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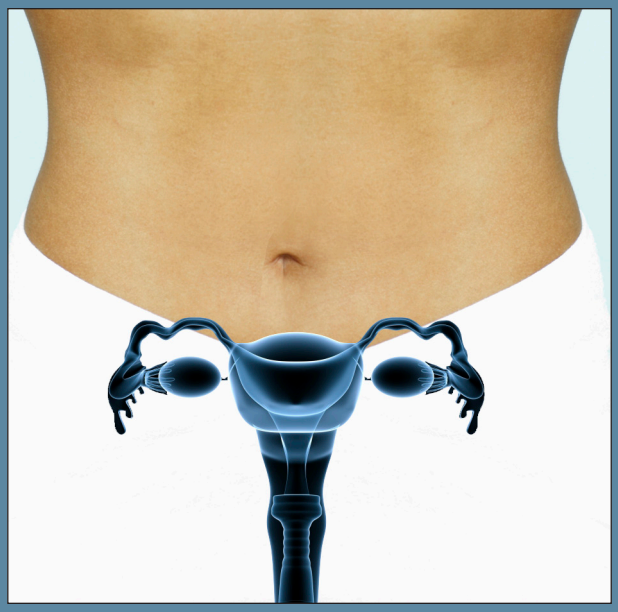

Abnormal Uterine Bleeding in Pre-Menopausal Women

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LA SOCIÉTÉ DES OBSTÉTRICIENS ET GYNÉCOLOGUES DU CANADA

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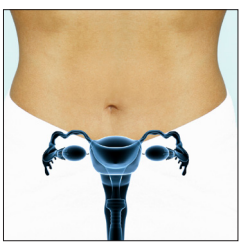

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Abnormal Uterine Bleeding in Pre-Menopausal Women

This clinical practice guideline has been prepared by the Clinical Practice – Gynaecology Committee, reviewed by the Canadian Paediatric and Adolescent Gynaecology/ Obstetrics Committee, and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

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Disclosure statements have been received from all members of the committee.

Abstract

Background: Abnormal uterine bleeding is the direct cause of a significant health care burden for women, their families, and society as a whole. Up to 30% of women will seek medical assistance for this problem during their reproductive years. This guideline replaces previous clinical guidelines on the topic and is aimed to enable health care providers with the tools to provide the latest evidence-based care in the diagnosis and the medical and surgical management of this common problem.

Objective: To provide current evidence-based guidelines for the diagnosis and management of abnormal uterine bleeding (AUB) among women of reproductive age.

Outcomes: Outcomes evaluated include the impact of AUB on quality of life and the results of interventions including medical and surgical management of AUB.

Methods: Members of the guideline committee were selected on the basis of individual expertise to represent a range of practical and academic experience in terms of location in Canada, type of practice, subspecialty expertise, and general gynaecology background. The committee reviewed relevant evidence in the English medical literature including published guidelines. Recommendations were established as consensus statements. The final document was reviewed and approved by the Executive and Council of the SOGC.

Results: This document provides a summary of up-to-date evidence regarding diagnosis, investigations, and medical and surgical management of AUB. The resulting recommendations may be adapted by individual health care workers when serving women with this condition.

Conclusions: Abnormal uterine bleeding is a common and sometimes debilitating condition in women of reproductive age. Standardization of related terminology, a systematic approach to diagnosis and investigation, and a step-wise approach to intervention is necessary. Treatment commencing with medical therapeutic modalities followed by the least invasive surgical modalities achieving results satisfactory to the patient is the ultimate goal of all therapeutic interventions.

Key Words: Menorrhagia, heavy menstrual bleeding, abnormal uterine bleeding, hysterectomy, endometrial ablation

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Evidence: Published literature was retrieved through searches of MEDLINE and the Cochrane Library in March 2011 using appropriate controlled vocabulary (e.g. uterine hemorrhage, menorrhagia) and key words (e.g. menorrhagia, heavy menstrual bleeding, abnormal uterine bleeding). Results were restricted to systematic reviews, randomized control trials/controlled clinical trials, and observational studies written in English and published from January 1999 to March 2011. Searches were updated on a regular basis and incorporated in the guideline to February 2013.

Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology-related agencies, clinical practice guideline collections, clinical trial registries, and national and international medical specialty societies.

Values: The quality of evidence in this document was rated using the criteria described in the Report of the Canadian Task Force on Preventive Health Care (Table 1).

Benefits, harms, and costs: Implementation of the guideline recommendations will improve the health and well-being of women with abnormal uterine bleeding, their families, and society. The economic cost of implementing these guidelines in the Canadian health care system was not considered.

Summary Statements

1. Abnormal uterine bleeding is a common condition affecting women of reproductive age that has significant social and economic impact. (II-2)
2. Contemporary terminology used to describe abnormal uterine bleeding in reproductive-aged women aims to simplify definitions and to provide standard descriptions related to patient presentation. (III)
3. The consequences of abnormal uterine bleeding on an individual's overall health determine the degree to which intervention may be required. (II-2)
4. A thorough history and physical exam will often indicate the cause of abnormal uterine bleeding and direct the need for further investigation and treatment (III).
5. Imaging and hysteroscopy offer the clinician additional information to assist in patient assessment and treatment in indicated circumstances. (I)
6. Once malignancy and significant pelvic pathology have been ruled out, medical treatment is an effective first-line therapeutic option for abnormal uterine bleeding. (I)
7. Medical treatment tailored to the individual woman's therapeutic goals, desire for contraception, underlying medical conditions, and tolerance of side effects will encourage compliance and maximize the likelihood of treatment success. (III)
8. Non-hysteroscopic ablation techniques offer similar patient satisfaction results with fewer risks of complications and less anaesthetic requirement than traditional hysteroscopic ablation. (I-A)
9. Hysterectomy provides definitive treatment for abnormal uterine bleeding.
10. Abnormal uterine bleeding secondary to submucosal fibroids may be managed by hysteroscopic myomectomy.
11. Inherited bleeding disorders may be an underlying cause of abnormal uterine bleeding, with von Willebrand's disease present in the majority of cases. (II-2)
12. Acute heavy menstrual bleeding may result in significant anemia and emergent care. (III)
13. Abnormal uterine bleeding in the adolescent most commonly represents ovulatory dysfunction related to immaturity of the hypothalamic-pituitary-ovarian axis. (II-2)

Recommendations

1. Adoption of standardized international terminology for abnormal uterine bleeding should be considered (III-C)
2. A complete blood count is recommended for women with heavy or prolonged bleeding. (II-2A)
3. If there is any possibility of pregnancy, a sensitive urine or serum pregnancy test should be performed. (III-C)
4. Testing for coagulation disorders should be considered only in women who have a history of heavy menstrual bleeding beginning at menarche or who have a personal or family history of abnormal bleeding. (II-2B)
5. Thyroid function tests are not indicated unless there are clinical findings suggestive of and index of possible suspicions of thyroid disease. (II-2D)
6. If imaging is indicated, transvaginal ultrasound should be the first line imaging modality for abnormal uterine bleeding. (I-A)
7. Saline infusion sonohysterography and diagnostic hysteroscopy should be used in the diagnosis and characterization of discrete intrauterine abnormalities such as submucosal fibroids. (I-A)
8. Endometrial biopsy should be considered in bleeding women over age 40 or in those with bleeding not responsive to medical therapy, as well as in younger women with risk factors from endometrial cancer. (II-2A)
9. Office endometrial biopsy should replace dilation and uterine curettage as the initial assessment of the endometrium for these women. (II-2A)
10. Focal lesions of the endometrium that require biopsy should be managed through hysteroscopy-guided evaluation. (II-2A)
11. Non-hormonal options such as non-steroidal anti-inflammatory drugs and antifibrinolytics can be used effectively to treat heavy menstrual bleeding that is mainly cyclic or predictable in timing. (I-A)
12. Combined oral contraceptive pills, depot medroxyprogesterone acetate, and levonorgestrel-releasing intrauterine systems significantly reduce menstrual bleeding and should be used to treat women with abnormal uterine bleeding who desire effective contraception. (I-A)
13. Cyclic luteal-phase progestins do not effectively reduce blood loss and therefore should not be used as a specific treatment for heavy menstrual bleeding. (I-E)
14. Danazol and gonadotropin-releasing hormone agonists will effectively reduce menstrual bleeding, and may be used for scenarios in which other medical or surgical treatments have failed or are contraindicated. (I-C)
15. Patients receiving a gonadotropin-releasing hormone agonist for longer than 6 months should be prescribed add-back hormone therapy, if not already initiated with gonadotropin-releasing hormone agonist commencement. (I-A)
16. The progestin intrauterine system has outcomes similar to endometrial ablation for women with heavy menstrual bleeding and thus may be considered prior to surgical intervention. (I-A)
17. In appropriate candidates, non-hysteroscopic ablation techniques should be the ablation methods of choice in view of their higher efficacy and safety than hysteroscopic techniques. (I-A)
18. With the exception of non-steroidal anti-inflammatory drugs, the same medical agents used to treat heavy menstrual bleeding among women with normal coagulation can effectively be used in the setting of inherited bleeding disorders. (II-1B)
19. Women with inherited bleeding disorders who have significant heavy menstrual bleeding or those who fail conventional

Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of evidence assessment*	Classification of recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case–control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D. There is fair evidence to recommend against the clinical preventive action
	E. There is good evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on Preventive Health Care.

Woolf SH, Battista RN, Angerson GM, Logan AG, Eel W. Canadian Task Force on Preventive Health Care. New grades for recommendations from the Canadian Task Force on Preventive Health Care. CMAJ 2003;169:207–8.

medical therapy are best managed with a multidisciplinary approach. (III-C)

20. Hysterectomy planning or blood product therapy should be performed in consultation with a hematologist in patients with inherited bleeding disorders. (III-C)

21. Acute heavy menstrual bleeding should be managed promptly and systematically to minimize patient morbidity and the need for blood transfusion. (III-C)

22. High-dose estrogen and tranexamic acid may help decrease or arrest acute heavy menstrual bleeding. (III-C)

23. For the adolescent presenting with heavy menstrual bleeding at or in close approximation to menarche, history and investigations should include an assessment for an underlying bleeding disorder. (II-2A)

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Introduction

Menstrual disorders are a common indication for medical visits among women of reproductive age[1] and heavy menstrual bleeding affects up to 30% of women throughout their reproductive lifetime.[2] These complaints may significantly affect quality of life,[3] result in time off work,[4] lead to surgical intervention including hysterectomy,[5] and ultimately have a significant impact on the health care system.[6]

The following guidelines provide a review of the current diagnosis and management options for abnormal uterine bleeding among women of reproductive age.

Summary Statement

1. Abnormal uterine bleeding is a common condition affecting women of reproductive age that has significant social and economic impact. (II-2)

ABBREVIATIONS

AUB	abnormal uterine bleeding
β-hCG	beta-human chorionic gonadotropin
CBC	complete blood count
CHC	combined hormonal contraceptives
cOCP	combined oral contraceptive pill
DMPA	depot medroxyprogesterone acetate
FIGO	International Federation of Gynecology and Obstetrics
GnRH	gonadotropin releasing hormone
IUS	intrauterine system
IV	intravenous
LNG	levonorgestrel
LNG-IUS	levonorgestrel-releasing intrauterine system
HPNCC	hereditary non-polyposis colorectal cancer
MPA	medroxyprogesterone acetate
NET	norethindrone (or norethisterone)
NSAIDs	non-steroidal anti-inflammatory drugs
OCP	oral contraceptive pill
PCOS	polycystic ovary syndrome
SIS	saline infusion sonohysterography
VTE	venous thromboembolism
vWF	von Willbrand's factor

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Definitions

Standardized universal terminology is essential in the discussion of AUB to improve communication among practitioners and to help guide research and education on this topic. Review of current terminology in medical and historical literature reveals confusing and inconsistent definitions referring to menstrual bleeding.[1] As a result, the FIGO Menstrual Disorders Working Group (an international expert consensus committee) has developed new guidelines for terminology related to this topic.[2] The suggested nomenclature for AUB aims to simplify descriptions of this clinical presentation and eliminate terminology such as menorrhagia, metrorrhagia, and dysfunctional uterine bleeding.

AUB may be defined as any variation from the normal menstrual cycle, and includes changes in regularity and frequency of menses, in duration of flow, or in amount of blood loss. Under the category of AUB, further definitions may be subdivided based on volume of menstruation, regularity, frequency, duration, chronicity, and timing related to reproductive status. Bleeding not related to menses may be further characterized as well. Tables 1.1 and 1.2 provides the terminology and descriptions consistent with the FIGO Menstrual Disorders Working Group consensus statement.[3,4]

Classic descriptions of AUB are based on the cyclicity and the quantity of menstrual flow. Although the patient's perception of the bleeding is not necessarily quantifiable, is paramount to the management of this problem. Ultimately, the woman's experience and the impact on her quality of life determine the degree to which intervention may be required. The patient's presentation of AUB depends upon her subjective experience and impression of the level of blood loss. As a result, a more holistic approach should be taken with these definitions.

Heavy menstrual bleeding is the most common complaint of AUB. It has been defined as "excessive menstrual blood loss which interferes with the woman's physical, social, emotional, and/or material quality of life . . . [that] can occur alone or in combination with other symptoms."[5]

Summary Statements

2. Contemporary terminology used to describe abnormal uterine bleeding in reproductive-aged women aims to simplify definitions and to provide standard descriptions related to patient presentation. (III)
3. The consequences of abnormal uterine bleeding on an individual's overall health determines the degree to which intervention may be required (II-2)

Recommendation

1. Adoption of standardized international terminology for abnormal uterine bleeding should be considered. (III-C)

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Table 1.1 Terminology for AUB

Terminology for variations in menstrual bleeding				
Volume	Regularity	Frequency	Duration	Other
Heavy	Irregular	Frequent	Prolonged	Intermenstrual
Normal	Regular	Normal	Normal	Premenstrual
Light	Absent	Infrequent	Shortened	Breakthrough

Table 1.2 Definitions of terms for uterine bleeding

Characteristic	Terminology	Description
Volume	Heavy menstrual bleeding	Excessive menstrual blood loss which interferes with the woman's physical, emotional, social, and material quality of life, and which can occur alone or in combination with other symptoms.
Regularity (Normal variation ± 2 to 20 days)	Irregular menstrual bleeding	A range of varying lengths of bleeding-free intervals exceeding 20 days within one 90-day reference period
	Absent menstrual bleeding (amenorrhea)	No bleeding in a 90-day period
Frequency (Normal every 24 to 38 days)	Infrequent menstrual bleeding	Bleeding at intervals > 38 days apart (1 or 2 episodes in a 90-day period)
	Frequent menstrual bleeding	Bleeding at intervals < 24 days apart. (More than 4 episodes in a 90-day period)
Duration (Normal 3 to 8 days)	Prolonged menstrual bleeding	Describes menstrual blood loss which exceeds 8 days in duration
	Shortened menstrual bleeding	Menstrual bleeding less than 3 days in duration.
Irregular, non-menstrual bleeding	Intermenstrual	Irregular episodes of bleeding, often light and short, occurring between otherwise fairly normal menstrual periods
	Post-coital	Bleeding post-intercourse.
	Premenstrual and post-menstrual spotting	Bleeding that may occur on a regular basis for one or more days before or after the recognized menstrual period.
Bleeding outside reproductive age	Post-menopausal bleeding	Bleeding occurring more than one year after the acknowledged menopause.
	Precocious menstruation	Bleeding occurring before the age of 9 years.
Acute or chronic AUB	Acute AUB	An episode of bleeding in a woman of reproductive age, who is not pregnant, that is of sufficient quantity to require immediate intervention to prevent further blood loss
	Chronic AUB	Bleeding that is abnormal in duration, volume, and/or frequency and has been present for most of the last 6 months

Evaluation

HISTORY, PHYSICAL EXAMINATION, AND LABORATORY INVESTIGATIONS

History and physical examination will help to establish the cause of the abnormal bleeding, to direct further investigations, and to guide options for management. Determining the amount, frequency, and regularity of bleeding, the presence of post-coital or intermenstrual bleeding, and any dysmenorrhea or premenstrual symptoms can help to distinguish anovulatory from ovulatory bleeding or to suggest anatomic causes such as cervical pathology or endometrial polyps. Ovulatory AUB is usually regular and is often associated with premenstrual symptoms and dysmenorrhea. Anovulatory bleeding, which is more common near menarche and the perimenopause, is often irregular, heavy, and prolonged. It is more likely to be associated with endometrial hyperplasia and cancer.

Further history should include the following:

- symptoms suggestive of anemia (i.e. light-headedness, shortness of breath with activity)
- sexual and reproductive history (i.e. contraception, risk for pregnancy and sexually transmitted infections, desire for future pregnancy, infertility, cervical screening)
- impact on social and sexual functioning and quality of life
- symptoms suggestive of systemic causes of bleeding such as hypothyroidism, hyperprolactinemia, coagulation disorders, polycystic ovary syndrome, adrenal or hypothalamic disorders, and
- associated symptoms such as vaginal discharge or odour, pelvic pain or pressure.

A family history of inherited coagulation disorders, PCOS, or endometrial or colon cancer should also be sought, as well as any co-morbid conditions, such as hormonally dependent tumours, thromboembolic disease, or cardiovascular problems that would influence treatment options. Finally, a list of medications including over-the-counter and natural/herbal remedies that may interfere with ovulation or otherwise be associated with bleeding should be obtained (Table 2.1).[1–6] Physical assessment (Table 2.2) should look for evidence of systemic conditions that can cause abnormal bleeding and should evaluate the lower genital tract and pelvis to confirm the source of bleeding and to look for anatomic causes such as fibroids or cervical polyps.

A complete blood count is recommended if there is a history of heavy bleeding.[7,8] There is no evidence that routinely measuring serum ferritin adds information that will affect management if the CBC is normal.[9] If there is any chance of pregnancy, it should be ruled out through serum β-hCG. Sensitive thyrotropin stimulating hormone levels should be measured only if there are other symptoms or findings suggestive of thyroid disease.[7–9] Testing for coagulation disorders should be considered in women who have a history of heavy bleeding starting at menarche, a history of postpartum hemorrhage or hemorrhage with dental extraction, evidence of other bleeding problems, or a family history suggesting a coagulation disorder.[8] There is no evidence that measurement of serum gonadotropins, estradiol, or progesterone levels is helpful in the management of AUB.[7]

The differential diagnosis of AUB can be classified according to the suspected cause, based on findings from the history and physical examination. Other investigations may then be undertaken to confirm the cause or to rule out premalignant or malignant disease.

PALM-COEIN FIGO Classification for AUB

There are 9 main categories within the classification system named for the acronym PALM-COEIN (Table 2.3). Women with what was previously called "dysfunctional uterine

Table 2.1 Medications that can be associated with abnormal uterine bleeding

Anticoagulants
Antidepressants (selective serotonin reuptake inhibitors and tricyclics)[1]
Hormonal contraceptives
Tamoxifen
Antipsychotics (first generation and risperidone)[2,3]
Corticosteroids
Herbs: ginseng,[4] chasteberry,[5] danshen[6]

Table 2.2 Physical assessment	
General assessment	Gynaecological examination
Vital signs	Inspection: vulva, vagina, cervix, anus, and urethra
Weight/BMI	Bimanual examination of uterus and adnexal structures
Thyroid exam	Rectal examination if bleeding from rectum suspected or risk of concomitant pathology
Skin exam (pallor, bruising, striae, hirsutism, petechiae)	Testing: Pap smear, cervical cultures if risk for sexually transmitted infection
Abdominal exam (mass, hepatosplenomegaly)	

bleeding" are likely to have one or more of coagulopathy, disorder of ovulation, or primary endometrial disorder.

An international expert consensus from the FIGO Menstrual Disorders Working Group has proposed a standardized classification system for AUB to facilitate greater appreciation of the complexities of this clinical entity.[10] This classification allows the characterization of more than one etiology in the same patient. The PALM side of the classification refers to structural causes that could be evaluated and diagnosed on imaging and/or biopsy. The COEIN side allows consideration of underlying medical disturbances that could result in AUB. The full details of this system are available through FIGO.[10]

Summary Statement

4. A thorough history and physical examination will often indicate the cause of abnormal uterine bleeding and direct the need for further investigation and treatment. (III)

Recommendations

2. A complete blood count is recommended for women with heavy or prolonged bleeding. (II-2A)
3. If there is any possibility of pregnancy, a sensitive urine or serum pregnancy test should be performed. (III-C)
4. Testing for coagulation disorders should be considered only in women who have a history of heavy menstrual bleeding beginning at menarche or who have a personal or family history of abnormal bleeding. (II-2B)
5. Thyroid function tests are not indicated unless there are clinical findings suggestive of an index of suspicions of thyroid disease. (II-2D)

IMAGING AND PATHOLOGY

Imaging and Hysteroscopy

Imaging studies in cases of AUB may be indicated when:

- examination suggests structural causes for bleeding,
- conservative management has failed, or
- there is a risk of malignancy

Ultrasound

Transvaginal sonography allows detailed assessment of anatomical abnormalities of the uterus and endometrium.[11] In addition, pathologies of the myometrium, cervix, tubes, and ovaries may be assessed. This investigative modality may assist in the diagnosis of endometrial polyps, adenomyosis, leiomyomas, uterine anomalies, and generalized endometrial thickening associated with hyperplasia and malignancy.

Saline infusion sonohysterography involves the introduction of 5 to 15 mL of saline into the uterine cavity during transvaginal sonography and improves the diagnosis of intrauterine pathology. Especially in cases of uterine polyps and fibroids, SIS allows for greater discrimination of location and relationship to the uterine cavity.[12–14] As a result, SIS can also obviate the need for MRI in the diagnosis and management of uterine anomalies.

CLINICAL TIPS

1. **Ultrasound endometrial assessment**: The endometrium is measured as the maximum anterior-posterior thickness of the echo on a long-axis transvaginal view of the uterus. The normal endometrium in a premenopausal woman varies in thickness according to the menstrual cycle from 4 mm in the follicular phase up to 16 mm in the luteal phase.
2. **SIS** is a useful imaging modality prior to planned hysteroscopic or laparoscopic procedures for fibroids, polyps, and uterine anomalies to ensure safe and appropriate interventions.

MRI

MRI is rarely used to assess the endometrium in patients who have menorrhagia. It may be helpful to map the exact location of fibroids in planning surgery and prior to therapeutic embolization for fibroids. It may also be useful in assessing the endometrium when transvaginal ultrasound or instrumentation of the uterus (i.e. congenital anomalies) cannot be performed.

Hysteroscopy

Hysteroscopic evaluation for abnormal uterine bleeding is an option providing direct visualization of cavitary pathology and facilitating directed biopsy.[15]

Hysteroscopy may be performed in an office setting with or without minor anaesthesia or in the operating room with regional or general anaesthesia. Directed biopsies under direct vision provide the main benefit over "blind" dilation and uterine curettage. The risks of hysteroscopy include perforation of the uterus, infection, cervical lacerations, creation of false passages, and fluid overload.

Summary Statement

5. Imaging and hysteroscopy offer the clinician additional information to assist in patient assessment and treatment in indicated circumstances. (I)

Recommendations

6. If imaging is indicated, transvaginal ultrasound should be the first line imaging modality for abnormal uterine bleeding. (I-A)
7. Saline infusion sonohysterography and diagnostic hysteroscopy should be used in the diagnosis and characterization of discrete intrauterine abnormalities such as submucosal fibroids. (I-A)

Table 2.3 PALM-COEIN Classification of AUB

Structural causes	Non-structural causes
Polyps	Coagulopathy
Adenomyosis	Ovulatory dysfunction
Leiomyomas – Submucosal – Other	Endometrial (primary disorder of mechanisms regulating *local* endometrial "hemostasis")
Malignancy and hyperplasia	Iatrogenic
	Not yet specified

Table 2.4 Risk factors for endometrial cancer[1–7]

Age
Obesity (BMI > 30 kg/m^2)
Nulliparity
PCOS
Diabetes
HNPCC

ENDOMETRIAL ASSESSMENT AND BIOPSY

Endometrial Assessment in Premenopausal Women with Menorrhagia

Malignant and premalignant conditions may result in abnormal uterine bleeding and hence pathologic assessment of the uterine cavity may be required in women at risk.

The evaluation of the endometrium in premenopausal women with bleeding can be performed by several modalities. The endometrium may be assessed directly by endometrial biopsy, ultrasound, hysteroscopy, or dilation and curettage.

Risk Factors for Premalignant and Malignant Conditions of the Endometrium

The average age for women with endometrial cancer is 61 years, but 5% to 30% of cases occur in premenopausal women.[16] Women under the age of 50 share many of the risk factors for endometrial cancer of older women including obesity, diabetes, nulliparity, history of PCOS, and family history of hereditary non-polyposis colorectal cancer.[16–22] (Table 2.4)

Women with HPNCC have a lifetime risk for endometrial cancer and colorectal cancer of 40% to 60% and a 12% risk for ovarian cancer. Women who developed 2 primary cancers in their lifetime were identified from 5 large HPNCC registries; 51% had endometrial cancer diagnosed first (mean age 44). Therefore health care providers should be aware that younger women with a diagnosis of endometrial cancer may be at greater risk of colon and ovarian cancer.[23–25] Women with irregular bleeding and a history of nulliparity, obesity, polycystic ovarian syndrome, and diabetes, and a family history of HPNCC are at greater risk for premenopausal endometrial cancer. Younger women with these risk factors should be triaged for endometrial assessment.

Endometrial Biopsy

Office endometrial biopsy is a minimally invasive option for endometrial evaluation in women at risk of malignancy. Detection rates for malignancy are higher in postmenopausal women than in premenopausal women.[26]

Endometrial biopsy can usually be performed easily in a premenopausal woman with a previous vaginal delivery. These parous women are statistically at very low risk for uterine cancer. There exist many sampling devices with almost equivalent accuracy. Biopsies are more difficult in women with previous Caesarean sections, who are nulliparous, or who have had previous cervical surgeries, such as cone biopsy. The sample detects over 90% of endometrial cancers.[27] The sample is blind and therefore will miss a focal lesion. Hysteroscopic directed sampling is recommended in the situation of a focal lesion found on ultrasound.[28,29]

Pathology of the endometrium may diagnose endometrial cancer or determine the likelihood of coexistent cancer or a future cancer. For instance, in a recent study, cumulative 20-year progression of risk among women is less than 5% for non-atypical endometrial hyperplasia, but is 28% for atypical endometrial hyperplasia.[30]

CLINICAL TIP

1. Indications for endometrial biopsy in women with abnormal uterine bleeding
   - Age > 40
   - Risk factors for endometrial cancer (see Table 2.4)
   - Failure of medical treatment
   - Significant intermenstrual bleeding
2. Consider endometrial biopsy in women with infrequent menses suggestive of anovulatory cycles.

Dilatation and Curettage

Dilatation and curettage is no longer the standard of care for the initial assessment of the endometrium. It is a blind procedure, with sampling errors and risks of complications similar to hysteroscopy.[31–33]

Recommendations

8. Endometrial biopsy should be considered in bleeding women over age 40 or in those with bleeding not responsive to medical therapy, as well as in younger women with risk factors from endometrial cancer. (II-2A)
9. Office endometrial biopsy should replace dilation and uterine curettage as the initial assessment of the endometrium for these women. (II-2A)
10. Focal lesions of the endometrium that require biopsy should be managed through hysteroscopy-guided evaluation. (II-2A)

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Medical Treatment

OVERVIEW

Once malignancy and significant pelvic pathology have been ruled out, medical treatment should be considered as the first line therapeutic option for abnormal uterine bleeding. Targeted treatment for an underlying medical condition that can affect menstrual bleeding, such as hypothyroidism, should be initiated prior to the addition of any of the medical agents described. Women found to be anemic due to uterine bleeding should start iron supplementation immediately.

Regular, heavy menstrual bleeding can be successfully treated with both hormonal and non-hormonal options. Non-hormonal treatments such as non-steroidal anti-inflammatory drugs and antifibrinolytics are taken during menses to reduce blood loss, and thus are effective mainly in the setting of heavy menstrual bleeding when the timing of bleeding is predictable.

Irregular or prolonged bleeding is most effectively treated with hormonal options that regulate cycles, decreasing the likelihood of unscheduled and potentially heavy bleeding episodes. Cyclic progestins, combined hormonal contraceptives, and the levonorgesterel-releasing intrauterine system are examples of effective options in this group, providing more predictable cycles while protecting the endometrium from unopposed estrogen and the risk of hyperplasia or carcinoma. Medical therapy can also be useful in some instances to reduce menstrual losses associated with fibroids or adenomyosis.

Regardless of the type of abnormal bleeding, a patient-centred approach to the selection of a specific medical therapy is essential. Satisfaction and continuation of any given treatment will be influenced not only by efficacy, but also by the individual woman's goals and tolerance of side effects. The decision to proceed with a trial of medical treatment should be based on a discussion of patient preference, desire for fertility or contraception, underlying medical conditions or contraindications, presence of dysmennorrhea, and severity of the bleeding. The medical treatment of acute uterine bleeding will be discussed separately. Table 3.1 summarizes the available medical treatments. The Appendix provides additional details on the mechanisms, dosing regimens, efficacy, adverse effects, and contraceptive benefits of each medical treatment option.

NON-HORMONAL TREATMENTS

NSAIDS

Elevated levels of prostaglandin E_2 and prostaglandin $F_{2-\alpha}$ have been demonstrated within the uterine tissues of women with heavy menstrual bleeding.[1] Cyclo-oxygenase converts arachidonic acid to prostaglandins within the endometrium. NSAIDS reduce total prostaglandin production through the inhibition of cyclo-oxygenase,[2] shifting the balance between prostaglandins and thromboxanes to promote uterine vasoconstriction.[3]

In a Cochrane review including 17 randomized trials, NSAIDs reduced menstrual blood loss by 33% to 55% when compared with placebo, without a significant difference in adverse effects.[4] NSAIDs also have the added benefit of improving dysmenorrhea for up to 70% of patients.[5] Although mefenamic acid and naproxen are the most extensively studied, ibuprofen, diclofenac, indomethacin, and ASA have all been shown be effective when taken during menses. Therapy ideally begins the day before menses, and continues for 3 to 5 days or until bleeding ceases. Contraindications to NSAID therapy include hypersensitivity, pre-existing gastritis, and peptic ulcer disease. Side effects such as gastrointestinal upset are unlikely to be significant or cause discontinuation since therapy continues only for a few days each month.

Clinical trials comparing NSAIDs to other medical agents have found them to be less effective in objectively reducing menstrual blood loss than tranexamic acid, the combined oral contraceptive pill, danazol, or the LNG-IUS.[6–10] Significant differences in efficacy between different NSAIDs have not been demonstrated, but Naproxen was found to have a higher risk of gastrointestinal side effects than mefenamic acid in one trial.[11]

Antifibrinolytics

Plasminogen activators are a group of enzymes that cause fibrinolysis, or the degradation of blood clots. Women

Table 3.1 Effective medical treatment options for abnormal uterine bleeding

Non-hormonal	Non-steroidal anti-inflammatory drugs
	Antifibrinolytics
Hormonal	Combined hormonal contraceptives
	Levonorgestrel-releasing intrauterine system
	Oral progestins (long phase, days 5 to 26)
	Depot-medroxyprogesterone acetate
	Danazol
	GnRH-agonists

with heavy menstrual bleeding have been found to have elevated endometrial levels of plasminogen activators, with more local fibrinolytic activity than women with normal menstrual losses.[12,13] Tranexamic acid is an antifibrinolytic agent (or plasminogen activator inhibitor) that reversibly binds to plasminogen to reduce local fibrin degradation without changing blood coagulation parameters.[14]

Tranexamic acid has been shown to be effective in placebo-controlled trials, with an overall reduction in menstrual blood loss between 40% and 59% from baseline.[15,16] The most commonly prescribed and studied treatment regimen includes 1 gram of tranexamic acid taken orally every 6 hours during menstruation, but a single daily dose of 4 grams has also been found to be effective.[17] Intravenous tranexamic acid is available for more acute scenarios, with a dose of 10 mg/kg every 6 hours. Tranexamic acid does not treat dysmenorrhea.

Randomized trials have demonstrated the superiority of tranexamic acid to luteal-phase progestins[18] and NSAIDS,[7] with no significant difference in reported side effects, and a trend towards increased patient-perceived improvement. Side effects are usually mild, but may include nausea, vomiting, diarrhea, and headaches.

Whether the risk of venous thromboembolism is elevated by tranexamic acid is controversial. There were no reported thromboembolic events among the trials investigating the efficacy of tranexamic acid for "menorrhagia," but the studies were underpowered to detect this particular outcome.[16] A small retrospective study examining the use of antifibrinolytics among women at increased risk did not indicate an elevated risk of VTE,[19] and a population-based study from the United Kingdom showed an incidence of VTE with tranexamic acid similar to the spontaneous frequency of VTE among all women.[20] Regardless of the lack of evidence, many still caution against the use of antifibrinolytics among patients with a past history of thromboembolism.[21] A recent case–control study of women on medical therapy for menorrhagia found a higher risk of VTE among tranexamic acid users than among users of other hormonal and non-hormonal medications, but the difference did not reach statistical significance.[22] The risk of VTE was elevated among all of the women being treated for menorrhagia in this study, suggesting that "menorrhagia" itself may be a pro-thrombotic state.

HORMONAL TREATMENTS

Combined Hormonal Contraceptives

CHCs, including the oral contraceptive pill, contraceptive patch, and vaginal ring, provide excellent cycle control, significantly reduce menstrual losses, and improve dysmenorrhea. Menstrual blood loss is reduced up to 40% to 50% in women who take cOCPs in the traditional cyclic fashion.[23,24] The progesterone component provides ovulation suppression and inhibits ovarian steroidogenesis to create endometrial atrophy, while estrogen provides support to the endometrium to reduce the likelihood of unscheduled breakthrough bleeding. The majority of the medical contraindications to CHCs, including history of thrombosis or stroke, uncontrolled hypertension, migraine with neurologic symptoms, coronary artery disease, liver disease, and a history of breast cancer, are dangers primarily because of the estrogen component.[25] Please refer to the SOGC clinical practice guideline, "Canadian contraceptive consensus"[25] for further details on contraindications, adverse effects, and troubleshooting tips for CHCs.

Despite the widespread use of cOCPs containing ethinyl estradiol for the treatment of heavy menstrual bleeding in clinical practice, there remains a paucity of data from randomized trials on their efficacy in this setting.[26] A placebo-controlled randomized trial of a triphasic cOCP among women with irregular, heavy menses reported that 73.2% of subjects had a significant improvement in menstrual blood loss compared with 39.6% in the placebo group.[27] The only randomized trial of a monophasic pill for ovulatory

menorrhagia included just 45 women, and compared a cOCP with 30 mcg of ethinyl estradiol in a crossover design with danazol, tranexamic acid, and naproxen.[8] The cOCP reduced menstrual losses by 43% from baseline, with a similar improvement found among the other treatment groups. The contraceptive patch and vaginal ring have not been studied specifically for the treatment of abnormal bleeding, but have been found to reduce menstrual losses among normally menstruating women,[28,29] theoretically making them additional treatment options.

Extended-cycle and continuous use of cOCPs, the contraceptive patch, and the ring reduce both the amount of blood loss per cycle and the number of bleeding episodes per year compared with cOCPs used with a monthly pill-free period.[30–32] This regimen, with prolonged ovarian suppression, is particularly helpful for women with dysmenorrhea and pelvic pain, and should be considered in women with abnormal bleeding who also suffer from these conditions. Overall and given in any regimen, CHCs represent an excellent treatment choice for women with abnormal bleeding who are seeking a reliable method of contraception.

Oral Progestins

Cyclic progestins, such as medroxyprogesterone acetate or norethindrone (or norethisterone) taken for 12 to 14 days each month are a recognized treatment for anovulatory bleeding. About 50% of women with irregular cycles will achieve menstrual regularity with this regimen,[33] with the added benefit of protecting the endometrium from the effects of unopposed estrogen. However, luteal phase progestin alone is not an effective treatment for regular heavy menstrual bleeding. Studies examining the impact of NET 5 mg taken orally 2 or 3 times daily for 7 to 11 days a month in women with regular heavy menses did not demonstrate a significant reduction in mean blood loss from baseline.[34] A Cochrane meta-analysis including 7 randomized trials concluded that cyclic luteal-phase progestin therapy is significantly less effective in treating "menorrhagia" than NSAIDS, tranexamic acid, or danazol.[35] Common side effects from oral progestins include breast tenderness, water retention, weight gain, headaches, and acne.

In contrast, long-cycle, high-dose oral progestins have been shown to reduce menstrual losses for women with heavy menstrual bleeding. An extended regimen of cyclic oral NET 5 mg taken 3 times daily for 21 days (days 5 to 26) was compared with the LNG IUS in one trial of 44 women with regular cycles.[36] Both groups had a significant reduction in mean blood loss from baseline (87%), but the reduction was greater still for those randomized to the LNG-IUS. However, the patients taking high-dose oral NET were more likely find their treatment unacceptable due to side effects, with 78% refusing to continue therapy after three months. The likelihood of significant side effects using this high-dose regimen likely limits its practicality.

A proportion of women will experience a reduction in menstrual blood loss while taking the progesterone-only pill for contraception. This daily (non-cyclic) low-dose regimen of oral NET 0.35 mg has not been studied as a treatment for abnormal uterine bleeding.

Injected Progestin

Depot medroxyprogesterone acetate, while providing excellent contraception, is often used in clinical practice for treating heavy menstrual bleeding.

DMPA suppresses ovulation and ovarian steroidogenesis, reducing the estrogen-mediated stimulation of endometrium and ultimately causing endometrial atrophy. In trials examining the contraceptive efficacy of DMPA, over half of the women became amenorrheic after 1 year, but many reported unscheduled bleeding in the first few months.[37] In addition to irregular breakthrough bleeding or spotting, other commonly reported side effects include breast tenderness, nausea, weight gain, mood disturbance, and a small reduction in bone mineral density that is reversible upon cessation. There are no published trials investigating the impact of DMPA on abnormal uterine bleeding.

The Levonorgestrel-Releasing Intrauterine System

In the absence of significant structural pathology, the LNG-IUS has been found to reduce menstrual losses significantly, and has recently been approved by Health Canada in the treatment of idiopathic menorrhagia.[38,39] It has also been found to improve dysmenorrhea[40] and pelvic pain due to endometriosis.[41,42] This 32 mm device administers 20 μg of levonorgestrel directly to the endometrium each day, inducing endometrial atrophy and reducing mean uterine vascular density.[42] Minimal concentrations of LNG are absorbed into the systemic circulation (0.4 to 0.6 nmol/L), limiting the likelihood of systemic hormonal side effects.[43] Both the contraceptive effect and the control of uterine bleeding have been shown to last up to 5 years.[43]

A reduction in menstrual blood loss of 86% at 3 months and 97% at 12 months was demonstrated in a single-arm study on the use of the LNG-IUS in women with menorrhagia, and numerous other studies have reported similar results.[38,44] Hemoglobin and serum ferritin levels have been shown to increase after insertion of the LNG-IUS among women with anemia due to heavy menstrual bleeding.[45,46] Many women will become completely amenorrheic, with reported rates in the range of 20%

to 80% at 1 year.[47] The LNG-IUS has been shown to be substantially superior to other medical treatments, including NSAIDS and tranexamic acid.[39] There currently are no published trials comparing the efficacy of LNG-IUS to combined hormonal contraceptives for abnormal uterine bleeding.

Several clinical trials have compared the efficacy and acceptability of the LNG-IUS to surgical treatments for abnormal bleeding including ablation and hysterectomy. A Cochrane meta-analysis of 8 trials comparing medical treatment to all surgical methods found that although endometrial destruction, and especially hysterectomy, more effectively reduce menstrual blood loss, the LNG-IUS provides an equivalent improvement in quality of life.[48] Hurskainen et al. randomized women with menorrhagia to receive either a hysterectomy or insertion of the LNG-IUS. The two groups had similar health-related quality of life scores at 5 years.[49] In a study of women awaiting hysterectomy, LNG-IUS users were compared with women who were maintained on a variety of other medical treatments.[50] Over two thirds of the women who had the LNG-IUS inserted cancelled their surgery versus just 14.3% in the control group.[50]

The most commonly experienced side effects after LNG-insertion include irregular bleeding and spotting, cramping, and hormonal side effects such as breast tenderness, mood changes, and acne. Hormonal symptoms are usually mild and dissipate with time, with only 1 to 2 per 100 women discontinuing therapy at 1 year due to these symptoms.[51] Irregular bleeding after insertion is common, but typically resolves, and thus patients should be counselled accordingly. Irregular, prolonged bleeding (more than 8 days) has been reported to decrease from 20% in the first month, to just 3% at 3 months.[52] Irregular post-insertion bleeding may take longer to settle among women with menorrhagia, with an average of up to 6 months reported.[53]

There are a limited number of contraindications to LNG, but insertion of the LNG-IUS requires an endometrial cavity that is 6 to 9 cm in length with minimal distortion. The risk of expulsion and perforation depends partially on the skill of the provider inserting the device. The overall risk of perforation with insertion is less than 1 per 1000.[54] The likelihood of expulsion is 1 in 20 over 5 years, but is most likely to occur with the first menses after insertion.[55] The LNG-IUS should be used with caution among women who are severely immuno-compromised or at high risk of sexually transmitted infections.[39] The risk of the development of pelvic inflammatory disease is greatest within the first 20 days following LNG-IUS placement, and is less than 1% among low-risk women.[56]

Danazol

Danazol induces endometrial atrophy by inhibiting ovarian steroidogenesis through suppression of the pituitary-ovarian axis,[57] and has been reported to reduce menstrual losses by up to 80%.[54,58] The typically prescribed regimens range between 100 to 400 mg/day in divided doses, with higher doses generally more effective in controlling bleeding than lower doses. With lower doses of 100 to 200 mg/day, approximately 20% of women will become amenorrheic, and the majority will become oligomenorrheic.[59] Danazol is associated with significantly more adverse effects than other medical therapies, specifically including weight gain, acne, and androgenic effects.

Gonadotropin Releasing Hormone Agonists

GnRH agonists induce a reversible hypogonadal state. Endometrial atrophy and amenorrhea are usually achieved among premenopausal women within a 3 to 4 week period.[60] In addition to effectively treating heavy menstrual bleeding, GnRH agonists provide relief from dysmenorrhea associated with adenomyosis and endometriosis.[60] Long-term use of GnRH agonists is limited by significant adverse effects, including bone pain, loss of bone density, and hypoestrogenic effects including hot flashes, night sweats, and vaginal dryness. Add-back therapy with low-dose estrogen and progestins will minimize adverse effects, and should be administered if therapy is to extend beyond 6 months.[61] GnRH agonists have been shown to reduce uterine and leiomyoma volume by up to 60%,[62] and thus are often used for short-term preoperative therapy, but the effects are reversed once treatment ceases.[62] The long-term use of GnRH agonists in the setting of abnormal bleeding should be limited to scenarios in which other medical or surgical treatments are contraindicated. Patients should be warned of the possible temporary "flare" or exacerbation of symptoms immediately after GnRH injection.

CLINICAL TIP

The long-term use of GnRH agonists in the setting of abnormal bleeding should be limited to scenarios in which other medical or surgical treatments are contraindicated.

Summary Statements

6. Once malignancy and significant pelvic pathology have been ruled out, medical treatment is an effective first line therapeutic option for abnormal uterine bleeding. (I)
7. Medical treatment tailored to the individual woman's therapeutic goals, desire for contraception, underlying medical conditions, and tolerance of side effects will encourage compliance and maximize the likelihood of treatment success. (III)

Recommendations

11. Non-hormonal options such as non-steroidal anti-inflammatory drugs and antifibrinolytics can be used effectively to treat heavy menstrual bleeding that is mainly cyclic or predictable in timing. (I-A)
12. Combined oral contraceptive pills, depot medroxyprogesterone acetate, and levonorgestrel-releasing intrauterine systems significantly reduce menstrual bleeding and should be used to treat women with abnormal uterine bleeding who desire effective contraception. (I-A)
13. Cyclic luteal-phase progestins do not effectively reduce blood loss and therefore should not be used as a specific treatment for heavy menstrual bleeding. (I-E)
14. Danazol and gonadotropin-releasing hormone agonists will effectively reduce menstrual bleeding, and may be used for scenarios in which other medical or surgical treatments have failed or are contraindicated. (I-C).
15. Patients receiving a gonadotropin-releasing hormone agonist for longer than 6 months should be prescribed add-back hormone therapy, if not already initiated with gonadotropin-releasing hormone agonist commencement. (I-A)

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Surgical Management

OVERVIEW

The role of surgery in the treatment of AUB requires a thorough evaluation of the underlying pathology and patient factors. The medical treatment of heavy menstrual bleeding is effective for many women, and treatment with the LNG-IUS may be comparable to surgical options for improving quality of life.[1]

The indications for surgery for women with AUB include

- failure to respond to medical therapy,
- inability to utilize medical therapies (i.e. side effects, contraindications),
- significant anemia,
- impact on quality of life, and
- concomitant uterine pathology (large uterine fibroids, endometrial hyperplasia).

Improvement in quality of life is the ultimate goal of treatment and may occur through achieving eumenorrhea or amenorrhea.[2]

Surgical options for managing AUB depend on several factors including the patient's expectations and uterine pathology (Figure). Surgical options include

- dilation and uterine curettage,
- hysteroscopic polypectomy,
- endometrial ablation,
- myomectomy, and
- hysterectomy

Dilatation and curettage, except possibly in cases of severe acute bleeding refractory to medical therapy, should be relegated to a diagnostic technique when endometrial sampling or hysteroscopic evaluation is not possible.[3,4]

HYSTEROSCOPY VERSUS ENDOMETRIAL ABLATION

Hysteroscopy refers to the direct visualization of the endometrial canal, with the goal of diagnosis or management. Polypectomy, directed biopsy, and myomectomy may all be conducted using this intervention.

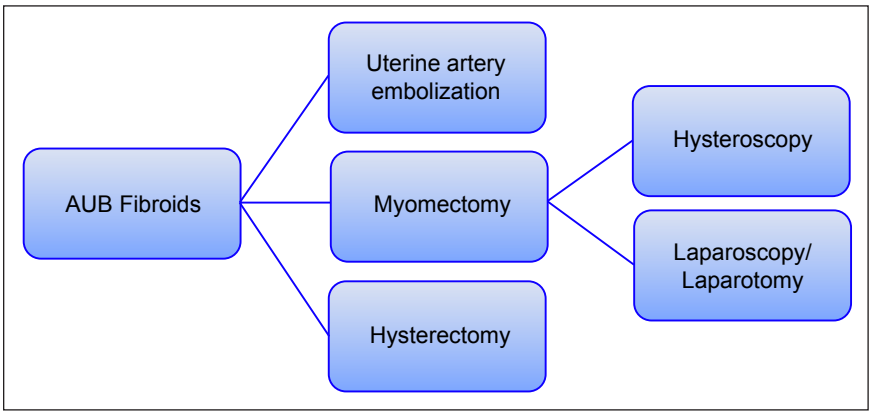
Endometrial ablation is a minimally invasive surgical option for heavy menstrual bleeding. It may be considered in women who have failed medical treatment, have completed childbearing, or who may not be candidates for major surgery. Two methods of endometrial ablation may be offered at the present time. The first method involves hysteroscopic resection and/or ablation. Previously termed "first generation" endometrial ablation, hysteroscopic guided endometrial ablation has a significant number of years of reported experience and effective results. Lethaby et al. reported in a meta-analysis of the trials in the Cochrane Database that hysteroscopic ablative methods are highly effective in controlling bleeding in from 87% to 97% of women.[5] Amenorrhea rates varied from 23% to 60%, with 6% to 20% ultimately requiring a further intervention (usually hysterectomy) in 1 to 5 years of follow-up.

Non-hysteroscopic techniques, or "second generation" technologies, include a number of varying modalities that all destroy the endometrium without direct visualization. Devices currently available in Canada include technologies that use a heated balloon, a radiofrequency bipolar technology, and a microwave device. These vary in type of energy used, time required, and outcomes. Comparisons of the varying technologies have been difficult because of the large number of competing options available. The main limitation of most non-hysteroscopic devices is their inability to treat uterine pathologies such as polyps and submucosal fibroids. Large or very small uterine cavities may also be contraindicated in some technologies.

Risks of endometrial ablation techniques include uterine perforation, infection, hemorrhage, and bowel or bladder injury. Post ablation syndrome is a condition associated with concomitant or previous tubal ligation and ablation and is a condition of hematometra resulting in cyclical pain with or without hematosalpinx. Risks specific to hysteroscopic techniques include fluid overload, especially with the use of hypotonic solutions (ex. 1.5% glycine), and resulting hyponatremia and its sequelae.[6]

Comparisons of hysteroscopic and non-hysteroscopic endometrial ablation techniques demonstrate similar patient satisfaction, with the main difference being risks

Management of AUB due to fibroids



of the procedure. Women undergoing non-hysteroscopic procedures were less likely to have fluid overload, uterine perforation, cervical lacerations, and hematometra than women undergoing hysteroscopic ablation.[5] In addition to patient safety, the non-hysteroscopic techniques require less time (average 15 minutes less) but do have more equipment problems.

A number of randomized controlled trials have been performed comparing endometrial ablative techniques to hysterectomy.[7–11] While an overall patient satisfaction rate of > 90% is reported for most types of endometrial ablation, up to 30% of women will require hysterectomy within 4 years.[12] However, hysterectomy is related to more risks for the patient and therefore a less invasive option, such as ablation, would offer the patient quicker recovery and a lower risk of complications.[13]

When compared with the progestin intrauterine system, ablation appears to have similar efficacy for bleeding control in women with menorrhagia and an otherwise normal uterine cavity.[14,15]

CLINICAL TIPS

Key points for counselling women planned for endometrial ablation:

1. confirm childbearing is complete;
2. require form of contraception;
3. rule out underlying uterine pathology (i.e. hyperplasia or malignancy);
4. clearly outline expectations (patient satisfaction, not amenorrhea); and
5. discuss the risk of requiring a hysterectomy in the future.

Summary Statement

8. Non-hysteroscopic ablation techniques offer similar patient satisfaction results with fewer risks of complication and less anaesthetic requirement than traditional hysteroscopic ablation. (I-A)

Recommendations

16. The progestin intrauterine system has outcomes similar to endometrial ablation for women with heavy menstrual bleeding and thus may be considered prior to surgical intervention. (I-A)
17. In appropriate candidates, non-hysteroscopic ablation techniques should be the ablation methods of choice in view of their higher efficacy and safety than hysteroscopic techniques. (I-A)

CLINICAL TIP

Several non-hysteroscopic ablation techniques are currently available. Balloon, microwave, and radiofrequency ablation devices have a large reported clinical experience. One of the main advantages of these techniques is their successful implementation in a surgical suite or clinic setting, which avoids the use of operating room resources and general anaesthetic.

HYSTERECTOMY

Hysterectomy offers women with AUB a definitive solution and is known to have high rates of patient satisfaction. However, less invasive options should initially be considered in order to avoid the potential complications that hysterectomy can entail.

If hysterectomy is required, the least invasive method should be offered to women to minimize morbidity and recovery time. According to a recent Cochrane review,[16] the ideal approach should be in order of least invasive to most. Since the publication of the last SOGC guidelines[17] on hysterectomy, the advantages of laparoscopic-assisted hysterectomy when the vaginal approach is not possible have been clarified in several studies, as well as in the Cochrane Review.[16] The details of hysterectomy approaches are not within the scope of this guideline.

Summary Statement

9. Hysterectomy provides definitive treatment for abnormal uterine bleeding. (I)

FIBROIDS

Uterine fibroids represent a common structural abnormality leading to AUB. Abnormal uterine bleeding may result if a part or entire fibroid is within the uterine cavity. Submucosal fibroids result in heavy and/or irregular bleeding due to a greater endometrial surface area, unstable vasculature which does not heal and repair as normal endometrium would, and inability of the uterus to contract to provide further compression of endometrial vessels.

The management of fibroids may include medical suppression, uterine artery embolization, or surgery. Surgery is dependent upon the patient's desire for future fertility and may include myomectomy or hysterectomy. Myomectomy may be conducted by laparotomy, laparoscopy, or hysteroscopy depending on the location and size of the fibroid and on the surgeon's experience.

Further details for the approach to the evaluation and management of fibroids are beyond the scope of this guideline.

CLINICAL TIPS

Fibroid localization with imaging is essential for appropriate management. Saline infusion sonohysterography and hysteroscopy provide information on the location of intrauterine or submucosal fibroids. These types of fibroids are related to heavy menstrual bleeding. AUB not responding to medical treatment may be due to intracavitary lesions such as submucosal fibroids.

Summary Statement

10. Abnormal uterine bleeding secondary to submucosal fibriods may be managed by hysteroscopic myomectomy. (I)

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Special Scenarios

INHERITED BLEEDING DISORDERS

Abnormal uterine bleeding is one of the most common manifestations of an inherited bleeding disorder, reported by up to 84% of women with von Willebrand's disease.[1] Conversely, 10% to 20% of all women presenting with heavy menstrual bleeding will ultimately be found to have an underlying bleeding disorder.[2,3] These conditions should therefore always be considered on the differential diagnosis for abnormal bleeding. Von Willebrand's disease is the most common inherited disorder, comprising 70% of cases.[4] Less common diagnoses include deficiencies in factor XI, VII, or XIII, carrier status for hemophilia A or B, and other inherited platelet function abnormalities.

Although all women with AUB should have a CBC including platelet count, the need for a further in-depth coagulation investigation is determined by a thorough history.[5,6] Important elements of the history include the pattern and severity of the bleeding, the past history of bleeding following other hemostatic challenges, and the family history of bleeding abnormalities or heavy menstrual bleeding. Women with bleeding disorders may present with a variety of different patterns of uterine bleeding at any age, but the majority will report heavy, regular, cyclic menses since menarche. Up to 50% of adolescents presenting with acute bleeding at menarche will have a coagulopathy,[7] and irregular or anovulatory bleeding is almost never caused by a hemostatic abnormality. Once structural uterine abnormalities have been ruled out, initial investigations should include prothrombin time, activated partial thromboplastin time, and ferritin when anemia is present. Special testing for von Willbrand's disease (factor VIII level, vWF antigen, and vWF functional assay) can be ordered by a family physician or gynaecologist, but interpretation and final diagnoses often require hematologic consultation. Please refer to the SOGC clinical practice guideline, "Gynaecological and Obstetric Management of Women with Inherited Bleeding Disorders,"[6] for a detailed discussion on the suggested evaluation and testing.

Many of the treatments for heavy menstrual bleeding used among women with normal coagulation can successfully be used among women with bleeding disorders. The exception is NSAIDS, which alter platelet function, and thus are contraindicated. The OCP[8] and the LNG-IUS[9] have both been found to reduce menstrual losses specifically among women with inherited bleeding disorders. Injected hormonal agents such as DMPA and GnRH agonists can be used for women with mild coagulation abnormalities, but more prolonged pressure applied to the injection site should be performed. Tranexamic acid can effectively used alone or added to any hormonal treatment method to help control menstrual bleeding among these women.[10]

When the typical hormonal and non-hormonal methods of treating uterine bleeding have failed, specific treatment including desmopressin or factor replacement can be considered. These treatments should only be administered with the assistance of a hematologist. Desmopressin, which releases vWF from platelets, has been used to treat bleeding in mild coagulation disorders.[11] It can be given during menstruation intravenously, intranasally, or subcutaneously. Conservative surgical treatment for refractory cases, including the various methods of endometrial destruction, can safely and effectively be performed in the setting of bleeding disorders.[12] Hysterectomy, if needed, should be planned carefully along with a hematologist, for measures to normalize coagulation factors preoperatively, intraoperatively, and postoperatively are needed in order to avoid excessive blood loss.

Summary Statements

11. Inherited bleeding disorders may be an underlying cause of abnormal uterine bleeding, with von Willebrand's disease present in the majority of cases. (II-2)

Recommendations

18. With the exception of non-steroidal anti-inflammatory drugs, the same medical agents used to treat heavy menstrual bleeding among women with normal coagulation can effectively be used in the setting of inherited bleeding disorders. (II-1B)
19. Women with inherited bleeding disorders who have significant heavy menstrual bleeding or those who fail conventional medical therapy are best managed with a multidisciplinary approach. (III-C)

20. Hysterectomy planning or blood product therapy should be performed in consultation with a hematologist in patients with inherited bleeding disorders. (III-C)

ACUTE BLEEDING

Abnormal uterine bleeding may present as an emergent and life-threatening condition if blood loss is significant. Significant uterine bleeding may signal a new presentation of an underlying systemic problem (i.e. a bleeding disorder), an acute or chronic bleeding problem, or a genital tract malignancy. Management of the symptomatic anemic patient with heavy uterine bleeding in the acute setting requires thorough and timely diagnosis and treatment.

In order to facilitate the acute treatment of patients with profuse abnormal uterine bleeding the following steps should be considered:

Stabilizing the Patient

General principles of acute resuscitation should be followed in all emergent cases. Assessment of vital signs (blood pressure, heart rate, cognition) will help triage patients who are actively bleeding. In patients with signs of hypovolemia due to bleeding, immediate intravenous fluid resuscitation should be started using crystalloid solution and blood products as necessary.

Examination/Diagnosis

Upon presentation a diagnosis is required to help direct therapy. Pregnancy must be ruled out upon presentation using history and chemical testing. Once pregnancy has been excluded, an examination will delineate the source of bleeding (see examination section). The volume of blood loss may be estimated by examining the patient for hemodynamic changes and hypovolemia.

- Although diagnosis is required, biopsy should be arranged in a timely fashion. If uterine bleeding is the cause, a biopsy may be performed but does not change management in an acute setting and may not provide an accurate result if bleeding is significant.
- Ultrasound will help determine whether fibroids, ovarian pathology, or other causes of bleeding are present.
- Bloodwork to assess for anemia, and in cases of significant blood loss, workup for disseminated intravascular coagulation, should be considered

Management of Acute Uterine Bleeding

Once a patient with acute uterine bleeding has been resuscitated with IV fluids and blood products, as necessary, the source of bleeding must be managed. Medical management is the preferred first line treatment and surgery should be reserved for cases unable to be managed medically. Medical management of acute uterine bleeding includes:

- IV estrogen is available as conjugated estrogens 25 mg every 6 hours.[13,14]
- Oral estrogen and/or OCP provided in high doses of cOCP, is the simplest form of treatment, and often will include a total of 100 mcg of ethinyl estradiol. Suggested regimens include two 35 mcg estrogen OCP tablets per day for 5 days, then reduced to once a day. This may be started with the IV therapy above.
- Nausea is a common side effect of high-dose estrogen and so should be mitigated by anti-nausea medications as needed.[14]
- Tranexamic acid may also be started at a dose of 1000 mg q6h IV or per os.
- Alternatives to the above regimens include high-dose progestins such as MPA (10 to 20 mg twice daily) or megestrol acetate (20 to 60 mg twice daily)

Maintenance Treatment

Once an acute episode has resolved, patients may be given daily OCP or tranexamic acid treatment until they are re-evaluated by endometrial biopsy or ultrasound. GnRH agonists may provide further suppression of the endometrium to offer patients symptomatic relief and time to correct anemia until a final treatment decision can be made. GnRH agonists when given alone may cause an exacerbation of uterine bleeding after the first dose. This may be avoided by maintaining patients on some type of suppressive therapy such as the OCP for the first week to 10 days.

Unable to Treat Medically or Failure of Medical Treatment

Medical treatment with high-dose estrogen or anti-fibrinolytics may be contraindicated in patients at high risk of thrombosis. This includes women with active VTE, inherited thrombophilias, myocardial infarction, cerebrovascular accidents, and diagnosed malignancy. If there is a clear contraindication or if medical treatment fails, a surgical approach may be required.

Surgery in the acute situation should remain a last resort due to the morbidity associated with operating on patients with acute anemia and the resulting impaired healing, further bleeding, and infection. Surgical options in the acute setting include uterine curettage and hysteroscopic ablation,[15] hysterectomy, and uterine artery embolization.

Summary Statement

12. Acute heavy menstrual bleeding may result in significant anemia and emergent care. (III)

Recommendations

21. Acute heavy menstrual bleeding should be managed promptly and systematically to minimize patient morbidity and the need for blood transfusion. (III-C)
22. High-dose estrogen and tranexamic acid may help decrease or arrest acute heavy menstrual bleeding. (III-C)

THE ADOLESCENT

AUB is common in the adolescent population, and heavy menstrual bleeding is experienced by 12.1% to 37% of adolescents.[16–18] Symptoms from AUB at puberty may be sufficient to cause interference with school performance. Adolescents' relative inexperience with menstruation may also lead to concern as to whether their symptoms are normal or not. A menstrual diary or pictorial blood assessment chart score can be helpful in this situation. The health care provider can assist the young woman and her family to understand what are normal versus abnormal menstrual cycles.

The etiology of AUB in adolescents has a similar differential diagnosis to that of adult women, however the relative proportion of causes differs. Within the PALM-COEIN Classification of AUB, the structural causes (leiomyomas, adenomyosis) are rare in adolescents.[19,20] AUB in adolescents is most often related to an immature hypothalamic-pituitary-ovarian axis. Within the first year following menarche up to 85% of cycles may be anovulatory. The proportion of ovulatory cycles increases with time from menarche but by the fourth gynaecologic year just over half (56%) are ovulatory.[21] Thus for an adolescent presenting within the first few years of menarche, after an appropriate directed history and focused investigations, ovarian dysfunction is often the etiology.

The age at presentation is important when considering etiologies beyond an immature hypothalamic-pituitary-ovarian axis. Oligomenorrhea at the age of 15 is most predictive of persistent cycle irregularity by early adulthood and warrants more widespread assessment.[22] Adolescents presenting with heavy menstrual bleeding at or close to menarche, particularly those who require visits to the emergency department, admission, or blood transfusion, may have a bleeding disorder in up to 48% of cases.[19,23–26] Other important diagnostic considerations are related to sexual activity. Confidential history taking should explore whether the adolescent is sexually active to rule out pregnancy related causes, contraceptive side effects, and sexually transmitted infections as an etiology for AUB.

Evaluation

For a sexually active adolescent the physical examination does not differ from that applied to an adult woman. However for the non-sexually active adolescent, assessment would generally not include a speculum or bimanual examination, but would rely on external assessment of the genitalia and abdominal examination. Ultrasound may therefore be helpful to rule out the rare structural cause of AUB in adolescents, but is again limited to the transabdominal approach based on sexual activity. Transvaginal ultrasound, saline infused sonohysterography, hysteroscopy, and MRI rarely play a role in the adolescent investigation.

The initial laboratory assessment in this age group does not differ from that recommended for adult women: an initial CBC, thyroid-stimulating hormone if there are symptoms of thyroid disease, and a β-hCG to exclude pregnancy. Further testing is directed by history, symptoms, and physical examination. As previously explained, investigations for a bleeding disorder should be performed if heavy menstrual bleeding onset is at or shortly following menarche.

Treatment

Therapy in adolescents, as in adult women, should be chosen based on the underlying etiology, the acuity of the presentation, and the side effect profile. All medical options, both non-hormonal and hormonal, can be applied to adolescents. An important consideration is the need for contraception. CHCs are an effective first line option for adolescent patients. Long-acting reversible contraceptives (injectable progestin, progestin IUS) may be also be considered first line therapies in sexually active adolescents, as well as in non-sexually active adolescents with individualized counselling. Past concerns regarding use of the progestin IUS for adolescents have included nulliparity, with smaller uteri and risks of expulsion, and pelvic inflammatory disease. Attitudes and guidelines have moved towards considering progestin IUS as a first line option in this younger population.[27–29] Multiple studies have shown their safety and efficacy, although their use in adolescents under 16 years of age has been limited.[30,31] The progestin IUS has also been used in adolescents with bleeding disorders, with drastic improvements in both pictorial bleeding assessment chart and quality of life scores.[32]

Danazol and GnRH agonists are not typically suggested for adolescents due to their side effect profiles.[33] Surgical therapy including hysteroscopy, endometrial ablation, and hysterectomy generally have no role in the management of AUB in adolescents. Surgery is limited to the rare structural anomaly (e.g. polyp or fibroid) that requires directed therapy.

Summary Statement

13. Abnormal uterine bleeding in the adolescent most commonly represents ovulatory dysfunction related to immaturity of the hypothalamic-pituitary-ovarian axis. (II-2)

CLINICAL TIPS

1. Selection of a medical therapy for AUB in adolescents should consider the need for contraception. Long acting reversible contraception may be considered first line therapy for both sexually active adolescents and, with individualized counselling, non-sexually active adolescents.
2. Oligomenorrhea at age 15 is highly predictive of persistent oligomenorrhea in early adulthood and warrants investigation.

Recommendation

23. For the adolescent presenting with heavy menstrual bleeding at or in close approximation to menarche, history and investigations should include an assessment for an underlying bleeding disorder. (II-2A)

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APPENDIX

SUMMARY TABLE OF MEDICAL TREATMENTS FOR ABNORMAL UTERINE BLEEDING

Treatment	Dose/Regimen	Mechanism	Contraindications	Adverse effects	Efficacy/Benefits	Contraception
Hormonal						
CHC (Combined hormonal contraceptives)	1. Daily pill (cOCP) for 21 days each month, 2. Continuous or extended regimen, 3. Contraceptive ring or patch cyclic or continuous	Suppression pituitary-ovarian axis, endometrial atrophy	History VTE or stroke, uncontrolled HTN, smoking > 15/day, over 35 years, migraine with aura, breast cancer, CAD, active renal/liver disease	Breast tenderness, mood change, fluid retention, BTB *Rare: VTE, stroke MI*	Menstrual regularity, 20% to 50% reduction in MBL, reduction in dysmenorrhea and PMS	Yes
LNG-IUS	20 µg per 24 hours local LNG, one IUS for up to 5 years	Local suppression endometrial proliferation and vascularity	Large intracavitary pathology, breast cancer, recurrent/recent PID	Irregular bleeding first 6 months, breast tenderness, acne, cramping, headaches	70% to 97% reduction in MBL, amenorrhea in up to 80% at 1 year, reduced dysmenorrhea	Yes
Cyclic oral progesterone	MPA 5 to 10 mg po for 10 to 14 d (luteal, anovulatory), NET 5 mg tid day 5–26 (long phase, ovulatory)	Inhibits endometrial proliferation	Pregnancy, breast cancer, liver disease,	Breast tenderness, mood changes, bloating, acne, headaches, weight gain	Bleeding reduced by up to 87% with long phase regimen	No (But will reduce ability to conceive while on tx)
Injected progesterone	DMPA 150 mg IM q90 days	Inhibits ovarian steroidogenesis and endometrial proliferation	Pregnancy, breast cancer, active liver disease, liver tumours	Irregular bleeding, breast tenderness, weight gain, mood changes, decreased BMD (reversible)	60% amenorrhea at 12 months, 68% at 24 months	Yes
Danazol	100 to 400 mg po daily	Inhibits ovarian steroidogenesis, endometrial atrophy	Liver disease	Weight gain, acne, muscle cramps, GI upset, irritability	80% reduction MBL, 20% amenorrhea, 70% oligomenorrhea	No
GnRH agonists	Leuprolide acetate (Lupron) IM monthly, 3 to 6 months (add back recommended if over 6 months)	Stops ovarian steroisogenesis, endometrial atrophy	Allergy, suspected pregnancy	Hypoestrogenic symptoms (hot flashes, night sweats, vaginal dryness), bone pain, loss of BMD, mood changes	Bleeding stopped in 89% by 3 to 4 weeks	No
Non-hormonal						
NSAIDS	Naprosyn 500 mg od-bid, ibuprofen 600 to 1200 mg od, Mefenamic acid 500 mg od starting day 1 or day before menses for 3 to 5 days or until ceases	Reduction in endometrial prostaglandins	Allergy, renal disease, untreated hypertension, platelet or coagulation disorders, active gastritis or peptic ulcers	Indigestion, worsening/ exacerbation of asthma, gastritis or peptic ulcers	20% to 50% reduction MBL, reduction in dysmenorrhea in 70%	No
Antifibrinolytics	Tranexamic acid (Cyclokapron) 1 gram po qid, 4 grams po daily single dose, during menses	Reversible blockade plasminogen, inhibits fibrinolysis	Past history VTE	Indigestion, diarrhea, headaches, leg cramps	40% to 59% reduction in MBL	No

HTN hypertension; CAD coronary artery disease; BTB breakthrough bleeding; MI myocardial infarction; MBL menstrual blood loss; PMS premenstrual syndrome; PID pelvic inflammatory disease; BMD bone mineral density; GI gastrointestinal; and IM intramuscular

NOTES

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