



Review

Clinical practice guidelines on menorrhagia: management of abnormal uterine bleeding before menopause

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ABSTRACT

Background: Normal menstrual periods last 3–6 days and involve blood loss of up to 80 ml. Menorrhagia is defined as menstrual periods lasting more than 7 days and/or involving blood loss greater than 80 ml. The prevalence of abnormal uterine bleeding (AUB) is estimated at 11–13% in the general population and increases with age, reaching 24% in those aged 36–40 years.

Investigation: A blood count for red cells + platelets to test for anemia is recommended on a first-line basis for women consulting for AUB whose history and/or bleeding score justify it. A pregnancy test by an hCG assay should be ordered. A speculum examination and Pap smear, according to the French High Health Authority guidelines should be performed early on to rule out any cervical disease. Pelvic ultrasound, both abdominal (suprapubic) and transvaginal, is recommended as a first-line procedure for the etiological diagnosis of AUB. Hysteroscopy or hysterosonography can be suggested as a second-line procedure. MRI is not recommended as a first-line procedure.

Treatment: In idiopathic AUB, the first-line treatment is medical, with efficacy ranked as follows: levonorgestrel IUD, tranexamic acid, oral contraceptives, either estrogens and progestins or synthetic progestins only, 21 days a month, or NSAIDs. When hormone treatment is contraindicated or immediate pregnancy is desired, tranexamic acid is indicated. Iron must be included for patients with iron-deficiency anemia. For women who do not wish to become pregnant in the future and who have idiopathic AUB, the long-term efficacy of conservative surgical treatment is greater than that of oral medical treatment. Placement of a levonorgestrel IUD (or administration of tranexamic acid by default) is recommended for women with idiopathic AUB. If this fails, a conservative surgical technique must be proposed; the choices include second-generation endometrial ablation techniques (thermal balloon, microwave, radiofrequency), or, if necessary, first-generation techniques (endometrectomy, roller-ball). A first-line hysterectomy is not recommended in this context. Should a hysterectomy be selected for functional bleeding, it should be performed by the vaginal or laparoscopic routes.

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1. Definitions

These guidelines describe the clinical practices recommended for abnormal uterine bleeding (AUB) in women of childbearing age, outside of pregnancy. They do not cover genital bleeding before puberty or after the menopause, or bleeding of cervical or vaginal origin.

Normal menstrual periods last 3–6 days and involve blood loss of up to 80 ml. Menorrhagia is defined as menstrual periods lasting more than 7 days and/or involving blood loss greater than 80 ml (QE2). The prevalence of AUB is estimated at 11–13% in the general population and increases with age, reaching 24% in those aged 36–40 years (QE2).

2. Diagnostic management [1–14]

2.1. History/interview

A specific targeted history is recommended for the diagnosis of AUB: any known uterine disease, induced vaginal bleeding, risk factors for hypothyroidism and any personal or family history of disorders of hemostasis must be sought with specific questions (Grade B). The prevalence of von Willebrand disease in women with menorrhagia averages 10%, higher than in the general population (level of proof 3). Appropriate questioning is needed to identify it (Grade B). It is important to ask women about whether they recently forgot to take one of more oral contraceptives, for that is a frequent cause of bleeding. Questions must also be asked about drug interactions and smoking, which can also cause bleeding (level of proof 2). Menstrual blood loss can be assessed simply, objectively and reproducibly with pictographs or a “bleeding score”. These can be used to manage patients and assess the efficacy of treatments (level of proof 2). For treatment trials, the most precise measurement of menstrual blood loss is recommended – the alkaline hematin method (Grade A) – but it can be approximated by the use of a menstrual pictogram (Grade B). Outside of clinical trials, a bleeding score remains useful for diagnostic management and treatment of AUB (Grade C).

2.2. Clinical examination

A complete clinical examination is recommended, including checking for signs of anemia, abdominal palpation, and a cervical examination, both digital and with a speculum (Professional Consensus), except for virgins or adolescents. When the history suggests nothing relevant, the pictogram is normal, the clinical examination is normal and no sign of anemia is present, no diagnostic investigation is recommended (Grade C).

2.3. Additional laboratory examinations

AUB is the most common cause of iron-deficiency anemia in non-menopausal women (level of proof 2). The clinical significance of iron deficiency without anemia is not clear. Physicians

should ask appropriate questions about AUB of all patients with anemia (microcytic or hypochromic) (Grade A). Inversely, a blood count for red cells + platelets to test for anemia is recommended on a first-line basis for women consulting for AUB whose history and/or bleeding score justify it (Grade B). A family or personal history of bleeding or disorders of hemostasis, in the absence of thrombocytopenia, calls for testing prothrombin and activated clotting time routinely and especially in the case of any surgery. Specific testing should be requested if von Willebrand disease is suspected (Grade B). For adolescents, especially, a broad range of reasons indicate the need for laboratory tests to look for a disease of hemostasis, the most frequent of which is von Willebrand disease (Grade C).

Depending on the context, a pregnancy test by an hCG assay should be ordered (Grade C), especially if the AUB is recent or associated with pelvic pain. A speculum examination and Pap smear, according to the French High Health Authority guidelines (http://www.has-sante.fr/portail/jcms/c_272243/conduite-atenir-devant-une-patiente-ayant-un-frottis-cervico-uterin-normal-actualisation-2002), should be performed early on to rule out any cervical disease (Grade C). A hormone work-up is not necessary for AUB except in patients with irregular cycles or risk factors for hypothyroidism (Grade B).

2.4. Imaging examinations [15–24]

Pelvic ultrasound: Pelvic ultrasound, both abdominal (suprapubic) and transvaginal, is recommended as a first-line procedure for the etiological diagnosis of AUB (Grade A). Doppler ultrasonography provides additional information useful for characterizing endometrial and myometrial abnormalities (Grade B).

Uterine exploration: Hysteroscopy or hysterosonography can be suggested as a second-line procedure when ultrasound suggests an intrauterine abnormality or if medical treatment fails after 3–6 months (Grade B). It is difficult to choose between these examinations, which perform similarly. Hysteroscopy is nonetheless preferred to hysterosonography for patients with risk factors for endometrial cancer (and should then be combined with a directed biopsy) (Grade B).

MRI is not recommended as a first-line procedure for the etiological diagnosis of DUB (Grade A) but may be proposed afterwards, if the ultrasound reveals a bulky, polymyomatous uterus, to map the fibromas, or if adenomyosis is suspected as well, to optimize the treatment strategy (Grade B). It can provide a diagnostic assessment of the endometrium when the uterine cavity is inaccessible (Grade C).

Hysteroscopy must be performed during the first part of the woman's cycle or after ensuring that she is not pregnant. Diagnostic hysteroscopy under general anesthesia is not recommended (Grade A). Saline is preferable to CO₂ for a diagnostic hysteroscopy, because it reduces the risk of pain and improves visualisation (Grade A). Similarly, a rigid small-diameter hysteroscope produces less pain and should be preferred (Grade B). In these conditions, antibiotic prophylaxis (Grade A), cervical

preparation with misoprostol (Grade A), and routine NSAID prescription (Grade C) are not recommended.

2.5. Endometrial biopsy

An endometrial biopsy must be performed in the case of any risk factor for endometrial cancer and for all patients older than 45 years (Grade C). A biopsy sample should be obtained with a polypropylene endometrial suction curette (Pipelle de Cormier) during the diagnostic hysteroscopy or hysterosonography (Grade B). Diagnostic curettage under general anesthesia is not recommended as a first-line treatment (Grade A). Hysteroscopic directed biopsies with forceps introduced through the instrument channel are now under evaluation.

3. Therapeutic management [25–57]

3.1. Continued fertility is desired

In idiopathic AUB, the first-line treatment is medical, with efficacy ranked as follows: levonorgestrel IUD (Grade A), tranexamic acid (Grade A), oral contraceptives, either estrogens and progestins (Grade B) or synthetic progestins only, 21 days a month (Grade B), or NSAIDs (Grade B). When hormone treatment is contraindicated or immediate pregnancy is desired, tranexamic acid is indicated (Grade A). Iron must be included for patients with iron-deficiency anemia (Grade A). Surgery has limited utility in this context. Curettage is the only surgical treatment that can be proposed, and its efficacy is random and temporary (Professional Consensus).

The management of organic AUB depends on the specific disorder identified:

- *Atypical endometrial hyperplasia*: Dilatation and curettage associated with medical treatment for 6 months (oral progestins (Grade B), GnRH analogs (Grade C), or levonorgestrel IUD (Grade C)), with an endometrial biopsy for a histologic assessment at the end of 6 months of treatment.
- *Endometrial polyps*: Hysteroscopic resection (Grade C): blind curettage without hysteroscopic control is not recommended (Grade C).
- *Uterine myomas*: Medical treatment can initially used to reduce the bleeding, correct anemia (Grade B) and reduce the volume of the fibroma.
 - In the case of intrauterine myomas, surgical treatment is preferred (Grade B), specifically, hysteroscopic resection as first-line treatment for the myomas of level 0, 1 (Grade B) and 2 (Grade C), less than 4 cm.
 - For interstitial or subserosal myomas: Initial management is medical (see idiopathic AUB) (Grade C). Should medical treatment fail or infertility result, an abdominal or laparoscopic polmyomectomy is then recommended (Grade C).
 - Data are currently insufficient to justify recommending arterial embolization for women with uterine myomas who want to become pregnant (Grade C).
- *Adenomyosis*: GnRH analog + add-back therapy or levonorgestrel IUD for 6 months (Grade C).
- *Arteriovenous malformation*: Uterine artery embolization has become the reference treatment for this; it does not harm ovarian function and preserves fertility (Grade B).

3.2. Continued fertility not desired

For women who do not wish to become pregnant in the future and who have idiopathic AUB, the long-term efficacy of conservative surgical treatment is greater than that of oral medical treatment (level of proof 1). Placement of a levonorgestrel IUD

(or administration of tranexamic acid by default) is recommended for women with idiopathic AUB. If this fails, a conservative surgical technique must be proposed (Grade A); the choices include second-generation endometrial ablation techniques (thermal balloon, microwave, radiofrequency), or, if necessary, first-generation techniques (endometrectomy, roller-ball) (Grade A). A first-line hysterectomy is not recommended in this context (Grade B). In all cases, the choice of surgical treatment must be determined with the patient after clear information about the benefits, risks, failure rate and satisfaction rate of each alternative (Grade B). Should a hysterectomy be selected for functional bleeding, it should be performed by the vaginal or laparoscopic routes (Grade A).

The management of organic AUB depends on the disease identified:

- *Atypical endometrial hyperplasia*: Because of the risk of development of endometrial cancer, radical surgical treatment (hysterectomy) should be suggested (Grade C).
- *Endometrial polyps*: Hysteroscopic resection of the polyp (Grade C), perhaps associated with endometrial resection or placement of a levonorgestrel IUD in non-menopausal women (Grade C).
- *Uterine myomas*: Medical treatment can be proposed initially, to reduce bleeding, correct anemia, or prepare for surgery (Grade B), or expectant management can be used to await the spontaneous disappearance of the symptoms at menopause (Grade C). Arterial embolization can be suggested as second-line (Grade A) treatment, as an alternative to surgery: Hysterectomy, the most effective treatment for fibromas, or, in the case of refusal, polmyomectomy. The site, size and number of fibromas are the essential indicators for guiding management while satisfying the patient's preferences.

Adenomyosis: The first-line treatment is a GnRH analogue or a levonorgestrel IUD (Grade C), endometrial resection or ablation (for superficial adenomyosis) (Grade C). In case of failure or refusal: hysterectomy.

3.3. Adolescents

In adolescents, AUB is usually associated with anovulation, polycystic ovaries, benign endometrial hyperplasia (level of proof 3) and, probably most often, coagulation disturbances (von Willebrand disease, thrombocytopenia, thrombopathies, etc.) (level of proof 3). The management of AUB requires, on the one hand, the identification and treatment of these disorders (Grade B) and, on the other, treatment of the blood loss, according to the outline described in the section on idiopathic menometrorrhagia in women who want to remain able to bear children. Of the medical treatments, the best choices are oral estrogen–progestin contraceptives and non-hormonal treatments (Grade C).

3.4. Patients receiving anticoagulant treatment or with a coagulation disorder

Multidisciplinary management is recommended (Professional Consensus). Treatment is identical to that for patients without coagulation disorders, with priority for medical treatment: the level of evidence for tranexamic acid, combined estrogen–progestins, and levonorgestrel IUDs is identical to that in the population without coagulation disorders. Surgical treatment should only be considered if medical treatment fails. Specific treatments can be used, such as desmopressin for von Willebrand disease (Grade C).

For patients taking anticoagulants, an emergency INR is recommended (Grade A). In case of overdose, measures to correct

the INR, whether or not the overdose is asymptomatic, are recommended (HAS 2007) (http://www.has-sante.fr/portail/upload/docs/application/pdf/2008-09/surdosage_en_avk_situations_a_risque_et_accidents_hemorragiques_recommandations_v2.pdf). If the INR is appropriate, showing the absence of an overdose, two questions must be asked:

1. search for an organic uterine disease, as in patients without anticoagulants;
2. the need to maintain a target INR as initially defined.

Some treatments are contraindicated, such as tranexamic acid or combined estrogen–progestins (Grade B), so that a levonorgestrel IUD would be preferable, or surgical treatments that should last over time, depending on the patient's age (Professional Consensus).

3.5. AUB while on contraceptives

Combined estrogen–progestins: Generally, the higher-dose pills cause less bleeding than the lower dose pills, for both estrogens and progestins (level of proof 1). The comparison of continuous vs cyclic pills shows less bleeding, in terms of duration and amount, but more breakthrough bleeding and spotting with the continuous pills (level of proof 1). Patients should most often be advised to wait 2 or 3 months before changing the pill prescription in the case of intermenstrual bleeding without an organic explanation (Grade C). When the bleeding does not improve, a more estrogenic or more antigonadotropic product should be recommended, if there are reasons to think there is an incomplete anti-gonadotropin effect (functional cyst) (Grade B). Continued administration might be suggested for women with heavy or prolonged (but irregular) bleeding (Grade B). After several unsuccessful trials of different products, another mode of contraception should be envisioned (Professional Consensus).

Progestin-only contraceptives: The onset of irregular intermenstrual bleeding/spotting may be improved in part either by administering an estrogen at a replacement dose or by reducing the duration of administration by 1 day, thus increasing the interruption window (8 days instead of 7) (Professional Consensus). Nonetheless this will not improve the situation for some women, and a different mode of contraception is then indicated. It is usual to recommend changing the type of pill or of contraception for women with frequent bleeding on progestin contraceptives (Professional Consensus). No data justify the recommendation of NSAIDs, antifibrinolytics, or added estradiol to diminish bleeding associated with the micro-progestin pills (Professional Consensus).

Appendix A

Grades of the HAS (French Health Authority) recommendations and guidelines:

Grade A: established scientific proof.

Grade B: scientific presumption.

Grade C: low level of proof or expert recommendation.

Level of proof 1–2–3 = level of scientific evidence (<http://www.eboncall.org/content/levels.html>)

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