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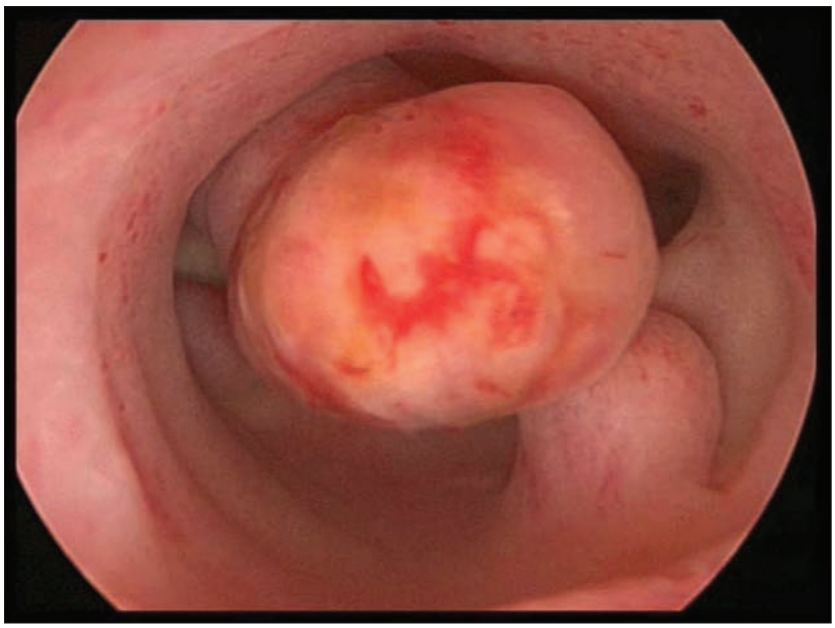

FIGURE 1
Hysteroscopy showing a pedunculated submucosal fibroid

What are the common causes?

How should patients be assessed?

What are the management options?

HEAVY MENSTRUAL BLEEDING HAS BEEN DEFINED AS 'EXCESSIVE MENSTRUAL BLOOD LOSS which interferes with a woman's physical, social, emotional, and/or material quality of life'.[1]

Heavy menstrual bleeding affects 25% of women of reproductive age and is estimated to be the fourth most common reason for referral to gynaecological services.[2] Each year, 30,000 women undergo surgical treatment for heavy menstrual bleeding in England and Wales.[3]

Normal periods last 3-7 days and do not interfere with everyday life or work. Periods are considered excessively heavy if a woman:

- Regularly needs both a tampon and a pad, or two pads at once to manage the bleeding
- Regularly gets blood on her clothes or sheets
- Regularly passes clots bigger than the size of a 50 pence piece
- Has iron deficiency anaemia because of her periods

If a woman is having to change the way she dresses, miss work or school, have a 'bed day', stop exercising and is planning her life around her periods, then she has heavy menstrual bleeding.

CLASSIFICATION OF ABNORMAL UTERINE BLEEDING

Abnormal uterine bleeding (AUB) as proposed by the International Federation of Gynecology and Obstetrics (FIGO)[4,5] replaces the terms menorrhagia, metrorrhagia and dysfunctional uterine bleeding. AUB includes heavy menstrual bleeding as well as irregular or intermenstrual bleeding.

FIGO has classified abnormal uterine bleeding (AUB) according to the acronym PALM-COEIN and updated this classification in October 2018.[6]

The components of the PALM group are structural and defined by imaging or histopathology: Polyp; Adenomyosis; Leiomyoma; Malignancy and hyperplasia.

The COEIN group are not structural and include: Coagulopathy; Ovulatory dysfunction; Endometrial disorders; Iatrogenic; and Not otherwise classified.

A woman presenting with AUB may have one or several contributory factors:

Polyps (AUB-P)

A diagnostic randomised controlled trial (RCT) of 683 women with AUB estimated that the prevalence of endometrial polyps in premenopausal women under the age of 40 was 6% and in premenopausal women over the age of 40 was 11.5%.[1] The evidence suggests that a single 1 cm endometrial polyp would not cause heavy menstrual bleeding.

Adenomyosis (AUB-A)

Adenomyosis is a condition where endometrial cells are found in the myometrium. Around one in ten women will have adenomyosis. It can occur in any woman who still has periods, but is most common in women aged 40-50 and in women who have had children. The most common symptoms are:

- Heavy, painful or irregular periods
- Premenstrual pelvic pain and feelings of heaviness/discomfort in the pelvis

Less common symptoms are:

- Pain during sexual intercourse
- Pain related to bowel movements

Around one third of women will not have any symptoms. Adenomyosis may be found coincidentally on a scan, for example. Symptoms cease at the menopause.

Leiomyoma (AUB-L)

The RCT of 683 women with AUB, mentioned above, estimated that the prevalence of uterine leiomyoma (fibroids) in premenopausal women under the age of 40 was 19% and in premenopausal women over the age of 40 was 36%.[1] »

Table 1

Likely rates of endometrial cancer per 10,000 consultations for heavy menstrual bleeding in primary care*

	Age range (years)			
	30-34	35-39	40-44	45-49
Rate of endometrial cancer per 10,000 consultations	1	1	3	8

*Based on the incidence of heavy menstrual bleeding of 38% in women with endometrial carcinoma, the 1987 incidence of cancer and the frequency of consultation in primary care with heavy menstrual bleeding of 5%. These figures have been updated with 2003 data[10]

Malignancy (AUB-M)

Women with AUB and associated malignant or premalignant lesions of the uterus (e.g. endometrial carcinoma, leiomyosarcoma, and atypical endometrial hyperplasia) are categorised as having AUB-M.

The NICE guideline on heavy menstrual bleeding[1] estimated that in women aged between 35 and 54 years, eight out of every 10,000 women who presented with heavy menstrual bleeding in primary care would have endometrial carcinoma. In women aged under 30 years the respective figure is < 0.01% or less than one per 10,000 consultations. The likely rates of endometrial carcinoma in older age groups are given in table 1, above.

Coagulation disorders (AUB-C)

Coagulation disorders are estimated to be the cause of heavy menstrual bleeding in up to 20% of cases. The most common cause of AUB, in otherwise healthy adolescents, is ovulatory dysfunction, although 5-36% of adolescents who present with heavy menstrual bleeding, have an underlying bleeding disorder. The most common form of bleeding disorder is von Willebrand's disease, affecting 13% of adolescents with abnormal uterine bleeding.[7]

Ovulatory dysfunction (AUB-O)

Regular periods every 24-38 days are usually, but not always, associated with ovulation, whereas bleeding associated with ovulatory disorders, such as polycystic ovary syndrome (PCOS), is typically irregular, both in timing and flow, and often interspersed with episodes of amenorrhoea.

Endometrial disorders (AUB-E)

There is an association between chronic endometritis and AUB. Although cervical testing for chlamydia seems reasonable, the relationship between cervically obtained results and the presence or absence of endometrial infection is unclear.

Iatrogenic (AUB-I)

AUB associated with pharmacological treatment or intrauterine devices such as the copper coil is classified as iatrogenic. It includes drugs that contribute to ovulatory disorders, such as those that affect dopamine metabolism, including phenothiazines and tricyclic antidepressants. Iatrogenic AUB includes the modern direct oral anticoagulants such as rivaroxaban and the traditional vitamin K antagonists, typically warfarin.

Not otherwise categorised (AUB-N)

The not otherwise classified category includes a spectrum of potential entities that may or may not be measured or defined by histopathology. These include, but are not limited to, conditions such as arteriovenous malformations and the lower segment or upper cervical niche or isthmocele frequently found in association with previous caesarean delivery and sometimes attributed as a cause of AUB.

ASSESSMENT AND INVESTIGATION

Assessment should include a history asking about length of the periods, regularity and the presence of intermenstrual or postcoital bleeding. It is important to check that the woman's cervical screening is up to date.

Screening for disorders of coagulation

A positive screening result would be indicated by:[8]

- Heavy menstrual bleeding since menarche

Plus one of the following conditions:

- Postpartum haemorrhage
- Surgery-related bleeding
- Bleeding associated with dental work

And two or more of the following:

- Bruising 1-2 times per month
- Epistaxis 1-2 times per month
- Frequent gum bleeding
- A family history of bleeding symptoms

This structured history is 90% sensitive for the presence of a coagulopathy in women with the symptom of heavy menstrual bleeding.[7] A woman with a positive screening result should be considered for referral to a haematologist and/or testing for von Willebrand factor and ristocetin cofactor.

Associated symptoms

Enquire about pelvic pain which might suggest endometriosis and pressure symptoms which might suggest significant fibroids. Examination should be offered if there are pain or pressure symptoms, if there is intermenstrual or postcoital bleeding and, if the woman was actively bleeding, could identify the source of the bleeding from the cervical canal. Chlamydia testing should be carried out at the time of examination or as a self-taken swab where examination is not indicated.

Initial investigations

The following investigations should be carried out: a urine pregnancy test to exclude pregnancy; full blood count; chlamydia testing as above.

Female hormone levels, thyroid function and ferritin do not need to be tested routinely, unless the patient is symptomatic.

Ultrasound

Transvaginal ultrasonography (TVUS) is an appropriate and important screening tool and, in most instances, should be performed early in the course of the investigation. The patient should be referred for a TVUS if the uterus is palpable abdominally or if there are associated symptoms of pressure or pelvic pain. TVUS is not 100% sensitive, even in ideal circumstances, because polyps and other small lesions may elude detection. However, as a pragmatic approach, if an ultrasound scan fails to show findings suggestive of endometrial polyps or submucosal leiomyomas, the structure of the endometrial cavity may be presumed to be normal and appropriate treatment initiated, see below.

Endometrial biopsy

In the 2018 updated NICE guideline,[9] the guideline committee discussed the fact that currently many women undergo endometrial biopsy unnecessarily and that the risk of

endometrial cancer in premenopausal women with heavy menstrual bleeding as the only symptom is very low.

Endometrial biopsy is painful and 'blind' biopsy may miss treatable pathology. However, if the ultrasound scan is normal and does not suggest features of an endometrial polyp or submucosal fibroid an endometrial biopsy is both highly specific and sensitive for endometrial hyperplasia or malignancy.

An endometrial biopsy is not required for all patients with AUB, so it is necessary to identify women at high risk of endometrial hyperplasia or malignancy.

Selection for endometrial sampling is based on a combination of risk factors for the presence of premalignant or malignant changes. These include persistent intermenstrual bleeding, persistent irregular bleeding, infrequent bleeding in women who are obese or who have PCOS (due to a prolonged unopposed oestrogen effect on the endometrium), women taking tamoxifen, and women in whom treatment has failed or was ineffective, age over 45, obesity, and family history of endometrial and/or colon cancer (possible Lynch syndrome), and endometrial thickness on ultrasound.

Although some studies have indicated that age is not important as an independent variable, most suggest that endometrial sampling be considered for all women over a certain age, usually 45 years.

It is also evident that obesity contributes significantly to the risk of premalignant and malignant change in the endometrium, a feature that increases the risk of endometrial neoplasia even in young women in the third and fourth decades of life.

Women with a family history of hereditary non-polyposis colorectal cancer syndrome (Lynch syndrome), have a lifetime risk of endometrial cancer of up to 60%, with mean age at diagnosis of 48-50 years.

Regardless of the clinical guideline recommendations, when AUB is persistent and either unexplained or inadequately treated, endometrial sampling is necessary, and ideally, in association with hysteroscopic visualisation of the uterine cavity.

There are a number of techniques for endometrial sampling, but it is important that an adequate sample be obtained before the patient can be considered at low risk for a malignant neoplasm.

CONFIRMING DIAGNOSIS

Outpatient hysteroscopy is recommended to confirm diagnosis for women with heavy menstrual bleeding if uterine cavity abnormalities are present.

The following patients should be referred to a specialist:

Urgent referral

- Vaginal examination reveals a pelvic mass of uncertain origin
- Anaemia with Hb < 70 g/dl

Routine referral

- Positive screen for a coagulation disorder
- Ultrasound scan suggests submucosal fibroids, polyps or endometrial pathology. This would be an indication for further assessment by hysteroscopy
- There are risk factors for endometrial pathology
- Women with fibroids that are palpable abdominally or the uterus is measured as > 12 cm on ultrasound scan
- If pharmacological treatment has failed, although it is reasonable to try more than one intervention in women under 40 years of age

PHARMACOLOGICAL TREATMENT

Treatment can be commenced without examination where the history suggests heavy menstrual bleeding without structural or histological abnormality.

If ultrasound scan fails to show findings suggestive of endometrial polyps or submucosal leiomyomas, the clinician may initially presume that the structure of the endometrial cavity is normal and start treatment.

Treatment for women with heavy menstrual bleeding who have fibroids < 3 cm in diameter and not impinging on the endometrial cavity is as detailed below.

The following options should be tried first line and can be started in primary care.

Tranexamic acid or NSAIDs

- Tranexamic acid 1 g by mouth three or four times a day on any day judged to be heavy for up to four days (maximum 4 g per day). It can be taken in combination with ibuprofen or mefenamic acid
- Ibuprofen 400 mg three times a day by mouth on any day judged to be heavy OR
- Mefenamic acid 500 mg up to three times a day by mouth on any day judged to be heavy

A review should be carried out after three cycles of treatment.

Hormonal therapies

A recent Cochrane review,[10] covering eight trials with 805 participants, suggested that, if the chance of successful treatment was 3% in women taking placebo, then the combined oral contraceptive pill (COCP) increased this chance to between 12 and 77% in women with unacceptable heavy menstrual bleeding. Minor adverse events, in particular breast pain, were more common with the COCP.

Limited evidence suggested that the COCP and the contraceptive vaginal ring had similar effects. There was insufficient evidence to determine comparative efficacy of combined hormonal contraceptives with NSAIDs, or long course progestogens.

The levonorgestrel intrauterine system (LNG-IUS) was more effective than the COCP in reducing menstrual blood loss; OR 0.21 (95% CI: 0.09-0.48) in two trials with 151 participants; $I^2 = 0\%$; low quality evidence) but it was not clear whether satisfaction with treatment or adverse effects varied according to which treatment was used. The LNG-IUS is a good option for women planning to use this method for at least 12 months.

Long-acting reversible contraceptives or cyclical progestogens can be used on days 5-26.

Depo-Provera 150 mg intramuscularly every 12 weeks can have a prolonged contraceptive effect, so is less suitable for women planning to start a family in the next 12 months. Nexplanon can be helpful in some women. Medroxyprogesterone acetate 2.5-10 mg once daily for 21 days starting on day 5 (counting the first day of the period as day 1) can be used as can norethisterone acetate 5 mg up to three times a day on days 5-26. (Note norethisterone 5 mg three times a day can be used to delay a period if a woman is going away on holiday but carries a risk of venous thromboembolism equivalent to the use of a combined oral contraceptive pill. If a woman has risk factors for venous thromboembolism (family history, a long flight, etc) the additional risk would have to be considered.[11]

There is no evidence that ethamsylate reduces heavy menstrual bleeding.

Ulipristal acetate was temporarily withdrawn following rare but serious cases of liver injury, including hepatic failure requiring liver transplantation, reported worldwide. On 7 August 2018, the MHRA updated its advice that ulipristal acetate (Esmya) may be used for the intermittent treatment of moderate to severe symptoms of »

key points

SELECTED BY

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Heavy menstrual bleeding has been defined as 'excessive menstrual blood loss which interferes with a woman's physical, social, emotional, and/or material quality of life'. Heavy menstrual bleeding affects 25% of women of reproductive age and is estimated to be the fourth most common reason for gynaecological referrals. Each year, 30,000 women undergo surgical treatment for heavy menstrual bleeding in England and Wales.

The International Federation of Gynecology and Obstetrics (FIGO) has classified abnormal uterine bleeding (AUB) according to the acronym PALM-COEIN. The components of the PALM group are structural and defined by imaging or histopathology: Polyp; Adenomyosis; Leiomyoma; Malignancy and hyperplasia. The COEIN group are not structural and include: Coagulopathy; Ovulatory dysfunction; Endometrial disorders; Iatrogenic; and Not otherwise classified.

Women should be asked about pelvic pain which might suggest endometriosis and pressure symptoms which might suggest significant fibroids. Examination is appropriate if there is intermenstrual or postcoital bleeding and, if the woman is actively bleeding, may identify the source of the bleeding. Chlamydia testing should be carried out at the time of examination or as a self-taken swab where examination is not indicated. A urine pregnancy test and full blood count should be performed.

Women should be referred for transvaginal ultrasonography if the uterus is palpable abdominally or if there are associated symptoms of pressure or pelvic pain. Women should be referred, ideally in combination with hysteroscopy, for gynaecological assessment if there is persistent intermenstrual bleeding, persistent irregular bleeding (or risk factors for endometrial pathology including obesity, PCOS and tamoxifen use). Women in whom treatment has failed should also be referred. In addition, most studies suggest that endometrial sampling should be considered for all women over the age of 45 years.

Treatment can be commenced without investigation where the history and examination suggests there is no structural or histological abnormality. Primary care treatment is also appropriate for those with a normal ultrasound or fibroids < 3 cm in diameter which are not impinging on the endometrial cavity. First-line options are tranexamic acid and/or ibuprofen/mefenamic acid. Hormonal options are the COCP or cyclical progestogens. The levonorgestrel intrauterine system is a good option for women planning to use this method for at least 12 months and is more effective than the COCP in reducing menstrual blood loss. Surgical treatment can be considered if pharmacological treatments have not worked.

uterine fibroids in women of reproductive age who are not eligible for surgery.[12]

Each treatment course should not exceed 3 months and should only be repeated after a break in treatment. Monitoring of liver function is required before starting, during and after treatment. It may also be used as a single course of preoperative treatment for moderate to severe symptoms of uterine fibroids. Treatment should be started by a physician experienced in the diagnosis and treatment of uterine fibroids.

Women should be advised to seek urgent medical attention if they develop any symptoms or signs of liver injury (such as unusual tiredness, yellowing of the skin, darkening of the urine, nausea and vomiting) and suspected adverse drug reactions should be reported using the Yellow Card system without delay.

The emergency contraceptive pill ellaOne also contains ulipristal acetate in a single dose of 30 mg. No cases of serious liver injury have been reported with ellaOne since it was authorised in the EU in 2009 and there are no concerns or changes to its use at this time.

SURGERY

Surgery is considered if pharmacological treatments have not worked. The aim is to reduce the period blood loss to an acceptable level and restore quality of life. The options include hysteroscopic removal of polyps and/or fibroids (see figure 1, p 11) or endometrial ablation in women with a uterus < 10 weeks' size, with hysteroscopy before placement of the device. Women should have completed their family as pregnancy is not advised following endometrial ablation. Contraception is still required and one option is the fitting of a Mirena at the time of the procedure.

Treatment options for heavy menstrual bleeding in combination with fibroids > 3 cm diameter include:

- Uterine artery embolisation
- Myomectomy which can be hysteroscopic, vaginal, or abdominal (open or laparoscopic)
- Hysterectomy which can be vaginal, or abdominal (open or laparoscopic) with the option of keeping the cervix and the ovaries should be discussed with the woman

NICE advises that hysterectomy should not be used as a first-line treatment solely for heavy menstrual bleeding. Hysterectomy should be considered only when:

- Other treatment options have failed, are contraindicated or are declined by the woman
- There is a desire for amenorrhoea
- The woman (who has been fully informed) requests it
- The woman no longer wishes to retain her uterus and fertility

Competing interests
Mrs Caroline Overton is a medical educator for Mylan Pharmaceuticals

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