecology, Tianjin Medical University General Hospital, Tianjin Key Laboratory of Female Reproductive Health and Eugenics, Tianjin, China
[3]Department of Obstetrics and Gynecology, Peking Union Medical College Hospital, Beijing, People's Republic of China

Correspondence to
Dr Xin Yang;
xinyang_2003@sina.com

INTRODUCTION

Abnormal uterine bleeding (AUB) is the most common reason adolescent females visit gynaecologists. From the onset of menarche, symptoms such as heavy menstrual bleeding (HMB) and/or prolonged menstruation can affect both physical and mental health, with potential lifelong impacts. Despite its prevalence, there are relatively few studies on AUB in adolescence, and China lacks relevant guidelines and consensus on the issue.

Adolescence is a critical developmental stage characterised by the immaturity of mental and physical development and the hypothalamus-pituitary-ovary (HPO) axis. Unlike AUB in adults, structural lesions are rare in adolescence. The most common form is AUB due to ovulatory dysfunction (AUB-O). Additionally, AUB is caused by coagulation-related diseases (AUB-coagulopathy (AUB-C)), including congenital coagulation factor deficiencies, which are also common. Based on these characteristics of adolescent AUB, this consensus focuses on the two predominant non-structural causes of AUB in adolescence, AUB-O and AUB-C. Based on domestic and international research, relevant guidelines and clinical practice experience, it is thoroughly discussed and formulated by a panel of experts.

The goal is to help physicians understand and manage AUB in adolescents, improving their quality of life and promoting reproductive health.

THE CLINICAL PROBLEM

DEFINITION OF ADOLESCENCE AND ADOLESCENCE AUB

Adolescence, defined by the WHO as ages 10–19, is a crucial stage of development from childhood to adulthood, marked by rapid physical, genital and endocrine maturation. This consensus recommends using the 'PALM-COEIN (Polyp, Adenomyosis, Leiomyoma, and Malignancy or Hyperplasia - Coagulopathy, Ovulatory dysfunction, Endometrial, Iatrogenic, and Not otherwise classified)' aetiology classification system,[1] commonly applied to AUB in adults, to define and classify adolescent AUB (abnormal uterine bleeding). Adolescent AUB refers to AUB originating from the uterine cavity in non-pregnant adolescents that deviates from normal menstruation in terms of frequency, regularity, volume or duration.

CLASSIFICATION OF ADOLESCENCE AUB

Classification by aetiology

While recommending the use of the 'PALM-COEIN' aetiology classification system, this consensus emphasises that AUB-O is the most common type in adolescence due to age-specific physiological characteristics. Approximately 95% of AUB-O cases are due to the immaturity of the HPO axis,[2] with the remaining cases caused by diseases such as polycystic ovary syndrome (PCOS) or hypothalamic dysfunction. Bleeding disorders (BDs), characterised by spontaneous or excessive bleeding from minor injuries, result from congenital, hereditary or acquired defects in haemostatic mechanisms (vessels, platelets, coagulation, anticoagulation and fibrinolysis). In gynaecology, BD typically presents as HMB without self-limitation or prolonged menstruation. In adolescent patients with HMB, AUB-C due to hereditary BD accounts for 21%–46%.[3 4] A 2024 systematic review and meta-analysis of 2770 adolescent patients with HMB found that among the 1216 patients with identified aetiologies, coagulation disorders, platelet abnormalities and anovulatory bleeding accounted for 35.9%, 11.5% and 43.2%, respectively.[5] Uterine structural lesions caused only 0.3%–1.3%[5 6] of adolescent AUB

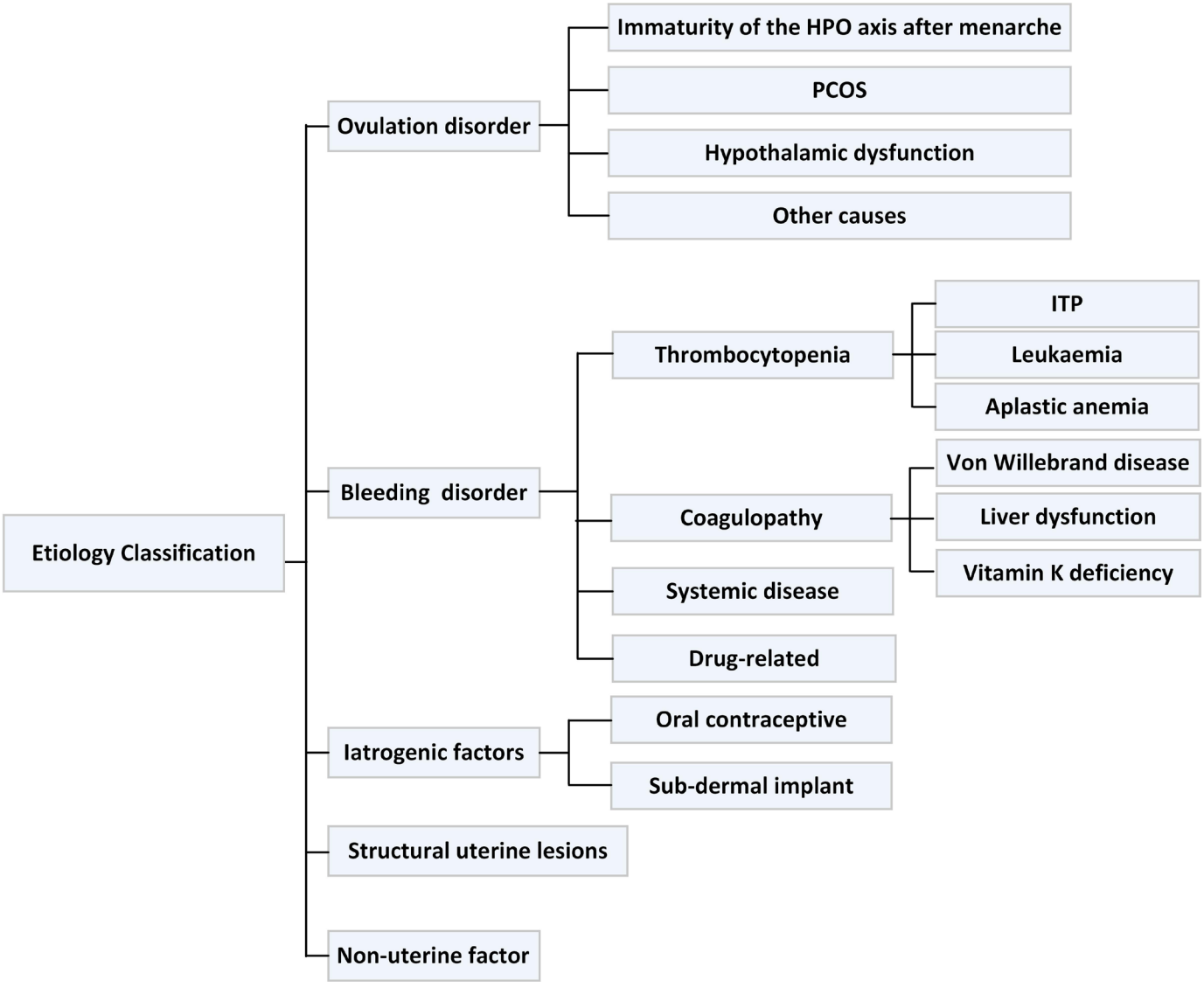

Figure 1 Etiological classification of adolescent abnormal uterine bleeding. Abbreviation: HPO, hypothalamic pituitary ovarian; PCOS, polycystic ovary syndrome; ITP, idiopathic thrombocytopenia

cases. However, they should still be considered in differential diagnoses, along with excluding pregnancy and bleeding from non-uterine factors such as genital trauma (figure 1).

Classification of abnormal bleeding patterns in AUB

AUB is categorised based on bleeding regularity, duration and volume (figure 2).

Amenorrhoea

Primary amenorrhoea is the absence of menstruation by age 15 or the absence of menstruation for more than 3 years after breast development, and secondary amenorrhoea is the cessation of menstruation for three cycles or more than 6 months after menarche.

Irregular bleeding

Unpredictable timing and amount. According to the '2023 International Evidence-Based PCOS Guidelines',[7] irregular menstruation and ovulatory disorders are irregular menstruation in the first year after menarche is considered a normal transitional phenomenon; abnormal if the menstrual cycle is <21 days or >45 days 1–3 years after menarche; abnormal if the cycle is <21 days or >35 days or <8 menstrual cycles per year, 3 years after menarche to perimenopause; and abnormal if any menstrual cycle is >90 days 1 year after menarche.

Heavy menstrual bleeding

Excessive menstrual blood loss is perceived by the patient as affecting their physical, social, emotional or material quality of life.[6 8]

Intermenstrual bleeding

Regular, predictable bleeding between menstrual periods, which can be random or occur at fixed times in each cycle. It can be classified by timing into follicular phase bleeding, periovulatory bleeding and luteal phase bleeding.

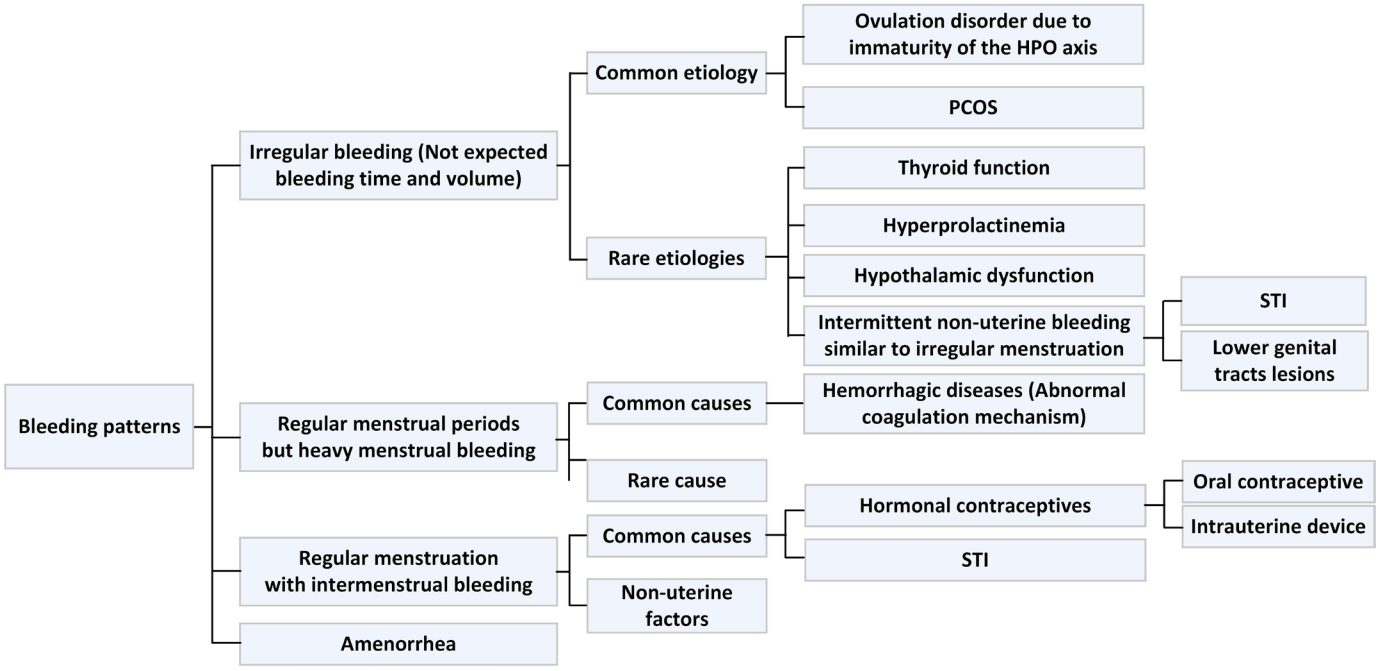

Figure 2 Classification of adolescent abnormal uterine bleeding according to the -etiology of bleeding patterns. Abbreviation: HPO, hypothalamic pituitary ovarian; PCOS: polycystic ovary syndrome; STI: sexually transmitted infection

Prolonged menstruation

Menstrual periods last more than 7 days.

Breakthrough bleeding: Unexpected uterine bleeding during the use of hormonal medications.

ASSESSMENT AND DIAGNOSIS OF ADOLESCENCE AUB

Assessment of bleeding urgency and severity

In evaluating adolescent patients with AUB, an important goal is to determine the severity of triage treatment alongside differential diagnosis through detailed history taking, physical examination and auxiliary tests.

Assessment of acute and chronic bleeding

1. *Chronic AUB* is defined as AUB with at least three episodes of abnormal bleeding in the past 6 months. It does not require emergency clinical treatment but needs standardised diagnosis and management.[1 3 8]
2. *Acute AUB* is characterised by severe, massive bleeding that necessitates emergency treatment to prevent further blood loss. It can occur in patients with or without a history of chronic AUB.

Assessment of bleeding severity

The severity of bleeding is determined by the amount of bleeding and haemoglobin (Hb) levels.[1 3 8] Acute AUB should first be evaluated for haemodynamic stability. Adolescents showing signs like tachycardia or hypotension should receive emergency treatment or hospitalisation. Once vital signs are stable, further evaluation of the bleeding cause and appropriate treatment is necessary.

1. *Assessment of HMB* is indicated by any of the following: needing to change sanitary napkins or tampons within 2 hours, using more than 21 sanitary napkins or tampons in one cycle, needing to change sanitary napkins or tampons at night, presence of blood clots larger than a one-yuan coin (25 mm in diameter and 1.85 mm in thickness), secondary anaemia and a total score of ≥100 on the Pictorial Blood Loss Assessment Chart.[9]
2. *Grading of bleeding severity*: Mild: prolonged menstrual period or shortened cycle lasting ≥2 months, with mild to moderate menstrual bleeding. Hb level is generally normal (≥120 g/L) or slightly lower (100–120 g/L).[10] Moderate: prolonged menstrual period or frequent menstruation (once every 1–3 weeks), with moderate to severe menstrual bleeding and Hb between 80 and 100 g/L.[11] Severe: heavy menstrual bleeding with or without unstable vital signs, Hb <80 g/L.[10 11]

Diagnosis and differential diagnosis

This consensus recommends that, through detailed medical history, physical examination and preliminary auxiliary tests, the bleeding pattern and severity can be preliminarily determined, distinguishing between acute and chronic bleeding. The cause of bleeding can be preliminarily diagnosed, and differential diagnosis can be made with related diseases. Further examinations should be conducted for suspected BDs or tumours to clarify the cause. Appropriate haemostatic and anaemia treatments should be administered.

Medical history

Detailed enquiries should cover growth and development, menarche, menstrual regularity, menstrual period, the presence of HMB, spontaneous bleeding spots and ecchymoses in other parts of the body, sexual history and

other endocrine disorders. Patients with HMB should be queried about their family history of BDs.

Physical examination

1. *General examination*: Check vital signs (including blood pressure and heart rate). Assess skin and mucous membrane colour for signs of excessive blood loss, bleeding spots, ecchymosis and other BD manifestations. Measure height and weight, evaluate breast development and check for short stature, obesity and hyperandrogenism (hirsutism and acne). Assess the thyroid gland for local enlargement.
2. *Gynaecological examination*: Evaluate the development of the vulva and the pubic hair distribution. Vaginal examination should be done only with patient and family consent in special cases. For those who are sexually active, perform a vaginal examination to identify the bleeding site and check for organic lesions in the vagina, cervix or pelvis. For those who are not sexually active, pelvic ultrasound should be the first-line imaging modality to assess for developmental abnormalities or masses in the vaginal, cervical or pelvic areas, as it is non-invasive and well-tolerated. If the ultrasound results are inconclusive or further evaluation is needed, a digital rectal examination may be considered, but it should be performed with caution and only when necessary.

Laboratory examination

1. Routine screening of complete blood count is recommended. Sexually active patients or those suspected of being pregnant should undergo blood or urine human chorionic gonadotropin tests to rule out pregnancy.
2. Patients with HMB should undergo initial screening of coagulation function, including tests for activated partial thromboplastin time, plasma prothrombin time, thrombin time and plasma fibrinogen levels. Furthermore, BD tests are recommended if the initial screening is abnormal (Appendix 1).
3. Reproductive hormones, including follicle-stimulating hormone (FSH), luteinising hormone (LH), androgens, oestrogens, prolactin, progesterone, thyroid function, adrenal function, liver and kidney function and serum ferritin levels, should be tested as appropriate.

Auxiliary examination

Transabdominal or transrectal ultrasound (transvaginal ultrasound can only be used if the patient is sexually active) to check for pelvic organic lesions and assess uterine and ovarian development. Hysteroscopy and fractional curettage should be considered only when drug treatment is ineffective or organic uterine lesions are suspected but not excluded. Units with the technology can perform corresponding vaginoscopic hysteroscopy examinations and obtain endometrial samples for pathological diagnosis.[12]

MANAGEMENT OF AUB IN ADOLESCENCE

The management goals include achieving emergency haemostasis and maintaining haemodynamic stability, correcting acute or chronic anaemia, restoring normal menstrual cycles, preventing recurrence and long-term complications, such as posthaemorrhagic anaemia and related complications, infertility associated with ovulatory disorders, endometrial hyperplasia or even cancer, abnormal glucose and lipid metabolism and bone loss or osteoporosis due to low oestrogen levels.

Treatment during the bleeding period

The first-line treatment for haemostasis in adolescence AUB is medication, including hormonal and non-hormonal haemostatic drugs, alone or in combination, based on bleeding severity. Hormonal haemostasis is central, and the medication regimen must be selected individually based on the pattern and amount of bleeding, volume of bleeding and severity of anaemia.

Mild AUB medical protocol

For patients with normal Hb levels, where bleeding does not significantly impact daily life, individualised treatment protocols should be determined based on patient and guardian preferences, as well as contraceptive needs. Options include short-term observation, symptomatic haemostasis or traditional Chinese medicine. Patients with Hb of 100–120 g/L can use the 'endometrial shedding method' with progestin alone, such as dydrogesterone 10–20 mg/day, micrograniulated progesterone capsule 200–300 mg/day, norethindrone 5 mg/day and medroxyprogesterone acetate 8–10 mg/day. These are typically used for 10–14 days. Alternatively, combined oral contraceptives (COCs) may be used.

Moderate to severe AUB medical protocol

Combined oral contraceptives

First-line treatment for acute bleeding in moderate to severe AUB. Use drugs containing 30–35 µg of ethinyl oestradiol, starting with one tablet every 8–12 hours. After 3–7 days of bleeding cessation, reduce the dose to 1 tablet every 12 hours. Tapering regimens vary, and doses of COCs should be maintained at the level needed to prevent bleeding until the Hb has increased to a level adequate for the patient to tolerate a potentially heavy withdrawal bleed.

Transition to 'adjusted cycle treatment' afterwards. If bleeding does not reduce significantly after 24 hours of COC, exclude BD, infection or uterine structural lesions. COC-related adverse reactions like nausea may reduce adherence to COC therapy. If necessary, antiemetic medications can be administered before each dose of COCs, such as 12.5–25 mg of promethazine orally or rectally or 4–8 mg of ondansetron orally.[13] Most adolescent women have completed rapid growth and reached at least 95% of their adult height by menarche, and using COCs will not affect their expected final adult height or reproductive function.[2 14 15] Ensure patients and parents understand

this to improve medication compliance. It is important to explain this to patients and their parents to improve adherence to the medication.

Progestins

Progestin therapy, also known as the 'endometrial atrophy method', is more applicable to patients with contraindications to COCs (eg, headache with focal neurological symptoms, systemic lupus erythematosus, arteriovenous thromboembolic disease, oestrogen-dependent tumours, acute viral hepatitis, cirrhosis or liver tumours and diabetes with renal, retinal or nervous system complications) or those intolerant or unwilling to take COCs.[16] Commonly used medications include the following. (1) Norethindrone has oestrogenic activity, which contributes to its rapid haemostatic effect. It is recommended internationally in several guidelines for emergency haemostasis in reproductive-age and adolescent HMB. The initial dose is typically 5 mg every 8 hours for 3–7 days until bleeding stops, then reduced to 5 mg every 12 hours for 3–7 days. If there is no breakthrough bleeding, the dose is further reduced to 5 mg once daily until anaemia improves. Withdrawal bleeding typically occurs 3–7 days after stopping the medication.[14 17] (2) Medroxyprogesterone acetate: initial dose of 10–20 mg every 8 hours, not exceeding 80 mg total daily dose, then reduced to 10–20 mg once daily after 3–7 days of use.

Emphasis: If bleeding does not significantly decrease after using the recommended high-efficiency progestin for more than 24 hours, exclude BD, infection or uterine structural lesions.

Oestrogen

High doses of oestrogen can quickly repair the endometrial surface to achieve haemostasis, referred to as the 'endometrial repair method'. This approach uses intramuscular injection of oestradiol benzoate (3–4 mg/day), divided two times per day to three times a day, to quickly repair endometrial wounds and stop bleeding. Gradually reduce dosage to 1–2 mg/day after bleeding cessation. When the general condition improves and Hb levels are normal or nearly normal, progesterone is added for 10–14 days before stopping. The dose and type of progestin used should follow the endometrial shedding method or switch to COC (one tablet daily) until normal Hb levels are achieved. Oral oestrogen preparations are slow to act and not recommended during acute AUB haemostasis.

Antifibrinolytic drugs

Both AUB-O and AUB-C are linked to the hyperactivity of the endometrial fibrinolytic system, and antifibrinolytic drugs can be used to halt bleeding. Tranexamic acid reduces menstrual volume by nearly 50%. For acute bleeding, intravenous injection (0.25–0.5 g/dose, with a total daily dose of 0.75–2 g) or oral administration (1–1.5 g/dose, 2–3 times daily) adjusted based on body weight may be administered. Aminocaproic acid (increases the risk of thromboembolism and is used with caution in renal insufficiency) may be administered intravenously (100–200 mg/kg every 4–6 hours, max 30 g/day) until the bleeding stops. Antifibrinolytic drugs can be used in combination with COCs. Current evidence does not indicate an increased risk of thrombosis with this combination.

Desmopressin or 1-desamino-8-D-arginine vasopressin (DDAVP)

Increases factor VIII and von Willebrand factor levels. Used in mild haemophilia A and type I von Willebrand disease to manage other BDs.[2 15] DDAVP is administered intranasally at a dose of 150 mg (body weight <50 kg) or 300 mg (body weight ≥50 kg) or subcutaneously or intravenously at a dose of 0.3 mg/kg. It is typically used in the first 3 days of severe menstrual bleeding, with adverse reactions mainly including water and sodium retention and hyponatraemia.[18] To avoid hyponatraemia, some fluid restriction following desmopressin administration is mandatory, and the concomitant administration of nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided.

Other treatments

Depending on primary disease and test results, supplement coagulation factor concentrates, fibrinogen, platelets, fresh freeze-dried plasma or fresh blood are needed. For patients receiving long-term platelet transfusions, the effect is poor due to autoantibody production. In such cases, recombinant factor VII can be used, which is effective but costly.

Recommended indications for hospitalisation

Patients with haemodynamic instability (including tachycardia and hypotension) require immediate intravenous rehydration, blood transfusion, plasma volume expansion and hormone therapy to control bleeding and stabilise haemodynamics.[14] Patients with Hb levels <70 g/L or <100 g/L with significant active bleeding and anaemia symptoms like fatigue and drowsiness necessitate hospitalisation for observation, intravenous rehydration, blood transfusion, plasma volume expansion and other treatments or surgical intervention.

Surgical treatment

Uterine balloon compression haemostasis

Uterine balloon tamponade is primarily indicated for patients experiencing severe bleeding that requires rapid haemostasis. This method is used while awaiting drug efficacy and can be applied after excluding significant organic uterine diseases, such as submucosal fibroids. An intrauterine Foley balloon can be placed for rapid, cost-effective haemostasis. Push saline (the amount varies depending on uterus size) into the Foley balloon until resistance is felt or mild abdominal pain. Leave for 12–48 hours and withdraw 1–2 mL of saline to shrink the balloon after the bleeding stops.[14 15]

Hysteroscopy and surgery

For adolescent patients with AUB suspected of having endometrial lesions, hysteroscopy and segmental curettage under anaesthesia can be performed to obtain endometrial samples for pathological diagnosis. It is important to note that excessive curettage can exacerbate bleeding, particularly in patients with BDs. If B-ultrasound reveals intrauterine blood clots or decidual casts, aspiration is recommended to remove the endometrial tissue, facilitating endometrial repair and a normal proliferative response.[2 15] For patients suspected of bleeding due to structural uterine abnormalities (eg, endometrial polyps and submucosal fibroids), timely hysteroscopy-guided biopsy, polyp removal or submucosal myoma removal for suspected uterine lesions causing bleeding is necessary. Consider vaginal endoscopy where feasible to preserve hymen integrity in young girls.

Recommendation: Drug treatment is the primary approach for adolescent AUB. Surgical options or endometrial pathology evaluation should be considered for refractory cases despite adequate drug therapy.

Correct anaemia

Oral or intravenous iron supplements may be used based on the severity of the iron deficiency. Recommended doses are as follows: oral iron supplements containing 60–150 mg of elemental iron (eg, ferrous sulphate 60 mg and polysaccharide iron complex 150 mg) 1–2 times per day. Iron supplementation should continue until the anaemia is alleviated, and an additional 3 months of supplementation is advised to build iron reserve. Monitor serum iron and ferritin levels for assessment.[19] Patients with aplastic anaemia or other conditions receiving frequent blood transfusions may require iron removal therapy due to iron overload.

Long-term management

Adjusting the menstrual cycle

It is challenging for adolescent patients with AUB with ovulatory disorders to establish regular menstrual cycles in the short term. Additionally, those with BD inherently have coagulation dysfunction. Hence, after acute haemostasis, ongoing medication is necessary to manage menstruation and prevent recurrence.

Progesterone alone

In this stage, near-physiological doses of progestins are primarily used, with a preference for natural progesterone or dydrogesterone. Maintenance treatment includes a full-cycle or second half-cycle scheme. After the Hb level normalises, the withdrawal bleeding after the first discontinuation of medication is typically pronounced and accompanied by dysmenorrhoea. Endometrial casts can be discharged from patients with thick endometrium. Regular medication can then improve the symptoms of HMB. (1) Second half-cycle medication: begin on day 15 of menstruation for 10–14 days. Recommended daily doses are similar to the endometrial shedding method of progesterone alone. Dydrogesterone does not inhibit the maturation and development of the HPO axis at daily doses of 10–20 mg. (2) Full cycle therapy: if excessive bleeding persists, use continuously for 20–22 days from day 5 of menstruation. The recommended daily doses are dydrogesterone 10–30 mg, norethindrone 5 mg and medroxyprogesterone acetate 4–10 mg.

Combined oral contraceptives

Low-dose oral contraceptives containing 20–30 µg of ethinyl oestradiol one tablet daily are given to patients needing contraception or with hyperandrogenism.

Sequential oestrogen-progestin therapy

If no withdrawal bleeding occurs after progestin treatment, a deficiency in endogenous oestrogen levels should be considered. In such cases, oestrogen-progestin therapy may be indicated (Appendix 3).

Recommendation: After bleeding control, continue medication for at least 3–6 months to manage menstruation.[20]

Reduce menstrual volume

Drugs for reducing menstrual volume include COC (1 tablet per day), progestogen drugs (same dosage as above), levonorgestrel-releasing intrauterine system (LNG-IUS), tranexamic acid and NSAIDs.

Combined oral contraceptives

COCs cause endometrial atrophy, thereby reducing menstrual volume. Besides being used cyclically, continuous use of COCs can help relieve dysmenorrhoea.

Levonorgestrel-releasing intrauterine system

For patients who have contraindications to COC use due to immune diseases like systemic lupus erythematosus leading to liver and kidney dysfunction and antiphospholipid syndrome and contraindications to COC use, patients who develop HMB due to congenital or secondary coagulation factor deficiency, platelet count and/or dysfunction but cannot take COC.[21] The LNG-IUS can be administered under intravenous anaesthesia and/or guided by vaginal endoscopy for the treatment of HMB in these patients.

Gonadotropin-releasing hormone (GnRH) analogue

GnRH analogues can induce temporary amenorrhoea and are mainly used as agonists; guidelines from many countries do not recommend their use for treating HMB or acute bleeding. Their use is limited to cases with precocious puberty, refractory AUB or severe anaemia requiring short-term amenorrhoea to improve anaemia while managing structural uterine abnormalities such as fibroids or adenomyosis.

Mifepristone

Mifepristone can induce amenorrhoea and is considered safe for up to 6 months of use.[22] Consider patients with HMB with uterine leiomyoma, patients with low platelet

count or those with contraindications to hormone therapy. Low-dose mifepristone 10–25 mg/day can be used for 3–6 months to prepare for further treatment.

Treatment of primary disease

For patients with BD and autoimmune diseases, the primary disease should be treated simultaneously.

Patient education

Most adolescent patients with AUB-O can improve their symptoms as they age, but they may also have persistent anovulation. Patients and their families should be educated on disease course, medication necessity and the precautions to take. By maximising adherence to treatment and long-term management, optimal therapeutic outcomes can be achieved. For patients with congenital coagulation factor deficiencies and other BDs, menstrual management should commence from menarche through menopause. Emphasise cooperation with treatment for optimal therapeutic outcomes, especially for patients with BD and those with congenital coagulation factor deficiencies.

Follow-up and monitoring

The function of follow-up and monitoring is to observe the treatment effect in the short term. If the effect is not ideal, adjustments may be made to the medication regimen. In the long term, attention should be paid to preventing complications.

This consensus emphasises that whether the drug can be halted depends on the removal of the cause of bleeding.[1] Patients with hereditary BD should take medication for a prolonged period until pregnancy, childbirth or menopause. Patients with AUB-O require regular evaluation of HPO axis function. For patients on long-term medication, it is recommended to undergo comprehensive physical examinations at least once a year, including liver and kidney function, blood lipid and blood sugar metabolism and uterine and breast ultrasound examinations, to promptly identify and address any abnormalities.

Patients with mild AUB-O

Patients who initially receive observation, reassurance, hormone therapy or iron supplementation should be followed up in 3–6 months to assess menstrual pattern improvement and/or determine the need for ongoing hormone therapy.

Patients with moderate AUB-O

Patients with moderate AUB-O should have follow-up visits approximately 1 month and 3 months postinitial bleeding. If bleeding does not improve, adjust the hormone therapy regimen. This could include increasing the drug dose and adding tranexamic acid as needed. If the patient's oral medication compliance is poor and bleeding does not improve, other hormone therapy regimens (eg, LNG-IUS) may be necessary. Follow-up should be performed every 3–6 months after the bleeding stops and once a year after the menstrual pattern stabilises.

Patients with severe AUB-O

Patients who do not require hospitalisation should have monthly follow-ups until a stable menstrual cycle and hormone therapy stabilise and Hb >100 g/L, if not hospitalised.

Long-term monitoring and follow-up

After hormone therapy cessation, reassess if there is no menstruation for more than 3 months (to exclude pregnancy); endocrine evaluation should be repeated, and progesterone should be used to induce withdrawal bleeding.[13] Long-term follow-up can prevent the potential outcomes of AUB-O (including chronic anaemia, infertility and endometrial cancer).

Postscript

This consensus addresses the common diagnosis and treatment challenges of AUB-O and AUB-C, the most prevalent non-structural causes of AUB in adolescence. Key and challenging aspects include principles and methods of hormone therapy. Long-term management is crucial for adolescent AUB patients, emphasising clinical standardisation, regular follow-up and patient education as enduring responsibilities.

The appendix of this consensus will specifically detail the examination and treatment of BD. Additionally, while adolescent PCOS and hypothalamic dysfunction (typically functional hypothalamic amenorrhoea (FHA) are less common in AUB-O, they remain significant clinical concerns. These topics will be briefly discussed in the appendix to clarify perspectives.

APPENDIX 1. AUB IN ADOLESCENCE PRODUCED BY BDS

Clinical manifestations

AUB-C in adolescence produced by BD typically presents as severe HMB at menarche, with considerable blood loss and secondary anaemia, heavy menstrual bleeding and frequent emergency department visits. A history of menstruation or bleeding, as presented in table 1, may suggest BD, and a history of autoimmune disease should be ruled out.[7]

Associated tests for common BDs in adolescence

The classification of common BD diseases in adolescence[7] and related tests are presented in table 2.

Treatment precautions

Drug efficacy

The effectiveness of medications is closely tied to the patient's platelet count, quality and degree of coagulation factor deficiency, as well as concurrent gynaecological diseases such as adenomyosis. In cases of acute severe bleeding due to low platelet count, using COCs at doses exceeding recommendations or in combination with multiple sex hormone drugs to control HMB may not necessarily enhance haemostatic efficacy. Instead, it can significantly increase adverse reactions,[7] warranting caution against routine use.

Table 1 Menstrual and bleeding history associated with bleeding disorder

Menstrual history	Bleeding history
Heavy menstrual bleeding at menarche	Spontaneous epistaxis >10 min (without allergic rhinitis)
Possible shortened cycle time	Gingival or oral bleeding fo r >10 min (no gingivitis)
Prolonged menstrual period >8 days	Skin bleeding from superficial cuts or abrasions >10 min
Severe iron deficiency anaemia	Heavy or unexpected bleeding from surgery or tooth extraction
Excessive bleeding soaking through clothing	Bleeding in muscles or joints
Blood clots, especially clots >2 cm in diameter, increased use of sanitary napkins, soaking through in 120 min or less, need to be changed.	Any severe bleeding requiring a blood transfusion

Breakthrough bleeding

Patients with thrombocytopenia and coagulation factor deficiencies are prone to breakthrough bleeding during COC and progesterone reduction.

Contraindications

1. NSAIDs, such as mefenamic acid, naproxen or ibuprofen, can affect platelet aggregation and interact with other drugs, potentially affecting liver function and coagulation factor production. Thus, they are contraindicated.[2 15]
2. Gonadotropin-releasing hormone agonists (GnRH-a) should not be used when the platelet count is $<10\times10^9$/L due to the risk of inducing severe bleeding through the 'flare-up effect'.[3]

Ovarian haemorrhagic cysts

Female patients with BD have an increased incidence of ovarian haemorrhagic cysts.[23] In cases of recurrent haemorrhagic cysts, COC treatment is recommended.

APPENDIX 2. POLYCYSTIC OVARY SYNDROME IN ADOLESCENCE

Clinical manifestations

Adolescent patients with PCOS commonly present with oligomenorrhoea or amenorrhoea, irregular bleeding, acne, hirsutism, hair loss and obesity. Some may also exhibit impaired glucose tolerance or diabetes and have an increased risk of cardiovascular disease. Depression is notably prevalent, with patients with PCOS experiencing rates four times higher than the general population.[24] This not only impacts their quality of life but also influences their medical adherence to diet, lifestyle changes and treatment plans.

Diagnosis

Diagnosing PCOS in adolescence requires caution and adherence to specific criteria, including that diagnosis should occur at least 3 years after menarche; confirmation of PCOS involves meeting at least three of the Rotterdam criteria (irregular menstruation, clinical or biochemical hyperandrogenism, ≥12 follicles with a diameter of 2–9 mm in one or both ovaries and an ovarian volume >10 mL[25 26]; adolescents not meeting full diagnostic criteria may be considered at risk for PCOS and should undergo regular follow-ups, with treatment tailored to their specific symptoms).

1. *Diagnosis of menstrual abnormalities*: Refer to the previous section on abnormal bleeding patterns.[7]
2. *Diagnosis of adolescent hyperandrogenism*: Clinical hyperandrogenism is primarily assessed through signs of hirsutism using the modified Ferriman-Gallwey scoring method, which includes assessment of nine areas: perioral, chin, areola, lower abdomen, pubic area, upper thighs, etc. For Chinese women, a score of ≥4 points indicates hirsutism. Alternatively, a simplified method may assess hirsutism based on the upper lip, lower abdomen and inner thigh, with a score of ≥2 points also suggestive of hirsutism.[27] Mild comedonal acne is common in adolescent girls, but moderate to severe cases (ie, 10 or more facial lesions), especially occurring before and after menstruation, are uncommon (less than 5%) and may indicate clinical hyperandrogenism. Hair loss is not recommended for diagnosing adolescent hyperandrogenism.[28] For those without obvious clinical symptoms, androgen levels in blood tests are necessary.
3. *Evaluation of polycystic ovarian morphology (PCOM)* is a physiological change during puberty. There are currently no clear criteria for defining an adolescent's PCOM, so it is not recommended for use in the diagnosis of PCOS in adolescence. Guidelines suggest considering an ovarian volume >10 mL as a potential diagnostic criterion for adolescent PCOS.[25 29]
4. *Impaired glucose tolerance and type 2 diabetes*: Regardless of age and body mass index (BMI), patients with PCOS should undergo regular blood glucose and insulin assessments every 1–3 years.[7] Oral glucose tolerance tests and insulin release tests (using 75 g of glucose powder) are recommended as the preferred evaluation methods for assessing glucose metabolism.
5. *Cardiovascular disease*: All patients with PCOS, irrespective of age and BMI, should undergo cardiovascular risk assessments, including blood pressure measurement, lipid testing and, where appropriate, C reactive protein testing.

Treatment

1. *Lifestyle intervention*: Lifestyle changes, including diet control, exercise and behavioural intervention, are the primary treatment for patients with PCOS, particularly those who are overweight or obese.
2. *Menstrual management*: Oligomenorrhoea or amenorrhoea in adolescent PCOS is primarily treated with

Table 2 Classification of common BD in adolescence and its related tests

Classification of BD	Common types of diseases		Recommended tests
Defects in vWF quantity or quality	Hereditary vWD (the most common hereditary BD, including types I, II and III)		1. Bleeding time (limited testing). 2. vWF antigen determination. 3. vWF activity assay. 4. Ristocetin-induced platelet aggregation assay. 5. APTT. 4. Factor VIII activity assay.
Defects in platelet quantity or quality	Decreased platelet quantity	ITP; aplastic anaemia, radiotherapy, bone marrow suppression due to other reasons, bone marrow failure, haematological malignancies, etc, causing abnormal platelet count; microthrombotic diseases (thrombotic thrombocytopenic purpura)	1. Platelet count and morphology examination. 2. Platelet antibody screening. 3. Recommended screening for thrombotic microangiopathy: fragmented red blood cells, Coombs test, ADAMTS13 activity assay, etc.
	Abnormal platelet quality	Glanzmann's thrombasthenia, Bernard-Soulier syndrome, platelet quality disorders like platelet granulation disorders.	1. Platelet count and morphology examination. 2. Platelet aggregation test. 3. Ristocetin-induced platelet aggregation assay. 4. Platelet membrane glycoprotein determination.
Abnormal blood coagulation	Inherited clotting factor deficiencies	Various coagulation factor deficiencies (factor VII deficiency is more common), haemophilia A (factor VIII deficiency) and haemophilia B (factor IX deficiency) are X chromosome recessive inheritance, female carriers of haemophilia B generally have a low risk of bleeding, but a mild tendency to bleed may occur in some special cases, such as when clotting factor IX is low; PT and APTT are normal when the factor XIII is deficient.	1. Prolonged APTT (to exclude lupus anticoagulant), screening for coagulation factors VIII, IX, XI, XII, vWF and their inhibitors. 2. Prolonged PT, screening of coagulation factors VII, X, V, and II. 3. Both APTT and PT are prolonged. Screen coagulation factors X, V, and II. Also, pay attention to whether fibrinogen activity is normal. 4. Fibrinogen activity assay. 5. PT and APTT are both normal and coagulation abnormalities caused by endothelial cells and platelets have been ruled out. It is necessary to screen for abnormalities in coagulation factor XIII.
	Abnormal fibrinogen	Hypofibrinogenaemia and dysfibrinogenaemia	1. Fibrinogen activity and content determination. 2. TT. 3. Two methods for measuring fibrinogen should be performed when dysfibrinogenaemia is suspected (the Clauss method and the PT-derived method).

ADAMTS13, a disintegrin-like metalloproteinase 13 with platelet-binding protein motif; APTT, activated partial thromboplastin time; BD, bleeding disorder; GT, Glanzmann thrombasthenia; ITP, immune thrombocytopenic purpura; PT, prothrombin time; TT, thrombin time; vWD, von Willebrand disease; vWF, von Willebrand factor.

progesterone to regulate the menstrual cycle. Patients with long-term low oestrogen levels may require artificial cycle treatment using oestrogen and progestogen. Severe hyperandrogenism is managed with androgen-lowering therapies. For patients experiencing frequent menstruation, HMB or irregular bleeding, haemostatic methods are applied as described above.

3. *Treatment of hyperandrogenism*: Short-acting COCs are the mainstay for managing symptoms like hirsutism, acne and hair loss in adolescent PCOS. Low-dose COCs containing 20–30 µg of ethinyl oestradiol with low thrombotic risk are recommended. Spironolactone (50–200 mg/day) can be considered for patients with poor response to COCs, contraindications to COCs or intolerance.[28]
4. *Treatment of metabolic-related conditions*: Lifestyle intervention remains the first-line treatment. Metformin is recommended for adolescents with evident insulin resistance, with a daily dose ranging from 1500 to 2000 mg (not exceeding 2000 mg/day), and is not recommended for children under 10 years old.[26]
5. *Psychological treatment*: In addition to addressing physical symptoms, it is crucial to identify and manage the psychological issues in adolescent patients with PCOS, offering appropriate clinical support and treatment.

APPENDIX 3. MENSTRUAL ABNORMALITIES CAUSED BY HYPOTHALAMIC DYSFUNCTION

Clinical manifestations

Typically presents as amenorrhoea (FHA) or infrequent or irregular menstruation. Prolonged oestrogen deficiency can negatively impact bone health, cognitive development and psychological well-being.

Diagnosis

FHA is often associated with rapid weight loss or severe stress. In severe cases, patients become emaciated, pale and depressed. Athletes or dancers who rigorously control their weight are also at risk of this type of AUB. Reproductive hormonal assessments typically show low or normal FSH and LH levels, low oestrogen levels or early follicular levels and no evidence of ovulation. A GnRH stimulation test is usually unnecessary if there is a typical history of hypothalamic dysfunction, as the pituitary response is typically expected.

Treatment

1. *Initial non-drug treatment* includes nutritional adjustments, psychological support and possibly reducing exercise intensity to increase BMI or fat mass to restore menstruation.[30] Evidence suggests menstruation may resume when ideal body weight reaches at least 90% of premenstrual weight and is maintained for 6–12 months or longer.[31]
2. *Psychological support therapy* includes cognitive behavioural therapy.
3. *Bone loss treatment* is critical due to potential bone loss from FHA. Patients should consume 1200–1500 mg of calcium daily and supplement with vitamin D. However, calcium and vitamin D supplementation alone may not suffice to prevent or treat bone density loss.
4. *Oestrogen-progesterone therapy*: if non-drug treatments fail to restore menstruation after a year,[32] cyclical oestrogen-progesterone therapy should be initiated. Earlier treatment initiation may be warranted for patients with significantly reduced baseline bone density (Z≤−2) or a history of fractures.[33] The recommended regimen includes 1–2 mg/day of oestradiol valerate and 10–20 mg/day of dydrogesterone for 10 days in the second half of the cycle or cyclical use of 17β oestradiol/17β oestradiol dydrogesterone tablets.
5. The use of COC is not recommended for these patients due to its impact on bone density. It is not recommended for adolescent patients with amenorrhoea[34 35] to use bisphosphonates, denosumab, testosterone or similar agents for improving bone density.[32 33]

Collaborators Consultants: Ling Xu (Peking Union Medical College Hospital, Chinese Academy of Medical Sciences), Dongzi Yang (Sun Yat-sen Memorial Hospital, Sun Yat-sen University), Lihui Wei (Peking University People's Hospital), Jie Qiao (Peking University Third Hospital), and Zijiang Chen (Reproduction Hospital Affiliated to Shandong University). Consensus review experts (in alphabetical order of surnames): Wenpei Bai (Beijing Century Altar Hospital, Capital Medical University), Xiaoxia Bao (Dongzhimen Hospital, Beijing University of Chinese Medicine), Rong Chen (Peking Union Medical College Hospital, Chinese Academy of Medical Sciences), Yan Ding (The First Affiliated Hospital of Xinjiang Medical University), Xue Du (Tianjin People's Hospital), Haixia Fu (Peking University People's Hospital), Chunxiu Gong (National Children's Medical Center, Beijing Children's Hospital, Capital Medical University), Jian Gu (The Third Affiliated Hospital of Sun Yat-sen University), Huiling Li (Peking University People's Hospital), Rong Li (Peking University Third Hospital), Yuan Lin (Fujian Maternal and Child Health Hospital), Jia Liu (Institute of Basic Clinical Medicine, China Academy of Chinese Medical Sciences), Songsong Lu (Peking University People's Hospital), Min Luo (Peking Union Medical College Hospital, Chinese Academy of Medical Sciences), Shulan Lv (The First Affiliated Hospital of Xi'an Jiaotong University), Xiaoxin Ma (Shengjing Hospital Affiliated to China Medical University), Ying Ma (Shengjing Hospital Affiliated to China Medical University), Mulan Ren (Zhongda Hospital Affiliated to Southeast University), Huirong Shi (The First Affiliated Hospital of Zhengzhou University), Kuanyong Shu (Jiangxi Maternal and Child Health Hospital), Aijun Sun (Peking Union Medical College Hospital, Chinese Academy of Medical Sciences), Buzhen Tan (The Second Affiliated Hospital of Nanchang University), Liangdan Tang (The First Affiliated Hospital of Chongqing Medical University), Zhijian Tang (Peking University People's Hospital), Qinjie Tian (Peking Union Medical College Hospital, Chinese Academy of Medical Sciences), Wenyan Tian (Tianjin Medical University General Hospital), Jianliu Wang (Peking University People's Hospital), Chaohua Wang (Peking University People's Hospital), Lijie Wang (Qilu Hospital of Shandong University), Shixuan Wang (Tongji Hospital Affiliated to Tongji Medical College, Huazhong University of Science and Technology), Jie Wu (The First Affiliated Hospital of Nanjing Medical University), Yin Ling (Peking University First Hospital), Yanfang Zhang (Tianjin Medical University General Hospital), Yu Zhang (Tianjin Central Obstetrics and Gynecology Hospital), Zhifen Zhang (Hangzhou Obstetrics and Gynecology Hospital), Qingmei Zheng (The Affiliated Hospital of Qingdao University), Shien Zou (Obstetrics and Gynecology Hospital Affiliated to Fudan University), Ying Zou (Hunan Provincial Maternal and Child Health Hospital) Academic secretaries: Huina Su (Peking University People's Hospital), Zijie Fu (The First Hospital of Hebei Medical University), Wenya Qiao (Taiyuan Maternal and Child Health Hospital).

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ORCID iDs
Xin Yang http://orcid.org/0000-0002-3275-2560
Huina Su http://orcid.org/0009-0009-2118-5861

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