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REVIEW

Diagnosis and medical management of abnormal premenopausal and postmenopausal bleeding

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ABSTRACT

Abnormal uterine bleeding is a common reason for presentation to health-care providers: it is estimated that one woman in three will present to a care provider with abnormal uterine bleeding (AUB) during the reproductive years, and that at least one woman in 10 will experience postmenopausal bleeding. Although there are some variations in national guidelines for investigation, diagnosis and management of premenopausal AUB, there are far more areas of agreement than disagreement. A comprehensive literature search was undertaken to review national and international guidelines regarding investigation, diagnosis and management of AUB in both premenopausal and postmenopausal women. Areas of controversy are identified, and latest evidence reviewed. Although efforts to reduce hysterectomies for premenopausal AUB through medical management have largely been successful, there are areas where more research is necessary to guide optimal investigation and management. Many countries have well-defined guidelines for investigation and management of premenopausal AUB: there are fewer well-developed guidelines for investigation and management of postmenopausal bleeding. There is a paucity of evidence-based data on management of unscheduled bleeding on menopausal hormone therapy.

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Abnormal uterine bleeding in the reproductive years

Abnormal uterine bleeding (AUB) is the term used to encompass bleeding from the uterus that deviates from normal menstruation with respect to quantity of bleeding, duration, frequency and regularity of flow [1]. Menstrual disorders are a common indication for medical visits, and heavy menstrual bleeding may affect up to 30% of women during their reproductive lifetime. These complaints may have a significant impact on quality of life, time missed from work and health-care expenditure [2]. Some guidelines have been updated to make quality of life the impetus for treatment, rather than focusing on blood loss [3].

For the purpose of this review, standard terminology developed by the International Federation of Gynecology and Obstetrics (FIGO) Menstrual Disorders Working Group will be used [4].

Initial assessment – history and physical examination

There is agreement that evaluation of AUB should consist of a history, a physical examination, laboratory tests and, in some circumstances, imaging.

A thorough history will incorporate regularity of bleeding (irregular cycles are more likely to be anovulatory), and the presence of post-coital bleeding or intermenstrual bleeding mandates investigations such as cervical cancer and sexually transmitted infection screening. Sexual and reproductive history, including obstetrical history, current contraceptive use and desire for pregnancy (now or later), may help identify co-needs to tailor therapy. Any symptoms of systemic disease such as hypothyroidism, hyperprolactinemia, coagulation disorders, polycystic ovarian syndrome or adrenal disorders can guide further testing. Associated symptoms such as dysmenorrhea, pelvic pressure or vaginal discharge may provide further clues. Comorbidities such as hormonally dependent neoplasms, personal history of venous thromboembolic events, cardiovascular disease, liver disease or rheumatologic disease may guide decisions around treatment options.

Medication history is important, as antidepressants, antipsychotics, oral contraceptives, tamoxifen, anticoagulants, and certain herbal and complementary health products may be implicated in AUB [2].

A family history of inherited coagulation disorders or endometrial and colon cancer should be sought and further testing initiated if these are present. Hereditary non-polyposis

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colorectal cancer is a genetic mismatch-repair syndrome. Affected women have a 13–47% lifetime risk of endometrial cancer, and a 3–17% lifetime risk of ovarian cancer, depending on mutation [5]. Recommendations for testing and surveillance will differ from those without a family history.

There is agreement among international guidelines that a complete physical assessment is indicated [6]. Assessment of vital signs, body mass index, abdominal examination and assessment for endocrinopathies may help guide further investigations. Assessment of the vulva, urethra, perianal region, vagina and cervix, and bimanual examination of the uterus and adnexa, can provide clues to the origin of the bleeding abnormality and guide further laboratory or imaging tests.

Laboratory tests

There is moderate concordance among national and international guidelines regarding laboratory tests [6]. A complete blood count is recommended to diagnose anemia; some guidelines recommend serum ferritin to assess iron deficiency. While a hemoglobin determination will diagnose anemia, ferritin is the diagnostic test of choice for iron deficiency. Pregnancy testing is recommended by most guidelines. Female hormone testing is reserved for specific circumstances and has little value in a routine setting [7]. Thyroid testing is generally recommended only if signs or symptoms of thyroid disease are present. Testing for coagulopathies is recommended if heavy menstrual bleeding has been present since menarche or a family history is suggestive.

The role of endometrial biopsy in assessment

Most guidelines agree that there is a role for endometrial sampling in patients with AUB to diagnose endometrial hyperplasia or cancer, but there is some disagreement regarding whom to biopsy.

The Society of Obstetricians and Gynaecologists of Canada (SOGC) guidelines recommend routine endometrial biopsy in women with AUB age 40 years and older, or younger if risk factors such as obesity, nulliparity, polycystic ovary syndrome, diabetes or hereditary non-polyposis colorectal cancer are present [2]. A recent Canadian study has suggested that the risk of malignant or pre-malignant pathology in low-risk women up to the age of 49 ages is very low, suggesting that age alone should be removed as an indication for endometrial biopsy [8]. The National Institute for Health and Care Excellence (NICE) in the UK recommends directed endometrial biopsy at the time of hysteroscopy for women at high risk of endometrial pathology (including traditional risk factors, as well as those on tamoxifen or who have failed empiric medical management), while stating that blind endometrial biopsy should not be offered to women with heavy menstrual bleeding [3]. The American College of Obstetricians and Gynecologists (ACOG) recommends endometrial biopsy starting at age 45 years for investigation of AUB, and at younger ages if risk factors are present [9]. Organizations recommending blind endometrial biopsy uniformly favor in-office aspiration techniques [6].

The role of imaging

When imaging is indicated, there is agreement that transvaginal ultrasound (TVUS) is the first-line imaging modality. The indications for imaging vary between guidelines. Abnormal or inconclusive physical examination is considered an indication in the ACOG, NICE and FIGO [10] guidelines. In addition, the ACOG and SOGC propose lack of therapeutic success with first-line therapy as an indication for TVUS. TVUS is reliable in identifying structural abnormalities of the uterine corpus, but may be less reliable in the detection of intracavitary lesions such as polyps and sub-mucous fibroids [11]. If intracavitary lesions are suspected, hysteroscopy or sonohysterography are the preferred investigations for greatest diagnostic accuracy [11]. Measurements of endometrial thickness in premenopausal women are of no value in predicting cavitary pathology [12].

Diagnostic framework

In 2011, the FIGO classification of causes of AUB was introduced [13]. The purpose of introducing this classification was to aid and assist clinicians in the investigation, diagnosis and management of AUB. It was recognized that that these recommendations needed to be flexible, subject to ongoing review and to be used as a comprehensive but practical guide which allowed interpretation and clinical judgment. The 2018 update of this framework is shown in Figure 1.

This framework allows classification of AUB into two categories. The PALM category encompasses discrete structural entities that may be evaluated using a combination of imaging and histopathology. The COEIN group are generally not definable by histopathology or imaging.

The frequency of specific etiologies of AUB changes as patients age. Adolescents are more likely to have AUB as a result of ovulatory dysfunction or coagulopathy and are less likely to have structural abnormalities. Women over age 40 years may experience AUB due to ovulatory dysfunction, endometrial hyperplasia or cancer, or structural abnormalities such as polyps or myomas [14]. A Brazilian study of more than 4000 hysteroscopies for AUB showed the prevalence of histologically confirmed polyps in 27.5% of cases, and submucous myomas in 7.5% [15]. A study of 433 perimenopausal women with AUB discussed in a recent review concluded that the etiology was anovulatory bleeding in 79% [16].

Treatment of AUB

For the purpose of this review, only medical management options will be discussed. Non-medical approaches to the management of structural abnormalities have been addressed in other reviews [16].

There are many medical treatment options available for treatment of AUB when structural abnormalities have been

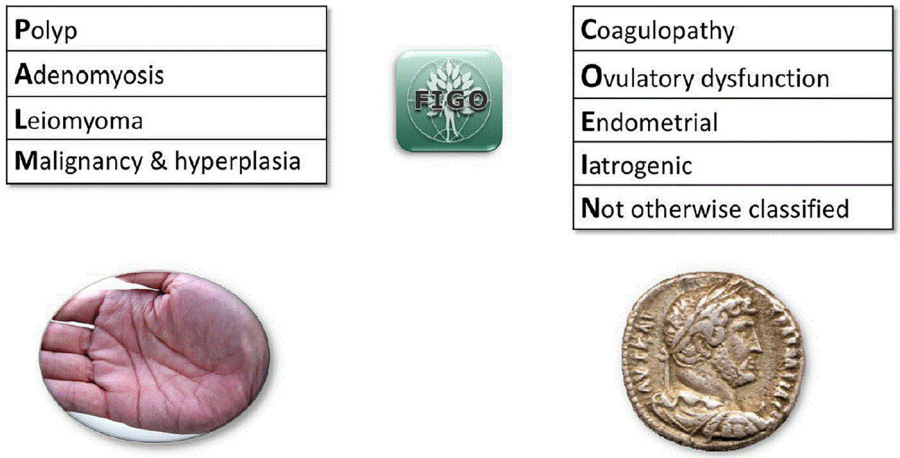

Figure 1. FIGO classification system of causes of abnormal uterine bleeding. From Munro et al. [10]. FIGO, International Federation of Gynecology and Obstetrics.

Table 1. Summary of medical treatments for AUB.

Treatment	*Dose*	*Efficacy for HMB (MBL)*	*Contraception*
Combined Hormonal Contraceptives	Cyclic or continuous	20–50% reduction	Yes
LNG-IUS 52 mg	continuous	70–97%	Yes
Cyclic oral progestin	Long phase (21 days)	87%	No
Injected progestin	DMPA 150 mg	60% amenorrhea	Yes
Danazol	100–400 mg daily	80%	No
GnRH agonists	Leuprolide acetate	89% amenorrhea	No
Tranexamic acid	1 g four times daily	40–59%	No
Non-steroidal anti-inflammatory drugs	Naprosyn 500 mg twice daily	20–50%	No

Adapted from Singh et al. [2, appendix]. DMPA, depo medroxyprogesterone acetate; GnRH, gonadotropin-releasing hormone; HMB, heavy menstrual bleeding; LNG-IUS, levonorgestrel-releasing intrauterine system; MBL, mean bloodloss.

ruled out. Suitability of various treatments should be ascertained based on each patient's medical history, risk and benefit discussion, co-need for contraception, and acceptability to the patient of any particular therapy.

The NICE guidelines [3] state that medical management is appropriate for women with no identified pathology, fibroids less than 3 cm in diameter which are not causing distortion of the uterine cavity or those with suspected or diagnosed adenomyosis.

Appropriate medical therapy may include the levonorgestrel-releasing intrauterine system (LNG-IUS) 52 mg, use of combined hormonal contraceptives, injectable progestins, long-phase oral progestins, tranexamic acid, danazol, and gonadotropin-releasing hormone (GnRH) agonists and antagonists (generally prescribed with add-back therapy) [6]. The SOGC guidelines [2] provide an estimate of efficacy and benefits (Table 1).

Attention should be paid to the contraindications and risk of each method. Advancing age is an important contributor to venous thromboembolism (VTE) risk, as women aged 45–49 years have almost four times the baseline VTE risk as a woman aged 15–19 years [17]. Body mass index has a substantial impact on VTE risk, and this risk is accentuated with use of combined hormonal contraceptives [18]. A large prospective trial estimates that women who use combined hormonal contraceptives, be they oral or non-oral, have a three-fold increase in VTE risk [19]. This study followed women using hormonal contraceptives containing ethinyl estradiol: newer combined hormonal contraception using the estrogen estetrol showed minimal increase in activated protein-C resistance [20]. Although this concept is promising, larger trials are necessary to determine whether the risk of VTE will actually be lower in women using this estrogen.

Women with heavy menstrual bleeding have been shown to have elevated levels of plasminogen activators compared to women with normal menstrual bleeding [21]. Tranexamic acid is an inhibitor of plasminogen activators, so has a role in management of heavy menstrual bleeding. The NICE advocates for use of tranexamic acid and/ or non-steroidal anti-inflammatory drugs while investigations and definitive therapy are being organized, and for as long as it is beneficial [6]. There is some disagreement as to whether or not tranexamic acid may be used as an adjunct to combined hormonal contraceptives in management of heavy menstrual bleeding: in the USA, current use of combined hormonal contraceptives is listed as a contraindication to concurrent use of tranexamic acid. There is little evidence in the literature to support this [22].

Use of the LNG-IUS has been shown to be extremely effective in the management of heavy menstrual bleeding, with reductions in menstrual blood loss of 86% at 3 months and 97% at 12 months [23]. A Cochrane meta-analysis demonstrated that use of LNG-IUS 52 mg in women with heavy menstrual bleeding produced an equivalent quality of life improvement to having surgery, including hysterectomy [24]. Choosing Wisely Canada, a medical initiative designed to improve quality of care and promote evidence-based management, advocates that surgical intervention for abnormal menstrual bleeding should not be entertained until medical management,

including the LNG-IUS 52 mg, have been declined by the patient or has failed [25].

Indications for surgical management

Indications for surgical management in the absence of structural abnormalities include failure to respond to medical therapies, inabilities to use medical therapies (side-effects, contraindications, cost), significant ongoing anemia or quality of life issues [2].

If endometrial ablation is chosen as a therapy, it should be restricted to premenopausal women at low risk of endometrial cancer with no desire for future fertility. They should have documented normal endometrial histopathology at a pre-ablation evaluation [16].

Uterine artery embolization, generally performed by an interventional radiologist, is a safe and minimally invasive procedure for management of heavy menstrual bleeding caused by uterine fibroids [16]. Although hysterectomy provides definitive treatment for AUB and is associated with high rates of patient satisfaction, less invasive treatment options should be considered to avoid the potential complications hysterectomy may entail [2].

Conclusions

AUB is a common problem, affecting as many as one in three women in their reproductive lifetime.

History and physical examination are important first steps. Minimal laboratory testing is indicated. Endometrial biopsy is indicated in those at elevated risk of endometrial cancer, or in those over age 40 or 45 years, depending on national guidelines. Further research into the worth of routine endometrial biopsies in low-risk women may change these recommendations.

If examination is normal, an empiric trial of medical therapy may be undertaken. If there is uncertainty about structural pathology, imaging is indicated, as large myoma or sub-mucous myoma may not respond to medical therapy.

Medical therapy may be dictated by the patient's desires, contraindications or co-needs (e.g. contraception). Medical therapy may consist of hormonal or non-hormonal entities. Surgery is generally not indicated in the absence of structural abnormalities, unless medical therapies are unsuccessful or unable to be utilized, or if there is a significant quality of life impairment.

Diagnosis and management of postmenopausal bleeding

Postmenopausal bleeding is defined as bleeding after 12 consecutive months of amenorrhea for which there is no other obvious physiological or pathological cause and in the absence of clinical intervention [26]. The frequency of spontaneous postmenopausal bleeding is widely accepted to be around 10%, with the incidence as high as 409 per 1000 women-years immediately after the first 12 months of amenorrhea, and falling to 42 per 1000 women-years 24 months after the first 12 months of amenorrhea [27].

It is recommended that evaluation be undertaken on all postmenopausal women not on menopausal hormone therapy (MHT) who bleed after 12 consecutive months of amenorrhea, women on unopposed estrogen who bleed, and women on cyclical estrogen and progestogen therapy who have atypical bleeding [28].

It is common for women on continuous combined MHT to have bleeding during the first 6 months of use; any bleeding after this time should be investigated [29].

Initial assessment

Initial assessment should include a complete medical history and thorough examination. Important elements in the history are reproductive history, tamoxifen exposure and family history, as these may be associated with an increased risk of endometrial cancer [30]. A physical examination should include elements such as body mass index, blood pressure, breast examination and comprehensive pelvic examination, including examination of the urethral and perianal regions. Cervical and sexually transmitted infection screening, if indicated, should be obtained. Although endometrial cancer is the diagnosis of exclusion, ruling out non-endometrial sources of bleeding is mandated.

What is the role of transvaginal ultrasound in diagnosis of postmenopausal bleeding?

TVUS is widely accepted as the initial investigation of choice. To be reassuring, the ultrasound examination must identify a thin, distinct endometrial echo. Any condition which precludes a satisfactory ultrasound examination (axial uterus, obesity, myomas, adenomyosis or previous uterine surgery) mandates further investigation with either sonohysterography, hysteroscopy or endometrial sampling [31]. Saline infusion sonohysterography is superior to TVUS for imaging of both focal and diffuse endometrial lesions, as it allows single-layer evaluation of the endometrium [32].

There is some debate around the upper limit of normal for endometrial thickness. A recent review has proposed the following criteria: for investigation of an initial episode of postmenopausal bleeding in a patient with low risk factors for endometrial cancer, an endometrial thickness of <4 mm is sufficient to exclude endometrial cancer. Those with endometrial thickness of >4 mm or elevated risk irrespective of endometrial thickness should be offered hysteroscopic assessment with directed biopsy [33]. For women with postmenopausal bleeding on MHT, those with an endometrial thickness of ≥ 8 mm should be offered hysteroscopic assessment [34]. Patients with postmenopausal bleeding on tamoxifen should be offered hysteroscopic assessment as an initial investigation [33].

Is there a role for blind endometrial biopsy?

Among patients with postmenopausal bleeding, endometrial carcinoma will be the final diagnosis in about 10% [35]. Tissue sampling is necessary to confirm the diagnosis.

There is little doubt that hysteroscopy with directed biopsy is superior to blind sampling [36]. However, resources (physical and human) may not make this approach feasible in all jurisdictions.

There are limitations to blind endometrial biopsy. Blind biopsy is only useful as an endpoint if it reveals endometrial carcinoma or atypical hyperplasia [14]. If a cancer occupies less than 50% of the endometrial cavity, it is more likely to be missed by biopsy [37]. Focal processes such as polyps or sub-mucous myomas are also unlikely to be diagnosed or sampled on blind biopsy.

Finally, it may not always be possible to obtain endometrial tissue sufficient for pathological examination by blind biopsy. There may be an inability to traverse the cervix, or insufficient tissue obtained for sampling. Conservatively, tissue insufficient for evaluation may be found in up to 47% of samples [38].

What are the most common diagnoses?

In women presenting with postmenopausal bleeding, there are several final diagnostic possibilities. In a study of 454 women with postmenopausal bleeding, at the endpoint of hysteroscopy or hysterectomy with histological evaluation, the most common finding was endometrial polyps in 38% of women. Atrophic tissue was next, at 31%. Malignancy or atypical hyperplasia was found in 6.8% [12].

Management of endometrial polyps

Asymptomatic endometrial polyps are present in between 13 and 38% of postmenopausal women. The risk of malignancy in a non-bleeding polyp is approximately 1.5% [39].

In postmenopausal women with bleeding and a polyp, the risk of malignancy has been reported to be 4.47% [39]. Risk factors for malignancy in a polyp are postmenopausal status, age over 60 years, postmenopausal bleeding, obesity, diabetes, hypertension and tamoxifen use [40]. It is recommended that all postmenopausal women with a bleeding polyp have it hysteroscopically resected, although individualized plans in consultation with the patient are allowed due to potential risks of surgery.

After individualized counseling regarding the low risk of malignancy, conservative management of asymptomatic polyps, especially in low-risk women with a polyp less than 2 cm in size, is recommended [41].

Recurrent postmenopausal bleeding

Women with recurrent postmenopausal bleeding are not more likely to have endometrial hyperplasia or cancer than women with a first episode of bleeding, but they are more likely to have endometrial polyps [42]. Recurrent bleeding requires a careful re-evaluation of all possible sources of bleeding. Hysteroscopic examination is recommended for evaluation of persistent or recurrent bleeding [43].

Bleeding while on MHT

Unscheduled bleeding while on MHT is not uncommon. The risk of malignancy on appropriate MHT is lower than in those not taking MHT. A recent review of women aged 60 years and under with postmenopausal bleeding while on MHT placed the risk of malignancy at 0.47% [44].

It is recommended that bleeding after the first 6 months of a continuous combined MHT regimen should be investigated, as well as unscheduled bleeding while on a cyclical regimen. Continuous regimens have a lower risk of malignancy than sequential regimens [29].

The most common reasons for unscheduled bleeding on MHT include polyps and sub-mucous fibroids.

There is controversy around the upper limit of normal for endometrial thickness while on MHT. For sequential therapies, ultrasound measurements should be performed during the first half of the cycle, where an endometrial thickness of 8 mm is the cut-off for biopsy among those with unscheduled bleeding [33]. For those on continuous MHT regimens, the recommendations are not clear and are often contradictory. An endometrial thickness of $\leq$5 mm is felt to be indicative of atrophy in a bleeding patient, and no further investigations are warranted. Other studies found no increase in endometrial cancers in bleeding patients with an endometrium $\leq$8 mm on ultrasound [33]. Much of the evidence for these suggestions are older, and do not necessarily reflect the current prescribing practices for MHT. More research is definitely necessary to establish contemporary, evidence-based recommendations.

Postmenopausal bleeding after endometrial ablation

Many patients who have had endometrial ablations for management of heavy menstrual bleeding are now entering menopause. There is very little guidance around investigation of postmenopausal bleeding in this population. Evaluation may be challenging, as iatrogenic scarring may impair the ability to sonographically evaluate the endometrium. Endometrial biopsy and hysteroscopy may not be feasible due to scarring.

A recent review of endometrial cancer after endometrial ablation showed an incidence of 0–1.6%. Of the 38 endometrial cancers in the review, vaginal bleeding was the initial presentation in 71% of patients. In only eight was an ultrasound able to measure thickness of the endometrial echo [45].

In the absence of evidence-based recommendations, decision-making around investigation and management should be done on a case by case basis [46].

Conclusions

Postmenopausal bleeding will affect about 10% of women, with a greater frequency of presentation in the first

12 months after the first 12 months of amenorrhea. Investigation begins with a history and physical examination. Endometrial carcinoma will be the diagnosis in 10% of women with postmenopausal bleeding and is the diagnosis to be excluded. TVUS is the first investigation of choice, as a uniform, thin, distinct endometrial echo will accurately identify the 40% of women in whom atrophy is the cause of the bleeding. If the echo is clearly and succinctly visualized in its entirety and is $\leq$4 mm, no further investigations are necessary in the average-risk woman.

A thickened endometrium is an indication for further investigation. This may take the form of hysteroscopy with directed biopsy and potential polypectomy, or sonohysterography. Where resources do not permit these investigations routinely, blind endometrial sampling may be undertaken. It is important to recognize the limitations of this approach, and to realize that endometrial sampling is an endpoint only if hyperplasia or malignancy is identified. In the absence of this finding, further evaluation by hysteroscopy is indicated. The most likely finding will be an endometrial polyp, or endometrial histological abnormality missed on blind biopsy.

Areas for further research and guideline development

There is a lack of sufficient evidence in the literature to guide evaluation of the bleeding postmenopausal endometrium under the influence of menopause hormone therapy. Endometrial carcinoma is rare while on MHT with appropriate endometrial protection, but evidence-based guidance on endometrial thickness and cancer risk would help to guide investigation and management. Uterine bleeding in the first 12 months after the diagnosis of menopause is common; endometrial cancer in this population is not. More data on this topic may help to change the definition of postmenopausal bleeding to eliminate the need for investigation in low-risk women. Finally, there is a dearth of published clinical practice guidelines to aid clinicians in evaluating postmenopausal bleeding in a concise, systematic manner.

The final word

For evaluation of abnormal bleeding in both premenopausal and postmenopausal women, a complete history and physical assessment is the first step, with a select few laboratory tests. In the premenopausal woman, a trial of medical therapy (depending on needs, co-needs and patient wishes) may be the next step. Imaging and histological evaluation may be reserved for those with abnormal physical findings or failure of medical management. Endometrial cancer is not common in this group. For patients with postmenopausal bleeding, where endometrial cancer is the diagnosis to exclude, imaging is the second step, with biopsy or hysteroscopic evaluation indicated for those with abnormal imaging or additional risk factors for endometrial cancer.

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References

[1] Fraser IS, Critchley HO, Broder M, et al. The FIGO recommendations on terminologies and definitions for normal and abnormal uterine bleeding. Semin Reprod Med. 2011;29(05):383–390.

[2] Singh S, Best C, Dunn S, et al. SOGC clinical practice guideline no 292—abnormal uterine bleeding in Pre-Menopausal women. J Obstet Gynaecol Can. 2018;40(5):e391-415–e415.

[3] Heavy Menstrual bleeding assessment and management. NICE guideline NG88. [Published 14 March 2018; cited 2021 May 24]. Available from: www.nice.org.uk/guidance/ng88.

[4] Fraser IS, Critchley HO, Munro MG, et al. Writing group for this menstrual agreement process: a process designed to lead to international agreement on terminologies and definitions used to describe abnormalities of menstrual bleeding. Fertil Steril. 2007; 87:466–476.

[5] Lim N, Hickey M, Young G, et al. Screening and risk reduction surgery for endometrial or ovarian cancers in lynch syndrome: a systematic review. Int J Gynecol Cancer. 2022;32(5):646–655.

[6] Tsakiridis I, Giouleka S, Koutsouki G, et al. Investigation and management of abnormal uterine bleeding in reproductive aged women: a descriptive review of national and international recommendations. Eur J Contracept Reprod Health Care. 2022;27(6): 504–517.

[7] National Collaborating Centre for Women's and Children's Health, National Institute for Health and Clinical Excellence. Clinical guideline CG44: heavy menstrual bleeding. London: Royal College of Obstetricians and Gynaecologists; n.d. http://www.nice.org.uk/nicemedia/live/11002/30401/30401.pdf.

[8] Cartier S, Mayrand MH, Gougeon F, et al. Endometrial biopsy in Low-Risk women: are we over-investigating. J Obstet Gynaecol Can. 2022;44(10):1097–1101.

[9] American college of obstetricians and gynecologists committee opinion number 557: management of acute abnormal uterine bleeding in nonpregnant Reproductive-Age women. Obstetrics and Gynecology. 2013;121(4):891–896.

[10] Munro M, Critchley H, Fraser I. The two FIGO systems for normal and abnormal uterine bleeding symptoms and classification of causes of abnormal uterine bleeding in the reproductive years: 2018 revisions. Int J Gynecol Obstet. 2018;143(3):393–408.

[11] Dueholm M, Lundorf E, Hansen E, et al. Evaluation of the uterine cavity with magnetic resonance imaging, transvaginal sonography, hysterosonographic examination, and diagnostic hysteroscopy. Fertil Steril. 2001;76(2):350–357.

[12] Van Den Bosch T, Ameye L, Van Schoubroeck D, et al. Intracavitary uterine pathology in women with abnormal uterine bleeding: a prospective study of 1220 women. Facts Views Vis ObGyn. 2015;7(1):17–24.

[13] Munro MG, Critchley HO, Broder MS, et al. FIGO working Group on menstrual disorders. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int J Gynecol Obstet. 2011;113:3–13.

[14] ACOG Practice bulletin no 128, july 2012. Diagnosis of abnormal uterine bleeding in reproductive-aged women. ACOG. 2012; 120(1):197–206.

[15] Lasmar R, Dias R, Barrozo P, et al. Prevalence of hysteroscopic findings and histologic diagnoses in patients with abnormal uterine bleeding. Fertil Steril. 2008;89(6):1803–1807.

[16] Goldstein SR, Lumsden MA. MA. Abnormal uterine bleeding in perimenopause. Climacteric. 2017;20(5):414–420.

[17] Silverstein MD, Heit JA, Mohr DN, et al. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. Arch Intern Med. 1998;158(6):585–593.

[18] Pomp ER, Le Cessie S, Rosendaal FR, et al. Risk of venous thrombosis: obesity and its joint effect with oral contraceptive use and prothrombotic mutations. Br J Haematol. 2007;139(2):289–296.
[19] Dinger J, Bardenheuer K, Heinemann K. Cardiovascular and general safety of a 24-day regimen of drospirenone-containing combined oral contraceptives: final results from the international active surveillance study of women taking oral contraceptives. Contraception. 2014;89(4):253–263.
[20] Douxfils J, Klipping C, Duijkers I, et al. Evaluation of the effect of a new oral contraceptive containing estetrol and drospirenone on hemoastasis parameters. Contraception. 2020;102(6):396–402.
[21] Gleeson N, Devitt M, Sheppard BL, et al. Endometrial fibrinolytic enzymes in women with normal menstruation and dysfunctional uterine bleeding. BJOG. 1993;100(8):768–771.
[22] Thorne JG, James PD, Reid RL. Heavy menstrual bleeding: is tranexamic acid a safe adjunct to combined hormonal contraception? Contraception. 2018;98(1):1–3.
[23] Bofill Rodriguez M, Lethaby A, Jordan V. Progesterone or progesterone-releasing intrauterine systems for heavy menstrual bleeding. Cochrane Database Syst Rev. 2020;6(6):CD002126.
[24] Marjoribanks J, Lethaby A, Farquhar C. Surgery versus medical therapy for heavy menstrual bleeding. Cochrane Database Syst Rev. 2006;(2):CD003855.
[25] Obstetrics and gynaecology: Twelve things physicians and patients should question. www.ChoosingWiselyCanada.org.
[26] World Health Organization. Research on the menopause in the 1990s. World health organization, technical report series 866. Geneva: WHO, 1996.
[27] Astrup K, Olivarius NdF Frequency of spontaneously occurring postmenopausal bleeding in the general population. Acta Obstet Gynecol Scand. 2004;83(2):203–207.
[28] Tempfer CB, Hilal Z, Kern P, et al. Menopausal hormone therapy and risks of endometrial cancer. Cancers. 2020;12(8):2195.
[29] Nams PS. The 2022 hormone therapy position statement of the North American menopause society. Menopause. 2022;29(7):766–794.
[30] Amant F, Moerman P, Neven P, et al. Endometrial cancer. Lancet. 2005;366(9484):491–505.
[31] ACOG. Committee opinion summary: the role of transvaginal ultrasonography in evaluating the endometrium of women with postmenopausal bleeding. Obstet Gynecol. 2018;131(5):945–946.
[32] Kumar S, Nepal P, Narayanasamy S, et al. Current update on status of saline infusion sonohysterosalpingography. Abdom Radiol. 2022;47(4):1435–1447.
[33] Saccardi C, Spagnol G, Bonaldo G, et al. New light on endometrial thickness as a risk factor of cancer: What do clinicians need to know? Cancer Manag Res. 2022;14:1331–1340.
[34] Lou Y, Kannappar J, Sathiyathasan S. Unscheduled bleeding on HRT—do we always need to investigate for endometrial pathology? Int J Reprod Contracept Obstet Gynecol. 2017;6(10):4174–4178.
[35] Gredmark T, Kvint S, Havel G, et al. Histopathological findings in women with postmenopausal bleeding. BJOG. 1995;102(2):133–136.
[36] Angioni S, Loddo A, Milano F, et al. Detection of benign intracavitary lesions in postmenopausal women with abnormal uterine bleeding: a prospective comparative study on outpatient hysterscopy and blind biopsy. J Minim Invasive Gynecol. 2008;15(1):87–91.
[37] Guido RS, Kanbour-Shakir A, Rulin MC, et al. Pipelle endometrial sampling. Sensitivity in the detection of endometrial cancer. J Reprod Med. 1995;40(8):553–555.
[38] Elsandabesee D, Greenwood P. The performance of pipelle endometrial sampling in a dedicated postmenopausal bleeding clinic. J Obstet Gynaecol. 2005;25(1):32–34.
[39] Lee SC, Kaunitz AM, Sanchez-Ramos L, et al. The oncogenic potential of endometrial polyps: a systematic review and meta-analysis. Obstet Gynecol. 2010;116(5):1197–1205.
[40] Sasaki LMP, Andrade KRC, Figueiredo A, et al. Factors associated with malignancy in hysteroscopically resected endometrial polyps: a systematic review and meta-analysis. J Minim Invasive Gynecol. 2018;25(5):777–785. 17
[41] Vitale S, Haimovich S, Lagana A, et al. Endometrial polyps: an evidence-based diagnosis and management guide. Eur J Obstet Gynecol Reprod Biol. 2021;260:70–77.
[42] Ghoubara A, Sundar S, Ewies AAA. Endometrial pathology in recurrent postmenopausal bleeding: observational study of 385 women. Climacteric. 2018;21(4):391–396.
[43] Renaud MC, Le T. SOGC-GOC-SCC policy and practice guidelines committee. Epidemiology and investigations for suspected endometrial cancer. J Obstet Gynaecol Can. 2018;40(9):e703–e711.
[44] Buchanan C, Robinson M, Macdonald M. Endometrial cancer rate in hormone replacement therapy users with postmenopausal bleeding: retrospective cohort study. Post Reprod Health. 2022;28(3):143–148.
[45] Oderkerk TJ, van de Kar MRD, Cornel KMC, et al. Endometrial cancer after endometrial ablation: a systematic review. Int J Gynecol Cancer. 2022;32(12):1555–1560.
[46] Goldstein SR. Appropriate evaluation of postmenopausal bleeding. Menopause. 2018;25(12):1476–1478.