Diagnosis and management of abnormal uterine bleeding in adolescence

An expert Consensus Statement of SIGO (Italian Society of Gynecology and Obstetrics) and SISET (Italian Society for the Study of Hemostasis and Thrombosis)

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ABSTRACT

During menarche and adolescence, abnormal uterine bleeding (AUB) may serve as a crucial indicator of a hidden bleeding disorder. When a young woman is suspected of having a bleeding disorder, the obstetrician-gynecologist should collaborate with a hemostasis specialist to arrange the necessary laboratory testing and determine the best course of action. The Italian Society for the Study of Hemostasis and Thrombosis and the Italian Society of Gynecology and Obstetrics jointly offer recommendations on the diagnosis and treatment of AUB. They also suggest diagnostic and therapeutic pathways to decrease diagnostic delay and improve treatment effectiveness and safety.

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Introduction

Abnormal uterine bleeding (AUB) refers to uterine bleeding, manifested as inter-menstrual bleeding (metrorrhagia) or excessive menstrual bleeding (menorrhagia) that may underlie a number of organic or dysfunctional disorders. These definitions concern female patients who are not in hormonal treatment.[1,2]

Pediatricians frequently refer cases of AUB manifesting during adolescence to gynecologists for consultations; AUB can have a significant impact on the patient's quality of life since it causes excessive school non-attendances and limits normal daily activities.[3] Menstruation in female adolescents is often irregular due to anovulation and immaturity of the hypothalamic-pituitary-gonadal axis, typical of the early post-menarche years. However, heavy menstrual bleeding (HMB), which manifests as menorrhagia and/or metrorrhagia, during menarche and adolescence (AUB) may indicate an underlying specific disorder.

A diagnostic approach can be complex and requires multidisciplinary expertise due to the multiple pathogenetic mechanisms underlying menorrhagia.

The frequent association of AUB with congenital or acquired hemorrhagic disorders,[4] which need targeted therapies requires a shared approach between obstetricians, gynecologists, and hemostasis experts.

In this document, the Italian Society for the Study of Hemostasis and Thrombosis (SISET) and the Italian Society of Gynecology and Obstetrics (SIGO), propose joint recommendations on the diagnosis and management of AUB, with the aim to guide and standardize the clinical management of potentially serious cases and suggest diagnostics and therapeutic pathways to reduce diagnostic delay and therapy-related side effects.

Materials and Methods

Following the approval of the project by the Presidents and Boards of SIGO and SISET, an inter-society working group was established, two coordinators were identified, and 4 expert members were appointed by each society.

Each member worked on an assigned field of study and submitted their results to the working group.

The resulting document was sent for review to the presidents and boards of the two Scientific Societies and was finally formally approved by them.

FINAL DOCUMENT

Diagnostic grading of abnormal uterine bleeding

It is of maximal importance to distinguish an emergency situation such as in case of massive uterine bleeding, from a stable clinical condition. In the first case, the blood loss can be of such magnitude as to lead the patient to hospitalization in an emergency unit when clinical elements (persistent abundant blood loss, significant anemia, signs of hemodynamic instability) are present.

In 2018, the International Federation of Gynecology and Obstetrics introduced a classification of potential causes of menometrorrhagia during adolescence, which are depicted in Table 1.

Assessment of menstrual blood loss

AUB is defined as menorrhagia in case of total blood loss per menstrual cycle greater than 80 ml (about one change of sanitary pad every 1-2 hours), or menstrual loss lasting more than 8 days.

It is not easy to quantify blood loss and obtain an empirical/objective assessment of bleeding given the subjective evaluation reported by the patient and/or the parent. Some useful practical questions to the young patient during medical evaluation are:

- Number of tampons used per day. >6 tampons/day on high flow days, or 2 tampons per hour, indicate heavy blood loss. If the clinical setting permits, detection patterns for menstrual flow are accessible.

Table 1. International Federation of Gynecology and Obstetrics classification (2018).[7,25]

Endocrinological	• Anovulation (the most frequent dysfunctional cause due to the immaturity of the hypothalamic-pituitary-gonadal axis; (may occur within the first 3-5 years after menarche) • Polycystic ovary syndrome • Thyroid disorders
Bleeding associated with pregnancy	• Abortion, ectopic pregnancy, gestational trophoblastic disease
Congenital and acquired hemorrhagic disorders	• Von Willebrand disease • Congenital platelets function and number disorders • Acquired platelet function disorders • Immune thrombocytopenia • Congenital coagulation factor deficiencies • Congenital hypo-dysfibrinogenemia • Acquired coagulation disorders
Medical therapies	• Antipsychotics • Anticoagulants • Antiplatelet agents
Organic disorders	• Congenital uterine malformations • Uterine polyps • Endometriosis • Infections • Uterine-ovarian tumors • Other tumors or myomas
Systemic disorders	• Liver disease, diabetes mellitus, chronic kidney disease, systemic lupus erythematosus etc.
Other	• Trauma/abuse • Foreign matter • Internal or external genital lacerations or lesions

Combined hormonal contraception methods and progestin-only contraception can cause blood loss not classifiable as abnormal uterine bleeding.

- Presence of clots: large clots, about 2 cm or more, indicate abundant flow.

The use of so-called "bleeding assessment tools" (*e.g.*, the Pictorial Blood Assessment Chart; PBAC) allows self-evaluation by the patients and monitoring (Figure 1).

In addition, some scores for the anamnestic evaluation of bleeding validated for congenital mucocutaneous hemorrhagic disorders, such as the International Society for Thrombosis and Hemostasis-bleeding assessment tool,[5] detect the frequency and severity of the HMB.

Diagnostic approach to abnormal menstrual flows

The anamnestic assessment, including an accurate medical and menstrual history, represents the milestone in the diagnostic approach to HMB, in providing insight into its pathogenesis (Table 2). This assessment should be jointly performed by a gynecologist and an expert in hemostasis.

The American College of Obstetricians and Gynecologists in the recent Committee Opinion No. 785 of 2019 proposed a simple tool to identify, HMB in adolescents, based on a questionnaire of 8 multiple-choice questions.

Physical examination

- Vital parameters (blood pressure, heart rate) measured both sitting and standing;
- Tanner staging assessment, to define primary and secondary sexual characteristics during puberty;
- Abdominal examination, anemia, bleeding disorders, and symptoms of hyperandrogenism;
- Physical examination of the external genitalia and the distal part of the vagina; in sexually active patients, a bimanual pelvic examination and a speculum examination are to be performed.

Table 2. Anamnestic data.

• Age of menarche and characteristics of the menstrual cycle
• Coitarca, sexual activity, possibility of pregnancy
• "Spy" signs/symptoms: asthenia, generalized fatigue (anemia), acne, hirsutism, seborrhea (hyperandrogenism)
• Habits/lifestyle: changes in body weight, eating habits, physical activity
• Familiarity for hemorrhagic bleeding and/or carrier condition
• Personal history of gingival bleeding, nosebleeds, bruising
• Post dental care or post-surgery bleeding (evaluation with BAT SCORE)5,26
• Recent history of infection
• Endocrine disorders and other known chronic diseases (hepatopathy, nephropathy)
• Dysmenorrhea (possible association with uterine pathology, adenomyosis)
• Prescribed medical treatment (chemotherapy, hormonal contraceptives, antipsychotics, anticoagulants, antiplatelet), supplements (gingko biloba, ginseng, resveratrol)
• Previous hemorrhagic ovarian cysts/hemoperitoneum from ruptured ovarian cyst (highest prevalence in subjects with hemorrhagic diathesis)

PBAC Scoring System

Pads		
1 point	For each lightly stained pad	
5 points	For each moderately stained pad	
20 points	For each completely saturated pad	
Tampons		
1 point	For each lightly stained tampon	
5 points	For each moderately stained tampon	
10 points	For each completely saturated tampon	
Clots/Flooding		
1 point	For each small clot (Australian 5 cent coin)	
5 points	For each large clot (Australian 50 cent coin)	
5 points	For each episode of flooding	

A score of 100 is equivalent to a loss of about 80 ml. The diameter of a 5 cent. (Australian) coin is 2 cm, of a 50-cent coin 3 cm.

Figure 1. Pictorial blood loss assessment chart (from American College of Obstetricians and Gynecologists Committee Opinion N. 785).[6]

In case of emergency, after massive blood loss, it is of utmost importance to first verify and prevent the occurrence of hypovolemic shock and to perform an urgent blood count to establish the degree of anemia and the need for intravenous iron therapy or blood transfusion. Pregnancy must be ruled out.

The next diagnostic step, when the patient is clinically stable, is the abdominal-pelvic ultrasound examination to rule out organic disorders. The transvaginal examination, when feasible, allows the evaluation of the uterine ecostructure when mild adenomyosis and fibromatosis are suspected, and any arterial venous malformations at the origin of HMB, in combination with color Doppler. Because benign dysfunctional neoplasms and some neoplasms, like for example, granulosa cell cancer, are associated with heavy uterine bleeding, an ultrasound examination which includes the ovaries should be performed.

Laboratory evaluation

Laboratory diagnostics (Table 3) includes a series of tests aimed at:

- Assessing anemia and its degree;
- Studying the basic coagulation profile;
- Confirming or excluding endocrine disorders.

Hemostasis test results require an expert evaluation to be performed by a hemostasis expert who, in case of diagnosis of hemostatic disorder, will oversee the management, treatment, and follow-up of the patient.[6]

The possibility of an underlying hemorrhagic coagulation disorder in HMB is not uncommon: about 20% of women with abundant menstruation have coagulation disorders, 13-60% of these are adolescents and up to about 30% of them are hospitalized for menorrhagia.[7]

Due to the large phenotypic variability of hemostasis defects and abnormalities, it is generally held that in many cases these are underestimated or undiagnosed. Often menarche and the first menstrual cycles are the first test of the efficiency of the hemostatic system and can therefore reveal congenital bleeding disorders. The laboratory assessment should include all parts of the hemostatic process involved in menstrual hemostasis: vascular endothelium, platelets, as well as the intrinsic and/or extrinsic coagulation pathway (Table 4).

In summary (Figure 2):

- It is recommended to discriminate a heavy menstrual flow from a normal one through the history, including the use of PBAC systems and the use of bleeding assessment tools;
- Different diagnostic pathways in emergency and clinically stable outpatients allow for targeted clinical, instrumental, and laboratory evaluations;
- Although HMB in adolescence in most cases is due to anovulation and immaturity of the hypothalamic-pituitary-gonadal axis, it could, however, be a sign of an underlying specific hemostatic disorder and therefore a close collaboration with an expert in hemostasis is highly warranted.

Clinical management

Most AUB in adolescence is caused by ovulatory dysfunction or coagulopathies.

Objectives of AUB management are:[7]

- To stop the bleeding;
- To prevent or treat anemia;
- To restore regular menstrual cycles;
- To improve the quality of life of adolescents.

Treatment options include:[8-11]

- Hormone therapy: combined oral contraceptives (COCs), progestins, intrauterine devices with levonorgestrel (IUS-LNG), GnRH analogs, and antagonists;[12]
- Non-hormonal therapy: tranexamic acid, aminocaproic acid, desmopressin, and ovulation inducers;

Table 3. Main laboratory tests required in case of heavy menstrual bleeding.

• Serum (or urinary) beta-hCG
• Complete blood count with platelet count, ferritin (+/- sideremia and total iron binding capacity)
• PT, aPTT, fibrinogen • Assessment of platelet function - when platelet disease is suspected it is necessary to perform light transmission aggregometry with various agonists to confirm diagnosis.
• Diagnosis of von Willebrand disease. Specific tests should be requested by the hemostasis expert • Individual clotting factor measurement: F II, V, VII, VIII, IX, X, XI, XIII (based on results of basic coagulation profile) • Thyroid function, prolactin, testosterone, FSH, and other targeted hormonal dosages according to the patient's medical history

HGC, human chorionic gonadotropin; PT, partial thromboplastin; aPTT, activated partial thromboplastin time; FSH, follicle-stimulating hormone.

Table 4. The most common coagulopathies that cause heavy menstrual bleeding in adolescents.

Von Willebrand disease	• Type 1 VWD: VWF quantitative deficiency, autosomal dominant inheritance • Type 2 VWD: qualitative defect with frequent autosomal dominant inheritance • Four different variants: 2A; 2B; 2M; 2N • Type 3 VWD: virtual absence of VWF, autosomal recessive inheritance
Thrombocytopenia	• Hereditary thrombocytopenias, immune thrombocytopenia
Defects in fibrin formation	• Dysfibrinogenemia

VWD, Von Willebrand disease; VWF, Von Willebrand factor.

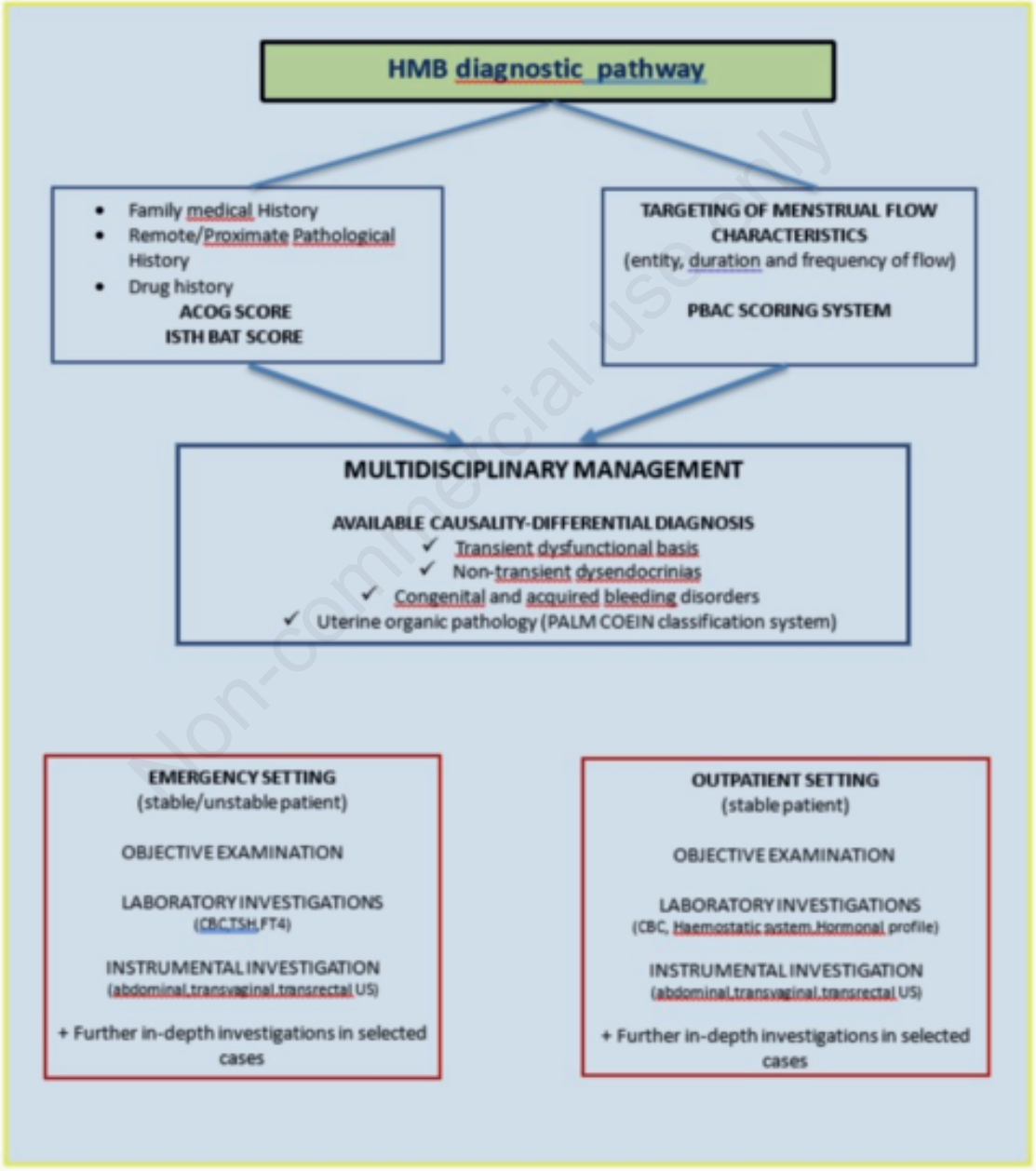
- Anemia therapy: iron, folic acid.
  The degree of anemia determines the management of AUB.

Severe anemia (Hb <7 g/dL)

Severe uterine bleeding of dysfunctional origin in adolescent patients must be medically managed and is based on hormonal therapy and hemostatic agents; it only very rarely requires surgery.

Hospitalization of the patient is necessary if:

- Hemodynamic instability (tachycardia, hypotension, dyspnea);
- Symptomatic anemia (lethargy, asthenia, syncope, tachypnea);
- Hb <7 g/dL. If the hemoglobin is between 8 and 10 g/dL in a hemodynamically stable patient, with a compliant family and able to maintain prompt contact by telephone, outpatient management with hormone therapy can be sufficient.
  Need for transfusion or surgery.



HMB, heavy menstrual bleeding; PBAC, pictorial blood assessment chart; ISTH BAT, International Society for Thrombosis and Hemostasis-bleeding assessment tool.

Figure 2. Diagnostic pathway in patients affected by heavy menstrual bleeding in both emergency and outpatient settings.

Therapy

Combined oral contraceptives

COCs with ethinyl estradiol are to be considered the first-line treatment in acute episodes, especially in the absence of endometrial substrate. The therapeutic scheme provides for:

- One pill every 8-12 hours until the bleeding stops. This normally occurs within 24-48 hours;
- Afterwards one pill every 12 hours for three days;
- Finally, one pill once a day until hemoglobin levels reach over and above 11 g/dl: withdrawal bleeding can be acceptable with this hemoglobin level after the therapy has been interrupted for at least 3 days.

Hemostatic agents

Tranexamic acid orally: 15-25 mg/kg body weight 3 times daily for 3-5 days during menstruation, with a maximum daily dose of 3900 mg/day. If a hemostatic disorder is present, a hemostasis expert should be consulted. The *Annex* provides a table with the main therapeutic indications for the most frequent coagulation disorders.[13-15]

Blood transfusion

Healthy adolescents often tolerate hemoglobin levels below 7 g/dL, and the decision to transfuse should be based not only on hemoglobin levels but also on the hemodynamic status and the presence of active bleeding.

Iron therapy

- Start oral therapy in adolescents once or twice a day depending on the severity of anemia;
- Monitor treatment with ferritin levels;
- Intravenous therapy with iron carbohydrate – Ferinject – in a single bolus at the dosage of 500 or 1000 mg (not recommended for age <14 years) is indicated if:
  1. Hemoglobin value <9 g/dL
  2. Intolerance to oral therapy;
  3. Pre/post-surgery;
  4. No response to oral therapy.

Iron therapy should be prescribed in association with folic acid.[8] In healthy carriers of thalassemia, the use of folic acid and in patients with confirmed hyposideremic anemia, iron is to be administered.

Surgery

Surgery should be reserved as a last option in cases when bleeding is unresponsive to other therapies, which put the patient's life at risk:

- Intrauterine tamponade: a 30 ml Foley to be inserted after calculation of uterine volume by ultrasound; it can be kept in situ for 12-24 hours, after which it is gradually deflated 5 ml at a time;
- Antibiotic prophylaxis may be taken into account when the balloon is placed in the uterine cavity;
- Hysterosuppression (method of choice) or curettage, if indicated, should be performed with caution to prevent the formation of scar adhesions at the endometrial level;
- The placement of an levonorgestrel-releasing intrauterine device (IUD-LNg) for long-term management of bleeding should be considered;
- Endometrial ablation, uterine artery embolization, and hysterectomy are invasive measures that cause infertility and should not be considered in this age group except in life-threatening cases.

Follow-up

The first follow-up should be scheduled between 7 and 14 days after hospitalization for severe AUB, and then every month until the hemoglobin levels rise >10 g/dL and the menstrual pattern is stable.

Patients with severe AUB treated on an outpatient basis should be evaluated weekly in case of persistent blood loss. Once hemoglobin levels reach 10 g/dl and the menstrual pattern is stable, a follow-up should be performed monthly.

Treatment may be discontinued when hemoglobin levels reach 11 g/dL and an adequate endometrial rhyme can be detected by ultrasonography.

The use of low-dose clomiphene for some cycles to promote follicular development may be useful.

Moderate anemia (Hb<10 and >7 g/dL)

Therapy

Combined oral contraceptives

The therapeutic regimen involves the intake of a monophasic COC pill containing a dosage of ethinyl estradiol higher than 30 µg.

If in 48 hours the expected benefits are not obtained, the therapy can be increased to 2 pills a day; American guidelines require the use of a pill every 8 hours until the bleeding stops, then a pill every 12 hours for 2 days, and finally, a pill once a day until anemia is resolved; however, this expert panel believes that a more gradual approach is to be preferred.

This therapy can be continued in association with natural estrogens (estradiol valerate E2/V + dienogest DNG or estradiol micronized E2 + nomegestrol acetate NOMAC). To avoid risks, it is recommended to continue the pill as supportive therapy, allowing to prevent recurrent bleeding.

Progestin-only pill

Medroxyprogesterone acetate 20 mg orally every 6-12 hours (up to 80 mg/day) until bleeding stops, and then gradually decrease the dose to 10 mg per day until maintenance therapy begins.

Noretisterone acetate 5-10 mg until bleeding stops and anemia is resolved. Once the anemia is resolved, the initial oral progestin regimen should be stopped for at least 5-7 days after suspension of hormone therapy to allow the endometrium to flake off.

Ovulation induction (in anovulatory forms, for recovery of normal endocrine order)

Administration of clomiphene at low doses (50 mg) 1 tablet daily for 5 days. Clinical and ultrasound check after 7 days from

the beginning of the treatment and possible repetition of the regimen in the following cycles from the 3rd to the 7th day of the cycle.

Hemostatic agents

Tranexamic acid: 15-25 mg/kg body weight 3 times a day for 5 days during bleeding, with a maximum daily dose of 3900 mg/day. If a hemostatic abnormality is present, a hemostasis expert should be consulted.

The *Appendix* contains the main indications for therapy of the most frequent pathologies and Tables (1A, 2A, 3A) on the use of drugs.

Anemia treatment

Folic acid should be prescribed in association with oral therapy.

In healthy carriers of thalassemia, use folic acid, and in patients with confirmed hyposideremic anemia iron is to be administered.

Follow-up

- Patients with moderate AUB should be monitored every 3-6 months until the menstrual pattern is stabilized, then annually thereafter.
- Low-dose clomiphene for some cycles to stimulate follicular development may be useful.

Mild anemia (Hb <12 and >10 g/dL)

Therapy

Combined oral contraceptives

Monophasic pill with at least 30 µg of ethinyl estradiol, with classical dosage (one pill per day, including placebo pills) progestins, not combined.

For subjects that do not require inhibition of ovulation, the use of progesterone or progestin in a cyclic treatment as a support to the second phase of the natural cycle may be considered.

Two regimens of progesterone or progestin administration may be proposed:

- Use in the second cycle phase for 12 days if a normal cycle is present.
- Use for the first 12 days of each month, is more easily applicable due to the absence of variations in the scheme.

Micronized progesterone is generally used at a dose of 200 mg per day, or 100 mg per 12 h (to be avoided in patients with peanut allergy).

Vaginal administration of micronized progesterone is suggested when possible and ensures more consistent endometrial concentrations.

Ovulation induction (in anovulatory subjects, for recovery of normal endocrine order)

Administer clomiphene at low doses (50 mg) 1 tablet daily for 5 days. Clinical and ultrasound check after 7 days from the beginning of treatment and possible repetition of the scheme in the following cycles from the 3rd to the 7th day of the cycle.

Intracavitary progestin: levonorgestrel (LNg) intrauterine device (IUD).

The insertion of an IUD is useful as maintenance therapy after acute bleeding phase has stopped.

Hemostatic agents

Tranexamic acid orally 15-25 mg/kg body weight 3 times a day for 5 days during bleeding with a maximum daily dose of 3900 mg/day.

Follow-up

- Patients with mild AUB should be monitored every 3-6 months until the menstrual pattern stabilizes, then annually thereafter.
- Low dose clomiphene for some cycles to stimulate follicular development may be useful.

Mild chronic (Hb >12 g/dl) iron deficiency treatment

- Informing and reassuring the patient and the family;
- Compiling calendar of bleeding;
- Tranexamic acid orally: 15-25 mg/kg body weight 3 times a day for 3-5 days during bleeding, with a maximum daily dose of 3900 mg/day;
- Hormone therapy;
- Option to be evaluated, especially in the presence of contraceptive needs, following the normal indications on the choice of contraceptive.

Follow-up

Follow-up to 3-6 months, re-evaluation if bleeding worsens.

Prognosis

- The long-term prognosis in girls with AUB depends on the underlying causes;
- Anovulation in AUB patients normally resolves with the maturation of the hypothalamic-pituitary ovary axis, but this may take place 6-8 months from the onset of menarche.

A long-term follow-up is essential to prevent relapse and adverse sequelae.

ANNEX

1. Von Willebrand disease

In the presence of a documented von Willebrand factor (VWF) deficiency, the diagnosis is made based on the type of von Willebrand disease: type 1, type 2 or type 3 (see diagnostic classification) as the treatment and/or prevention of hemorrhagic manifestations in these three main types are different.

Testing with desmopressin

In Type 1 and Type 2 forms, except the 2B variant, it is suggested to perform desmopressin testing to see if plasma levels of VWF increase after desmopressin administration. Desmopressin causes the release of endogenous VWF from endothelial deposits present in Weibel-Palade granules, resulting in increased plasma levels of VWF for 24-48 hours in all responsive cases, except for type 1C which exhibits accelerated VWF clearance. Patients who are responsive to desmopressin exhibit at least a 2-fold increase in levels of VWF antigen, VWF ristocetin co-factor and F VIII after two hours of infusion.

Desmopressin can be administered intravenously and diluted in 100 cc of saline to be infused in 30-40 minutes, either subcutaneously or intravenously. Endonasal administration may not guarantee treatment efficacy due to response variability linked to the mode of administration and absorption.

Before dosing and 1 and 4 hours after dosing, VWF Ag, ristocetin cofactor activity or VWF activity and FVIII should be sampled.

The response to desmopressin is generally considered positive if VWF levels increase by at least 2 times the baseline level or if they exceed the concentration of 0.5 IU/mL (or 50%). Typically, patients with VWD type I are responsive to desmopressin treatment, whereas patients with VWD type II are generally less responsive, but may still benefit from it to regulate mild to moderate bleeding.

It is reported that in patients with VWD 2B variant desmopressin is contraindicated as it can cause thrombocytopenia because of increased platelet-VWF binding.

Desmopressin is an antidiuretic hormone; therefore, on the day of administration, it is good clinical practice to recommend reducing liquids to avoid the risk of hyponatremia and fluid overload.

Desmopressin testing should be avoided during pregnancy.

Hemostatic therapy of heavy menstrual bleeding in patients with type 1 von Willebrand disease (American Society of Hematology guidelines)

The low certainty of evidence available is based on two studies:

A randomized clinical study comparing tranexamic acid with desmopressin administered intranasally and an observational study comparing hormone therapy alone with desmopressin.[16,17] Based on the first study, the American Society of Hematology guidelines suggest the use of tranexamic acid instead of desmopressin despite the low level of evidence.[18] It is noted that both studies used desmopressin intranasally, the efficacy of which may be reduced compared to intravenous administration. The hemostatic agents available for patients with HMB and von Willebrand disease are shown in Table 1A.[19]

In women with HMB, it is important to periodically assess and manage anemia by means of iron therapy to be administered by oral route, or intravenously in women who have issues with iron absorption or intolerance.

2. Management of abnormal uterine bleeding in patients with inherited or acquired platelet disease

In women with acquired or congenital platelet disorders who manifest AUB, hormonal therapy is the best choice to control the bleeding. However, some women do not want to take hormones because they want to get pregnant or suffer side effects that lead to the interruption of hormonal therapy.

The hemostatic therapies available for these situations are shown in Table 2A.

However, there is no strong evidence to support the following recommendations, which are based on expert reviews.[20] In the presence of quantitative and/or qualitative platelets disorders, non-steroidal anti-inflammatory drugs, including mefenamic acid, are contraindicated because they inhibit cyclooxygenase and thromboxane production, thereby suppressing platelet function.

Tranexamic acid

Tranexamic acid is an antifibrinolytic agent commonly used for the treatment of AUB. It has a short half-life and requires administration every 6-8 hours. Since it is usually employed in the days when the flow is most abundant (4 days/month), side effects are minor. These include gastrointestinal disorders and headache.

Tranexamic acid should be used with caution in women with a history of thromboembolism, although there is no clear evidence that its use increases the risk of thrombotic events.

It has been reported that it can result in a 50% reduction in menstrual flow.[21,22] It is indicated both in congenital and acquired platelets disorders.

Desmopressin

Desmopressin improves the hemostatic response in patients with some type of platelet disorders as it increases the levels of circulating VWF which facilitates the adhesion of platelets to the endothelium and the aggregation response.[23]

Only one study showed that desmopressin administered intranasally reduces menstrual flow in patients with platelet disorders.[21]

Recombinant activated factor VII

Recombinant activated factor VII (rFVIIa) is indicated for the management of severe acute bleeding in patients with Glanzmann thrombasthenia.[23] The proposed mechanism by which it acts in platelet disorders is the local procoagulant effect at the site of vascular damage, mediated by the generation of thrombin independent of tissue factor induced by the rFVIIa binding to the surface of activated platelets.

Although there is no evidence that it can be effective in other platelet disorders, in severe AUB patients who are refractory to antifibrinolytic therapy its administration can be considered.

Due to the risk of thrombosis in patients with a history of thromboembolism, care should be taken when administering rFVIIa.[20]

Platelet transfusions

Platelet transfusions may be necessary in patients with platelet disorders and those with severe bleeding not managed by other treatments such as tranexamic acid and desmopressin. In women of child-bearing age, consideration should be given to the fact that the administration of platelet transfusions may lead to the formation of antiplatelet antibodies, which may, in addition to platelet transfusion refractoriness, also cause fetal and neonatal alloimmune thrombocytopenia.

3. Treatment of rare coagulation defects

In the case of symptomatic hemophilia carriers A and/or B with reduced levels of FVIII/FIX, tranexamic acid may be administered at a dosage of 15-25 IU/kg every 8 hours after the start of flow. If this dose is not enough to stop bleeding in carriers of hemophilia A, desmopressin can be administered with a dose of 0.3-0.4 µg/kg if initially responsive.

In extreme cases, substitution therapy with FVIII/FIX may be administered at a dosage of 20 IU/kg. Table 3A shows the clinical management to be carried out in case of mild to severe bleeding in the presence of rare hereditary hemorrhagic coagulopathies.[24] The hemostatic levels to be reached for adequate hemostasis and the units of concentrate or plasma required to be administered are reported.

Table 1A. Hemostatic therapy of heavy menstrual bleeding in patients with von Willebrand disease (American Society of Hematology Guidelines) during days of increased menstrual flow.[19]

Drug	When to use it	Administration routes	Posology
Tranexamic acid	In all the types of VWD	Oral	15-25 mg/kg every 8 hours
Desmopressin*	VWD type 1, VWD type 2 responsive	Intravenous or subcutaneous Nasal spray	0.3 µg/kg (up to a maximum of 20 µg) Spray (150 µg) per weight <50 kg Spray (300 µg) per weight >50 kg

VWD, Von Willebrand disease. *It can be repeated, if necessary, up to a maximum of three doses (due to tachyphylaxis). It should not be administered for three consecutive days due to the risk of hyponatremia.

Table 2A. Hemostatic therapy of heavy menstrual bleeding in patients with congenital and/or acquired platelet disorders.

Drug	When to use it	Administration routes	Posology
Tranexamic acid	In all patients with platelet disease on days of increased flow	Oral	15-25 mg/kg every 8 hours
Desmopressin	In patients with some types of platelet disorders	Intravenous or subcutaneous	0.3 µg/kg (up to a maximum of 20 µg)[2]
Desmopressin	In patients with some type of platelet disorders	Nasal spray	1 spray (150 µg) per weight <50 kg 2 sprays (300 µg) per weight >50 kg
Factor VIIa recombinant	In patients with Glanzmann thrombasthenia, severe bleeding	Intravenous	90 µg/kg bolus, repeatable every 2 hours
Platelet transfusion	In the presence of severe bleeding not managed by other treatments	-	-

Table 3A. Clinical management in case of bleeding in the presence of rare hereditary hemorrhagic coagulopathies.

Deficiency factor	Hemostatic plasma levels (U/dL)	Half-life factor (hours)	Dose of concentrate to be administered	Dose of plasma (mL/kg)
Fibrinogen	30-50 µg/dL	72	Fibrinogen 20-30 µg/kg	15-20
Prothrombin (II)	20-30	72	Prothrombin complex 20-30 U/kg	15-20
Factor V	10-15	36	Not available	15-20
Factor VII	10-15	4-6	Plasma factor FVII: 30-40 U/kg Recombinant FVII: 15-30 µg /kg	-
Factor X	10-15	40	Plasma factor X 25 UI/kg	15-20
Factor XI	10-15	40	Plasma factor XI 15-20 U/kg	15-20
Factor XIII	5-10	60	Plasma factor XIII: 10-20 U/kg Recombinant factor XIII: 35 UI/kg	2-3

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