The management of perimenopausal menstrual symptoms

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Abstract

Abnormal bleeding around the time of the menopause is common and may be a sign of premalignancy such as endometrial hyperplasia or even endometrial carcinoma. As such all will 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; tranexamic acid

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 flushes, 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. For this paper, the search engine *Sirius* was used via the UNSW-Library website using the keywords — perimenopause, abnormal uterine bleeding, investigation, terminology, management, fibroid, adenomyosis, polyp, endometrial hyperplasia, endometrial cancer, hormone replacement, levonorgestrel intra-uterine device, endometrial ablation, hysterectomy, contraceptive pill, progestin, and tranexamic acid. Preference was given to reviews, especially meta-analyses and systematic reviews.

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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 and divided this phase into two parts. "Stage-0" is menopause (last period). "Stage-2" (early menopause transition) is characterised by more than 7 days of cycle variation compared with normal and "stage-1" (late menopause transition) as greater than two skipped cycles with at least 60 days of amenorrhoea.

Pelvic pathology is also commonly found in this age group. As such some 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-mucus 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, gum bleeding, bruising and epistaxis. Endometrial causes suggest a primary problem in the endometrium and as research in this area progresses, it is likely that specific biochemical and/or genetic problems will be defined. *The Iatrogenic group* includes breakthrough bleeding on hormone preparations such as the oral contraceptive Pill (OCP), hormone therapy (HT) 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 several groups have suggested as being useful in scientific trials and papers on menstruation and by FIGO.

When to investigate

A concise history and examination needs to be performed first. 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.

Physical examination may reveal a polyp, a fibroid uterus or some other lesion. Pallor may indicate anaemia. Laboratory tests may include a Papanicolaou smear, cervical 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.

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	Heavy	>80
	Normal	5–80
	Light	<5

Table 1

Around 70% of women presenting with AUB will have a benign cause, 15% carcinoma and 15% a premalignant condition. Management algorithms have been published but in the end, 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, 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 the intent of this review of perimenopausal menstrual symptoms to describe the management of endometrial hyperplasia; although it needs to be stated that any degree of atypia will usually necessitate hysterectomy because of the risk of small occult carcinoma being already present as well as the significant risk of progression to carcinoma.

However, some patients may enquire about medical therapies for endometrial hyperplasia with atypia, or even early stage endometrial carcinoma, to preserve fertility. Gallos and colleagues have performed a systematic review of medical therapies for early stage endometrial cancer and atypical complex endometrial hyperplasia (using progestins). For atypical hyperplasia, the pooled regression rate was 86% with a live birth rate of 26%.

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 main draw backs include the need for a general anaesthetic, missed pathology or incomplete removal of an intra-cavity lesion, free floating tissue left in-situ and a high false negative rate. Complications included uterine perforation and intra-uterine adhesions.

Endometrial biopsy combined with TVUS

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 very useful for assessing postmenopausal bleeding (later) but unfortunately, many perimenopausal women will have thick ET because of unopposed oestrogen surges and so some form of tissue sampling is very 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 (Table 2). Typically, the Pipelle system is very good at detecting pathologies that involve most of the endometrial cavity but can miss small focal lesions, including cancers. In one study, Pipelle sampling was done prior to hysterectomy for known endometrial cancer. Over 95% of the samples were adequate for histological examination and the sensitivity for picking up the malignancy was 83%. In another study, Pipelle sampling missed most endometrial polyps.

Hysteroscopy

Hysteroscopy allows the entire uterine cavity to be visualised and any lesions found can be visualised and biopsied. This can be performed in the office or in theatre. Hysteroscopy cannot assess the myometrium and so may miss adenomyosis and will not allow evaluation of the size and depth of fibroids. A systematic review comparing carbon dioxide with normal saline as the distension medium suggested that saline was superior.

Sonohysterogram (SHG)

A small catheter is placed into the uterine cavity via the endocervical canal. Saline is then instilled into the uterine cavity and this permits ultrasound to visualise 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 cheaper than hysteroscopy. If a lesion is found then hysteroscopy and biopsy will be indicated. Meta-

Limitations of endometrial biopsy

- Factors that might make it difficult to perform an endometrial biopsy:
  - Cervical stenosis (cervical surgery, multiple caesarean sections)
  - Pain
  - Sharply anteverted or retroverted uterus
- Has the cavity been adequately sampled? Considerations:
  - Uterine shape and size (e.g. bicornuate uterus)
  - Location of a lesion (e.g. it is difficult to sample a cornual lesion)
  - Size of lesion
  - Is the lesion affecting most of the endometrium or localised?

Table 2