The management of perimenopausal abnormal uterine bleeding

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Abstract

Abnormal uterine bleeding around the time of the menopause is common and may be a sign of premalignancy such as endometrial hyperplasia or even endometrial carcinoma. All such women therefore need uterine assessment, which may include transvaginal scan combined with endometrial biopsy, hysteroscopy or a sonohysterogram. Having excluded (pre) cancer, treatment can then be offered. Medical treatment options include tranexamic acid to reduce blood loss, low-dose contraceptive pills, the levonorgestrel intra-uterine device and cyclic progestins. Surgical options include resecting sub-mucus fibroids hysteroscopically, endometrial ablation and hysterectomy.

Keywords abnormal uterine bleeding; adenomyosis; contraceptive pill; endometrial ablation; endometrial cancer; endometrial hyperplasia; fibroid; hysterectomy; levonorgestrel intra-uterine system; polyp

Introduction

The forties are often a time of hormonal turbulence in a woman's life. Fluctuating sex-hormone levels and anovulatory cycles can affect the brain, causing hot flushes, night sweats and mood swings. The breasts may swell and become painful and there may be abnormal uterine bleeding (AUB). It is this latter dilemma, namely AUB that is the focus of this article. Perimenopause is defined as the time of menstrual irregularity leading up to the last period (menopause) and the 12 months following the last period. The Stages of Reproductive Ageing Workshop (STRAW) suggested the term "menopause transition" leading up to the last menstrual period.

Pelvic pathology is also commonly found in this age group. Such women will need to be investigated to exclude (pre-) malignancy and to help decision making about the best treatment option. A FIGO working group has classified AUB into nine categories - Polyp, Adenomyosis, Leiomyoma, Malignancy and Hyperplasia, Coagulopathy, Ovulatory disorders, Endometrium, Iatrogenic and Not Classified (acronym: "PALM-COEIN"). Leiomyoma (L) are further subclassified into those who have at least one sub-mucous fibroid (Lsm) and those with fibroids which do not impact on the endometrial cavity (Lo). Endometrial hyperplasia and malignancy and occasionally cervical cancer can present with AUB. The Coagulopathy group includes conditions such as von Willebrand disease, although this usually declares itself in the teenage years and is often associated with abnormal bleeding after childbirth, dental work or surgery and epistaxis. The Iatrogenic group includes breakthrough bleeding on hormone preparations such as the oral contraceptive pill (OCP), hormone replacement therapy (HRT) and levonorgestrel releasing intrauterine systems (LG-IUS).

There is a lack of consensus of definitions and terminology of AUB and outcome measures. Until recently there has been an abundance of old descriptive terms for AUB which have not been helpful. Table 1 contains some modern descriptive terms for menstrual loss which (in scientific trials and papers on menstruation and by FIGO) several researchers have proposed.

When to investigate

Initially, a concise history should be taken and an examination performed. Large fibroids may present with the woman noticing a pelvic mass or urinary frequency, but most will be concerned about a change in their menstrual pattern. As outlined in Table 1, menstrual history should focus on frequency, cycle regularity, duration and heaviness of flow. Frequent, heavy and or prolonged bleeding usually requires some investigations as does postmenopausal bleeding. Pelvic examination may reveal a polyp, a fibroid uterus or some other lesion. Pallor may indicate anaemia. Laboratory tests may include cervical cytology and cultures, full blood count, iron studies and occasionally tests for bleeding disorders.

All women with AUB who are in the perimenopausal age range will need their uterus assessed because many will have structural anomalies and some premalignant and malignant conditions, the commonest being endometrial hyperplasia. Management algorithms have been published but, if endometrial hyperplasia is suspected, then the endometrium will need to be assessed and most will require at least transvaginal pelvic ultrasound (TVUS).

Risk factors for endometrial hyperplasia or cancer include obesity, diabetes, nulliparity, age over 40 years, polycystic ovary syndrome, exposure to unopposed oestrogen therapy, tamoxifen usage and post-menopausal bleeding. Many will present with AUB. It is not within the scope of this review of perimenopausal menstrual symptoms to describe the management of endometrial hyperplasia.

Investigations

The guidelines of the American College of Obstetricians and Gynaecologists (ACOG) mandate that all women over 35 years with AUB should have an endometrial assessment (ACOG Committee on Practice Bulletins 2001). The tests available will vary according to location but include TVUS, endometrial biopsy, sonohysterogram (SHG or saline infusion sonogram), dilation and curettage (D&C) and hysteroscopy. Historically, D&C was the mainstay of endometrial assessment. However, its disadvantages include the need for a general anaesthetic, missed pathology or

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FIGO Terminology for describing menstrual loss

	Descriptive terms	Range
Frequency, days	Frequent	<24
	Normal	24–38
	Infrequent	>38
Cycle regularity (Cycle to cycle variation over 12 months, in days)	Absent	–
	Regular	Variation 2-20
	Irregular	Variation >20
Duration of flow, days	Prolonged	>8
	Normal	4.5–8
	Shortened	<4.5
Volume, mls per cycle	Heavy	>80
	Normal	5–80
	Light	<5

Table 1

incomplete removal of an intra-cavity lesion, free floating tissue left in-situ and a high false negative rate. Complications include uterine perforation and intra-uterine adhesions.

Office endometrial biopsy (EB) using the pipelle device is a cost-effective tool for investigating AUB especially when combined with TVUS. Endometrial hyperplasia and carcinoma are unlikely if the endometrial thickness (ET) is 4 mm or less. This is also useful for assessing postmenopausal bleeding (later), though many perimenopausal women will have thick ET because of unopposed oestrogen surges, and so some form of tissue sampling is helpful in this group (NICE recommends EB in all cases of AUB, age greater than 40). The Pipelle device can provide a histological diagnosis of most endometrial pathologies with some limitations. The Pipelle system is good at detecting pathologies that involve most of the endometrial cavity but can miss small focal lesions, including cancers.

Hysteroscopy allows the entire uterine cavity to be inspected and any lesions identified can be biopsied. This procedure can be performed in the office or in theatre. Hysteroscopy cannot assess the myometrium and may miss adenomyosis, nor will it help with the evaluation of the size and depth of fibroids.

Sonohysterogram (SHG) involves a small catheter being placed into the uterine cavity via the endocervical canal (Figure 1). Saline is then instilled into the uterine cavity and this permits ultrasound to visualize its contents. 3-D imaging appears to give better quality pictures then 2-D. The uterine cavity is evaluated and then the catheter is removed to allow imaging of the lower uterine segment and cervix. Doppler can be used to differentiate between polyps and blood clots. SHG can accurately distinguish between polypoid lesions and thickened endometrium. The procedure is best performed just after completion of menses. It is an accurate test and is cheaper than hysteroscopy. If a lesion is found then hysteroscopy and biopsy will be indicated.

Which test to choose?

Investigation of all patients with perimenopausal AUB should include an EB as the first procedure, backed up with a TVUS. According to RCOG guidelines, if there is persistent intermenstrual bleeding, in a woman aged 40 years or above and failed or ineffective treatment of the bleeding, then an EB is indicated to exclude endometrial cancer or atypical hyperplasia. If a focal lesion is identified on TVUS, then hysteroscopy can be used to inspect and biopsy the lesion. If a uterine anomaly such as a septum is found on TVUS, then an LG-IUS is more likely to be expelled. Fibroids are common in this age group and TVUS is accurate in detecting, measuring and locating them (with perhaps the exception of sub-mucus fibroids). These factors will be important in determining the likely success of treatment options such as LG-IUS, hormonal therapies and endometrial ablation. If a fibroid uterus is found on examination or at TVUS, then an SHG can be helpful in assessing sub-mucus fibroids prior to attempting hysteroscopic resection. SHG can also detect most polyps.

Postmenopausal bleeding

Bleeding after menopause always requires uterine assessment. Numerous trials and systematic reviews have shown that TVUS is a very good first test and if the ET is 4 mm or less then significant endometrial pathology is unlikely. ET greater than 4 mm (5 mm or more) or repeated episodes of postmenopausal bleeding (even if the ET is 4 mm or less) is an indication for hysteroscopy.

Case 1

A 47-year-old woman presents to her GP with worsening heavy painful periods. Her cycle varies between 21 and 28 days and lasts 7 days with the passage of clots during the first three days of bleeding. She has had two normal vaginal deliveries and her partner had a vasectomy a few years ago. Investigations included a full blood count showing hypochromic microcytic anaemia with a Hb of 10, a low ferritin, normal TSH and cervical screening test.

What steps would you take next?: a full history, observations (pulse, BP) and abdomino-pelvic exam should be performed. A TVUS is the first-line investigation.

Ultrasound findings: a TVUS demonstrates a 10 cm uterus with prominent adenomyosis (Figure 2) involving the inner third of the posterior wall of the uterus, and two small intramural fibroids with an ET of 5 mm and small normal ovaries. A pipelle EB is performed.

Pathophysiology: fibroids are benign fibromuscular tumours involving the myometrium. Intra-mural fibroids will bulk up the uterus and can cause pain and excessive menstrual loss. Sub-mucus fibroids can particularly aggravate menstrual loss. Adenomyosis involves the endometrium invading the myometrium and typically causes pelvic pain and heavy periods. In this patient's age group, both pathologies are common. A pipelle endometrial biopsy confirms benign endometrium.

What are the management options for this patient?: tranexamic acid (TA) in a dose of 1 g 3–4 times a day (during menses) typically halves menstrual loss and if combined with a Non-Steroidal Anti-Inflammatory can be very effective. The LG-IUS is an excellent

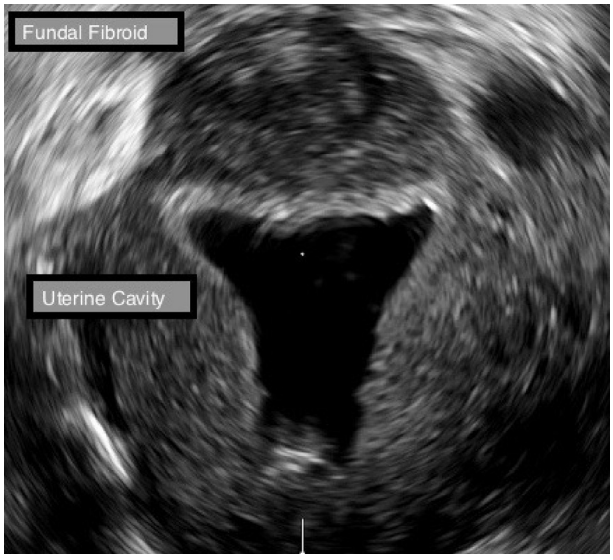

Figure 1 Sonohysterogram (and fundal fibroid). (Kindly provided by Dr Yasmin Tan WHRIA with permission.).

option for menstrual control for many perimenopausal women. It is the most cost-effective option for the treatment of menstrual disorders. Irregular bleeding is common immediately after insertion but this can be minimized if the ET is thin at insertion. This can be achieved by either inserting the device just after menstruation or by pre-treatment with a progestin or contraceptive pill. In the long-term, the LG-IUS reduces menstrual blood loss by over 90%. It is most effective in those with a normal uterus, although it can be beneficial in a fibroid uterus, especially if there are no sub-mucus lesions and if the uterus isn't too large. There may be a higher expulsion rate if fibroids are present. In this patient's case, the success rate will be around 70–80%.

If menopausal symptoms such as hot flushes are present, then concomitant oestrogen may be prescribed as the LG-IUS will prevent endometrial hyperplasia. Systematic reviews have demonstrated that the LG-IUS and endometrial ablation produced similar results for heavy menstrual loss, if sub-mucus fibroids are not present.

Figure 2 Sonogram (Kindly provided by Dr Yasmin Tan WHRIA with permission.).

If there are no contra-indications, then a low-dose OCP can control both the irregular cycle and the symptoms of the perimenopause. Long-cycle regimens can be used to "skip" periods. There are scant data on the use of OCP in women over 50 years, although OCPs containing oestradiol, rather than ethinyloestradiol are now available. Theoretically, these should be safer for perimenopausal women, although definitive data are not yet available.

Progestins have anti-oestrogenic, anti-proliferative and atrophying effects on the endometrium. Their impact depends upon the type, dose and regimen used. These can be given alone or in combination with oestrogens as in the OCP or HRT. Continuous progestins, in adequate dosage, can completely suppress menstruation (e.g. depot-injection of medroxyprogestrone acetate [MPA]) but most commonly progestins are given cyclically. Ten days of luteal phase progestin has not been shown to be effective for AUB, whereas a 21-day cyclical progestin regimen can reduce menstrual blood loss by around 50%. Moderately high doses of norethisterone (e.g. 15 mg or more daily) are commonly used to control heavy menstrual loss acutely. Around one in eight women will develop PMT-type side-effects with progestins including bloatedness, mood swings (even depression), and fluid retention.

Endometrial ablation is an effective treatment for AUB and is useful for those who fail hormonal therapy or for those who do not wish to take a hormone treatment and avoids hysterectomy. It is essential that endometrial hyperplasia and cancer be excluded prior to the ablation. Sub-mucus fibroids can be hysteroscopically resected and then endometrial ablation performed in the one procedure. If significant adenomyosis is present (as in this case), then endometrial ablation can result in severe pain (by sealing menstrual crypts) sometimes requiring hysterectomy. Early techniques involving laser or roller-ball electrocoagulation have largely been replaced by techniques such as thermal balloon ablation, and impedance controlled, electrocoagulation. Over 80% of patients are generally satisfied with the results after one of these ablative procedures. Between 10 and 20% of patients who have had endometrial ablation will go on to have a hysterectomy.

Uterine artery embolization (UAE) for symptomatic uterine fibroids was first described in 1995. UAE is performed by an interventional radiologist who accesses the uterine arteries via the femoral artery in the groin. An angiogram is performed to ensure correct placement and then microbeads or Gelfoam are injected into the uterine artery (on both sides). Post-UAE around 90% of women report a reduction in menstrual loss, 90% report an improvement in pain and 70% have smaller fibroids on subsequent imaging. Complications following UAE include: discharge and fever 4%, pain 3%, groin complications 3%, fibroid expulsion 2%, uterine infection 1% and early menopause 5% because of inadvertent ovarian embolization.

In the past, hysterectomy was the mainstay for persistent AUB. The LG-IUS and endometrial ablation have resulted in far fewer hysterectomies being performed now. Increasingly, hysterectomy is performed laparoscopically. The main indications for hysterectomy in the perimenopausal phase include,

endometrial cancer (as part of the staging procedure), endometrial hyperplasia (especially if atypia is present), large symptomatic fibroids, and some cases of adenomyosis or endometriosis when medical measures have failed.

Case 2

A 52-year-old woman presented to her GP with prolonged vaginal bleeding (lasting 21 days) after 14 months of amenorrhoea. Routine blood count, TSH and cervical screening were all normal. She is mildly diabetic, controlled with diet and metformin.

What steps would you take next?: a full history and examination reveal that she is nulliparous, with a BMI of 35 kg/m^2. Blood pressure is 140/95. Her cervix is healthy and the bimanual exam unrevealing. A TVUS is ordered.

Ultrasound findings: TVUS reveals an 8 cm uterus with grossly thickened, cystic endometrium (ET 15 mm), and normal inactive ovaries. A hysteroscopy is performed which confirms thick abnormal, polypoid endometrium. Pathology confirms a well-differentiated endometrial adenocarcinoma.

Discussion

This patient was high risk for endometrial carcinoma (nulliparity, obesity, diabetes). The initial treatment is radical hysterectomy with pelvic lymph node sampling. Depending on the final pathology, she may require adjuvant radiotherapy.

Case 3

A 49-year-old woman presents to the menstrual clinic of the local hospital with a 6-month history of irregular vaginal bleeding. Her cycle varies from 14 days to 49 days and from light to very heavy with clots. She is also suffering episodic hot flushes which can severely disrupt her sleep. She had two full term pregnancies, both babies delivered by C-section. Her partner has been using a condom for contraception and she is worried about an accidental pregnancy. Routine FBC and TSH are normal. She is not taking any regular medications.

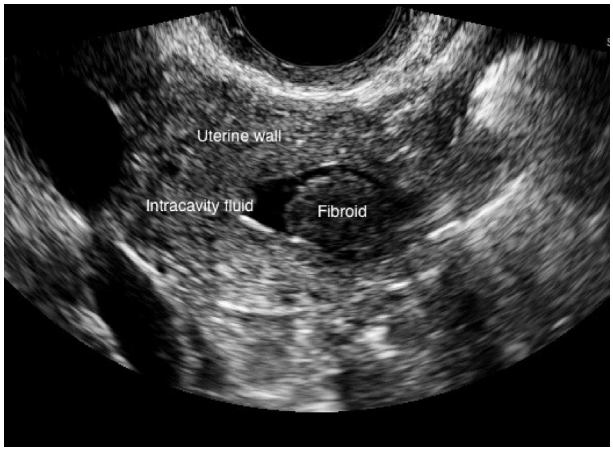

Figure 3 Sonogram (Kindly provided by Dr Yasmin Tan WHRIA with permission.).

What next steps would you take next?: on examination, she is not clinically anaemic, pulse is 80/min, BP 120/80 and abdominal and vaginal findings are normal. A TVUS scan is performed.

Ultrasound findings: the uterus is 8 cm long with no evidence of fibroids or adenomyosis. The ET is 10 mm. The ovaries appear normal.

What is your next step?: the patient is keen to try a LG-IUS but is concerned about discomfort during insertion and is admitted to hospital for a day-surgery procedure performed under a GA. Hysteroscopy appears normal and endometrial curettage is performed. A LG-IUS is fitted. The pathology is benign. After 4–6 weeks of irregular bleeding, the menses become significantly lighter.

Management of hot flushes: now that the uterine bleeding has been investigated, and appears to be under control, it is reasonable to commence oestrogen such as oestradiol 1–2 mg orally daily or an oestradiol patch or gel to control menopausal symptoms.

Case 4

A 52-year-old woman, G4P4 presents to the emergency department of the local hospital having a very heavy period for the last 14 days. She is pale with tachycardia and hypotension. Her haemoglobin is 7. Her periods have been getting progressively heavier over about a year. They now typically last 2 weeks. Abdominopelvic examination reveals a multifibroid uterus about 12 cm long.

What steps would you take?: she is given TA intravenously followed by oral TA 1 g 6 hourly, as well as norethisterone (NE) 10 mg every 4 h and is transfused. Within 4 h, the bleeding has markedly slowed, her observations have stabilized and her post-transfusion Hb is 12. She is admitted to the gynaecology ward.

What steps would you take next?: the TA and NE are continued in the ward and a TVUS is ordered.

Ultrasound findings: a 13 cm multi-fibroid uterus is found with several intra-mural fibroids (the largest is 8 cm) and one intracavity fibroid, 2 cm in maximum diameter (Figure 3).

What steps would you take next?: the woman does not want a hysterectomy and would like to discuss medical methods to shrink the fibroids. She does not want a Mirena device nor radiological embolization. She agrees to a hysteroscopic resection of the intra-cavity mass. The bleeding stops after 48 h. She goes to theatre the next day and an intra-cavity fibroid is resected, and the endometrium sampled. The pathology of both tissues samples comes back benign.

What medical options would you offer her?: there are at least three medical options available to her. She could continue on the NE 5–10 mg daily to produce amenorrhoea, anticipating menopause to shrink the fibroids. Unfortunately, there is no test available that predicts the last menstrual period, and it is not unusual to menstruate up to 55 years or even beyond. GnRH

agonists such as Goserelin 3.6 mg depot (every 28 days) or Nafarelin nasal (one sniff twice a day) produce a hypogonadal state and can shrink the size of the fibroids. Use of these agents for longer than 3–6 months without hormonal 'add-back' therapy results in a reduction of bone mineral density. Other side effects mimic those of menopause (such as hot flushes, aches and pains, headaches) and if symptoms are severe tibolone 2.5 mg can be used as add back therapy.

Selective progesterone receptor modulators (SPRMs) are a novel new therapy for the management for fibroids. Ulipristal is one such agent, and it has been shown to have a direct shrinkage effect on fibroids via inhibition of cellular proliferation and induction of apoptosis (programmed cellular death). Ulipristal 5 mg daily is normally given for 3 months which usually results in amenorrhoea and a significant decrease in the size of most of the fibroids. Whilst on treatment, the endometrium undergoes particular benign changes termed, "Progesterone receptor modulator associated endometrial changes (PAEC)." Typically, the epithelium is inactive with stromal asymmetry and prominent cystic glandular changes. It is important that these changes are not confused with endometrial hyperplasia. They reverse when the treatment is stopped. This treatment for the uterine fibroids can be repeated for four treatment cycles of 12 weeks each, with a treatment free interval of up to 8 weeks between each treatment cycle. There have been reports of abnormal liver function (LFTs) and serious liver injury attributed to this drug. As a result, more than one course of Ulipristal is only recommended in women who are not eligible for surgery, and LFTs should be measured monthly whilst the patient takes Ulipristal. Head to head studies suggest that Ulipristal is superior to GnRH agonists for the shrinkage of fibroids.

Conclusions

AUB during the menopausal transition is common. Apart from taking a clinical history and performing a physical examination, all such women will need some type of uterine assessment. For the majority, this will be an endometrial biopsy backed up with a TVUS. SHG is a cost-effective method for assessing the endometrial cavity. If a focal lesion is identified on imaging, then hysteroscopy and biopsy are indicated. Having excluded endometrial hyperplasia and uterine carcinoma, polyps and submucus fibroids in particular, the first-line treatment will usually be medical rather than surgical. The most effective option is the LG-IUS, although some women will prefer to try an oral medication first such as tranexamic acid, a low-dose OCP or cyclic progestins. Fibroids may now be managed by medical options such as GnRH agonists or Ulipristal or radiological embolization.

Surgery is usually a second-line option. However, if sub-mucus fibroids or polyps are present, then these can be resected hysteroscopically. Endometrial ablation and the LG-IUS have been shown to give similar results for most patients with heavy menstrual bleeding. Hysterectomy is usually a last resort treatment for abnormal bleeding unless (pre) malignancy is present. ◆

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Practice points

- All perimenopausal patients presenting with AUB require uterine assessment
- Endometrial hyperplasia is common in this age group
- The usual first line test is endometrial biopsy backed up with TVUS
- NSAIs, tranexamic acid, OCPs and cyclic progestins given for at least 21 days are effective oral medical options for heavy menstrual bleeding
- The most effective medical option for AUB is the LG-IUS
- For most patients, endometrial ablation and the LG-IUS give similar results