Diagnosis of abnormal uterine bleeding

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Abnormal uterine bleeding is an extremely common indication for referral to a gynaecologist. This chapter examines the modes of presentation and the causes of such symptoms, which range from physiological variations to more sinister underlying pathology. A thorough understanding of these causes is required to direct investigation in an appropriate manner. The full range of possible investigations is discussed with emphasis on how to choose the most appropriate tests for a particular patient. This is fundamental to ensure that tests are pertinent and streamlined, and to prevent unnecessary anxiety and delay. Once the underlying causes have been clarified, a suitable management plan can be made.

Key words: menorrhagia; postcoital bleeding; intermenstrual bleeding; postmenopausal bleeding; dysfunctional uterine bleeding; endometrial neoplasm; cervix; leiomyoma/fibroid; polyp; hysteroscopy; ultrasonography; endometrial biopsy.

The vast majority of women will, at some time in their life, experience a degree of menstrual cycle disturbance. A significant proportion of these women will seek medical attention, and these symptoms therefore place a large burden on healthcare services. Menorrhagia alone accounts for 12% of all gynaecology clinic referrals.¹ In many cases, the symptoms will be relatively minor and related to self-limiting alterations in normal physiology. However, many women experience debilitating
symptoms, and for some women, abnormal uterine bleeding will be a sign of significant or sinister underlying pathology. In order to manage women with abnormal uterine bleeding in a safe and efficient manner, methods are required to quantify and investigate these symptoms. These investigations should be pertinent and streamlined to prevent unnecessary anxiety and delay. Once the underlying causes have been clarified, further action can be tailored to the individual, whether that takes the form of simple reassurance or appropriate treatment.

**DEFINITION OF ABNORMAL UTERINE BLEEDING**

Abnormal uterine bleeding is a broad term encompassing a range of presentations. Those most commonly prompting referral to a gynaecologist are as follows.

**Menorrhagia**

Menorrhagia may be defined in two ways. The Royal College of Obstetricians and Gynaecologists has defined it as ‘heavy cyclical bleeding over several consecutive cycles’. However, this is a subjective definition and women’s own retrospective account of bleeding heaviness has been shown to have little consistency with measured blood loss. The generally accepted objective definition of menorrhagia is of menstrual blood loss greater than 80 mL per cycle. This definition is based upon population studies which demonstrated that approximately 10% of women experienced this level of bleeding and that it carries an association with iron deficiency. Methods for the objective measurement of menstrual blood loss are considered later in this chapter.

**Postcoital bleeding**

Postcoital bleeding (PCB) is genital tract bleeding after intercourse. It may be a manifestation of cervical dysplasia, polyps, ectropion or genital tract infection, and therefore warrants thorough investigation. In a recent case series of 142 women with PCB, 19% were found to have cervical intra-epithelial neoplasia (10% high grade), of whom 74% had a recent negative smear test. This suggests that all women with this presentation should be referred for colposcopy.

**Intermenstrual bleeding**

Intermenstrual bleeding (IMB) is bleeding arising from the genital tract, not during menstruation or following intercourse in a woman having periods.

**Postmenopausal bleeding**

Postmenopausal bleeding (PMB) is defined as genital tract bleeding occurring more than 12 months after the last menstrual period.

The term ‘menorrhagia’ generally supposes bleeding from the uterus. PCB, IMB and PMB describe presentations and do not refer to a specific site of bleeding. The whole genital tract, the gastrointestinal tract and the urinary tract must be considered as possible sources of bleeding.
The choice of appropriate investigations for abnormal uterine bleeding will depend upon the particular combination of the above symptoms, as well as the presence or otherwise of associated risk factors for malignancy, such as age (Table 1).

**QUANTIFICATION OF MENSTRUAL BLOOD LOSS**

As discussed above, women's own descriptions of levels of bleeding often have a poor correlation with objective measurements. Many methods have been described for quantifying blood loss, such as collection of menstrual blood in a menses cup or the alkaline haematin method, which involves chemical extraction of haem from sanitary pads.

In clinical practice, these techniques have little relevance, as the focus must be on improving quality of life for any woman who feels that she has a problem with heavy bleeding. However, pictorial blood loss assessment charts (Figure 1) have been shown to be simple and quick to use, and can be particularly useful in the monitoring of therapy.

**CAUSES OF ABNORMAL UTERINE BLEEDING**

An understanding of the causes of these symptoms is required in order to direct history, examination and investigation in a rational manner. In practice, the non-uterine causes of abnormal bleeding will also need to be excluded in women with the presentations discussed above. Table 2 outlines the non-uterine causes of abnormal genital tract bleeding.

The causes of abnormal uterine bleeding can be classified as follows:

**Pregnancy related**

Pregnancy must be excluded in any woman of reproductive age presenting with abnormal uterine bleeding. This may be by urine pregnancy test or serum β-human chorionic gonadotrophin measurement.

**Physiological**

Menstrual cycle disturbance is common at the extremes of reproductive life. In addition, IMB is sometimes caused by a decrease in oestrogen levels following the follicular phase peak, allowing shedding of the endometrium.

<table>
<thead>
<tr>
<th>Table 1. Risk factors for endometrial carcinoma.</th>
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<tbody>
<tr>
<td><strong>Raised body mass index</strong></td>
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<td><strong>Diabetes mellitus</strong></td>
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<tr>
<td><strong>Early menarche</strong></td>
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<td><strong>Late menopause</strong></td>
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<td><strong>Prolonged irregular bleeding</strong></td>
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<td><strong>Nulliparity</strong></td>
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Benign endometrial or cervical pathology

Fibroids

Uterine leiomyomas (fibroids) are benign smooth muscle tumours of the myometrium and are present in one in five women of reproductive age. The majority of these women will be asymptomatic, but a significant proportion (between 20% and 50% in different series) will experience menstrual disturbance, pressure symptoms, or fertility- and pregnancy-related problems. Certainly the most commonly attributed symptom is menorrhagia, although much of the evidence for this relates to the reduction in blood loss following myomectomy. There is no clear evidence that size or location of fibroids affects symptoms, although it is often felt that submucous fibroids distorting the uterine cavity are more likely to cause abnormal bleeding. The malignant potential
of fibroids is debatable, but is extremely low. Therefore, this should not be used as a clinical justification for their removal in an asymptomatic woman.

Endometrial polyps

A significant cause of menorrhagia or IMB, particularly in the later reproductive years, is the formation of endometrial polyps. These are the result of focal overgrowth of endometrial glands and stroma, and may also cause PMB. The risk of malignancy is approximately 1%\cite{11}, although this is predominantly in the postmenopausal group.

Endocervical polyps

Endocervical polyps consist of connective tissue stroma and cervical glands covered with columnar epithelium, which may undergo squamous metaplasia. There is a very low risk of malignancy (approximately one in 6000). They are often asymptomatic but can be a cause of abnormal bleeding, classically PCB.

On speculum examination, these polyps are usually identified protruding through the cervix and can commonly be avulsed in the outpatient clinic. However, the endometrium must be assessed if abnormal bleeding does not resolve after removal of the polyp.

Cervical ectropion

When endocervical columnar epithelial cells are everted on to the ectocervix, they appear as an ‘erosion’. This is thought to be induced by exposure to higher levels of oestrogens and is therefore more common at puberty and during pregnancy. It is also seen more frequently in women taking the combined oral contraceptive pill\cite{12}, although this association is less strong with modern low-dose pills.

An ectropion is a common incidental finding and, when asymptomatic, does not require treatment. It may, however, lead to increased vaginal discharge, PCB or predispose to cervicitis. Cervical dysplasia and infection should be excluded before any destructive treatment, such as cryotherapy, is performed.

Malignant endometrial or cervical pathology

The possibility of cancer of the cervix or endometrium must be considered in any patient with abnormal bleeding. The need to exclude these conditions formally will depend upon the particular risk factors and presentation.
Endometrial carcinoma and endometrial hyperplasia

The most significant risk factor for endometrial cancer is increasing age and it must be excluded in any woman presenting with PMB. However, 20–25% of cases occur in premenopausal women who may present with menorrhagia.

Other risk factors include obesity, nulliparity and polycystic ovarian syndrome (see Table 1). These share a common pathway of excessive endometrial oestrogenic stimulation, and therefore tamoxifen therapy also predisposes to endometrial malignancy. This same aetiology is also implicated in the development of endometrial hyperplasia.

Endometrial hyperplasia is excessive proliferation of the endometrial glands and, to a lesser extent, the endometrial stroma. It may present with menorrhagia, IMB or PCB and is classified as simple, complex or atypical. Simple and complex hyperplasias carry a 1–3% risk of malignant transformation. The risk of endometrial carcinoma with a diagnosis of atypical hyperplasia has been reported to be between 23% and, more recently, 43%.

Cervical cancer and cervical intra-epithelial neoplasia

In the UK, the death rate from cervical cancer has halved since the introduction of nationwide screening. Worldwide, however, it remains the most common gynaecological malignancy, and even in the developed world, it must not be forgotten as an important cause of abnormal bleeding. The age distribution of these tumours shows a bimodal peak of incidence at 35–39 years and 60–64 years. The vast majority (85–95%) are squamous cell carcinomas, but the prevalence of adenocarcinomas is rising and these often present in women under 35 years of age.

Although premalignant changes in the cervix are common and generally asymptomatic, cervical intra-epithelial neoplasia may also provoke symptoms such as PCB or IMB.

Systemic causes

Exogenous hormones

The use of any form of hormonal contraceptive can lead to a disturbance of the normal menstrual cycle, particularly around the time of their commencement. The combined oral contraceptive pill may cause IMB, and progestogen-only contraceptives are associated with irregular bleeding. Similarly, hormone-replacement therapy in post- or perimenopausal women can lead to abnormal bleeding. Despite these associations, it is important to exclude other pathology in a woman in whom these symptoms do not settle swiftly.

Medical conditions

Numerous medical conditions have been postulated to influence the menstrual cycle, often without firm evidence. In particular, a wide variety of disorders have been suggested as causes of menorrhagia, a summary of which is given in Table 3. A few of these conditions are considered further here.

Thyroid disease. There is evidence that hypothyroidism is associated with menorrhagia, and that return to the euthyroid state with thyroxine treatment reduces objectively measured losses significantly. Conversely, there are data supporting the link between hyperthyroidism and oligo- or amenorrhoea.
Haematological conditions. That coagulation disorders can lead to abnormal menstruation seems irrefutable\(^\text{22}\), and thrombocytopenia has also been implicated. In addition, iatrogenic anticoagulation has been shown to increase menstrual blood loss.\(^\text{23}\) Although only a small proportion of menstrual disturbances can be attributed to such conditions, these patients pose a particular challenge as diagnosis can easily be missed and they may not be amenable to conventional treatments.

**Pelvic infection**

Infection of the upper or lower genital tract can lead to abnormal bleeding. Cervicitis, which may be caused by chlamydia or gonorrhoea infection for example, is a common cause of IMB and PCB. Women with pelvic inflammatory disease, endometritis or salpingitis may present with non-scheduled bleeding, with or without associated symptoms such as fever and pain. Infection screening must therefore be considered, particularly in young women.

**Dysfunctional uterine bleeding**

Dysfunctional uterine bleeding (DUB) can be defined as ‘excessive uterine bleeding (excessively heavy, prolonged or frequent), which is not due to demonstrable pelvic disease, complications of pregnancy or systemic disease.’\(^\text{24}\) It is therefore a diagnosis of exclusion and includes both ovulatory and anovulatory bleeding. The majority of cases of DUB are secondary to hormonal dysfunction, and occur in perimenopausal women or after the menarche.\(^\text{25}\) In adolescence, this is usually of hypothalamic-pituitary origin, whilst in the perimenopause, it is related to unstable and reducing ovarian function. A wealth of observational data\(^\text{4,26}\) supports the idea of increasing variability of the menstrual pattern as women approach the menopause. This may make the detection of underlying pathology particularly challenging in this age group.

**HISTORY**

The taking of a good history is essential to any therapeutic encounter. The history should focus on the likely causes of abnormal menstrual bleeding (see **Table 4**) as well as aiming to establish the amount and frequency of the bleeding.
Features within the history that are identified risk factors for endometrial carcinoma should be looked for specifically, as the identification of endometrial carcinoma or hyperplasia is clearly of importance (see Table 2). A relevant family history should be established. Enquiries should be made about IMB and PCB. Pregnancy must always be excluded. A contraceptive history should be taken, as recent-onset menorrhagia may be explained by, for example, the cessation of the combined oral contraceptive pill following male or female sterilization, or by the recent insertion of a copper-containing intra-uterine device. The wish for preservation, or otherwise, of fertility should be noted, as this will have much importance when planning management options.

The date and result of the last cervical smear should be noted, and any previous cervical smear abnormalities, colposcopy attendances or cervical surgery reviewed.

The presence of pelvic pain and/or pressure effects should be investigated, as these may indicate the presence of uterine pathology or other disorders. Questions should be directed specifically to ensure that the bleeding is from the genital tract, and is not being confused with urological or gastrointestinal bleeding which require different investigations and appropriate referral.

In order to provide a holistic approach, the clinician should explore the woman’s perspective of her symptoms. By exploring the woman’s ideas, concerns and expectations regarding her bleeding and potential treatments, the requirements of therapy, education and reassurance may be determined.

### EXAMINATION

General examination should include assessment for anaemia, thyroid disease and clotting disorders.

Abdominal palpation may detect a grossly enlarged fibroid uterus, which should trigger referral from primary to secondary care. Inspection of the vulva and vagina is essential in order to exclude any gross pathology.

Speculum examination of the cervix is vital to exclude a cervical polyp or macroscopic cervical tumour. A cervical smear should be taken if due or clinically indicated. If there is a suggestion of invasive tumour, urgent colposcopic assessment should be sought. Vaginal and cervical swabs should be taken for microbiology where appropriate.

### Table 4. Causes of abnormal uterine bleeding.

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
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<tbody>
<tr>
<td>Pelvic</td>
<td>Uterine fibroids</td>
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<td></td>
<td>Adenomyosis</td>
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<td></td>
<td>Endometrial polyps</td>
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<td></td>
<td>Pelvic infection</td>
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<td>Endometrial hyperplasia</td>
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<td></td>
<td>Endometrial adenocarcinoma</td>
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<td></td>
<td>Presence of copper-containing intra-uterine contraceptive device</td>
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<tr>
<td></td>
<td>Uterine vascular malformations</td>
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<tr>
<td></td>
<td>Myometrial hypertrophy</td>
</tr>
<tr>
<td>Systemic</td>
<td>Coagulation disorders, i.e. thrombocytopenia, von Willebrand disease</td>
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<tr>
<td></td>
<td>Hypothyroidism</td>
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<tr>
<td></td>
<td>Systemic lupus erythematosus</td>
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<tr>
<td></td>
<td>Chronic liver failure</td>
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<tr>
<td>Functional</td>
<td>Dysfunctional uterine bleeding</td>
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Bimanual pelvic examination will allow for the assessment of uterine size and mobility, pelvic tenderness and adnexal masses.

INVESTIGATIONS

The need to exclude local pelvic pathology and systemic disease is the driving force behind investigations for uterine bleeding. However, the vast majority of women investigated for menorrhagia have ‘normal’ endometrium, and would therefore be considered to have a functional disorder, DUB. Therefore, those women most likely to have abnormal endometrium should be identified through history and examination findings to limit unnecessary investigations, which have economic implications and may, to varying degrees, be difficult for women to tolerate.

The latest guidance from the National Collaborating Centre for Women’s and Children’s Health states that if the history obtained suggests menorrhagia without structural or histological abnormality, pharmaceutical treatment (with the exclusion of the levonorgestrel-releasing intra-uterine system) can be commenced without carrying out a physical examination or other investigations at the initial consultation in primary care.

If, however, the history suggests menorrhagia with structural or histological abnormality, with symptoms such as IMB or PCB, pelvic pain and/or pressure symptoms, a physical examination and/or other investigations should be performed.

Blood tests

A full blood count should be obtained from all women with menorrhagia who require investigation in order to recognize iron deficiency and anaemia. Iron supplements should be prescribed as needed. A serum ferritin level may be useful if there is any doubt about iron deficiency, but should not be a routine investigation. The full blood count will also provide information about the platelet count and thereby identify those women with thrombocytopenia.

Systemic diseases are rare causes of menorrhagia and investigations to treat them should not be routine. Thyroid function tests are only indicated in women where the history or examination findings are suggestive of thyroid disease. The same is true for bleeding disorders. A coagulation screen may be indicated where there is a history of easy bruising or dental bleeding. Testing for coagulation disorders (e.g. von Willebrand disease) should be considered in women who have had menorrhagia since menarche and have a personal or family history suggesting a coagulation disorder.

Assessment of the uterine cavity

In women at high risk for endometrial carcinoma (see Table 1) or those for whom symptoms do not resolve following first-line medical therapy, the endometrium should be assessed for both structural and histological abnormalities. Imaging should be undertaken if the uterus is palpable abdominally or when vaginal examination reveals a pelvic mass of uncertain origin.

The assessment may be by:

- ultrasound;
- endometrial biopsy;
dilation and curettage (no longer conducted alone); hysteroscopy; or magnetic resonance imaging.

These modalities may be used in isolation or in combination.

**Ultrasonography**

Ultrasonography using transabdominal or transvaginal probes can be used to assess the size, number and location of fibroids and to measure endometrial thickness; a useful indicator to determine the need for further endometrial assessment.

The introduction of transvaginal ultrasound has allowed higher frequency probes to be employed, resulting in high-quality image resolution and improved predictive ability.

It is possible to obtain more information about the endometrium by the use of saline instillation at the time of ultrasonography. This allows distension of the endometrial cavity to allow improved imaging of the cavity. Ultrasonic detection of submucous fibroids is improved substantially with saline infusion sonography.

Transvaginal ultrasound is less limited by patient obesity than the transabdominal route, and is a quick, simple and reproducible procedure. The failure rate of transvaginal ultrasound is negligible.

Endometrial thickness of 5 mm or less over the whole cavity is said to exclude endometrial carcinoma; this is mainly of value in postmenopausal women. Where the endometrial thickness is found to be greater than 5 mm on transvaginal ultrasound, endometrial sampling should be performed in the postmenopausal setting.

Endometrial thickness measurement using ultrasound is of minimal use in premenopausal women because specific cut-off levels or morphological features do not define accurately the presence or absence of endometrial hyperplasia or cancer. However, the Royal College of Obstetricians and Gynaecologists’ Guideline Development Group concluded that 10–12 mm represented a reasonable cut-off to decide if further investigations are indicated when using transvaginal ultrasound in premenopausal women.

**Endometrial sampling**

An endometrial biopsy should be performed for all women with ultrasonic abnormalities and should be considered for all women with persistent menorrhagia. An endometrial biopsy is important even if a hysteroscopy is normal.

Outpatient endometrial biopsy has high accuracy in diagnosing endometrial cancer and hyperplasia, and should be employed when serious endometrial disease is suspected in both pre- and postmenopausal women.

Following acceptability trials in the 1980s, the Pipelle endometrial sampler has been adopted as the preferred device.

The main concern of ‘blind’ sampling of the endometrium is that serious pathology may be missed. The incidence of false-negative results is now known to be so high that serious consideration needs to be given to discarding this investigation in favour of the more precise modern methods of imaging and tissue collection.
Dilation and curettage

Dilation and curettage is now largely of historical interest. Available evidence suggests that dilation and curettage no longer has a place in either the treatment or investigation of abnormal uterine bleeding.27

Hysteroscopy

Modern hysteroscopes combine miniaturization with excellent image resolution and visualization29; therefore, hysteroscopy can be performed in the outpatient setting without the need for a general anaesthetic. Outpatient hysteroscopy is generally very well tolerated by and acceptable to women.

Instrumentation and distension of the uterine cavity, whether using saline infusion sonography or outpatient hysteroscopy, is comparatively more painful than transvaginal ultrasound, but both procedures appear to be equally well tolerated.29 The use of saline as opposed to carbon dioxide for uterine distension and attention to pain control help to minimize discomfort during hysteroscopy.29

Hysteroscopy can fail due to the inability to pass the scope along the endocervical canal or due to patient discomfort. Once the hysteroscope is within the uterine cavity, the view obtained can be limited by bleeding or intra-uterine debris.29

Hysteroscopy should be used as a diagnostic tool only when ultrasound results are inconclusive, e.g. to determine the exact location of a fibroid or the exact nature of an abnormality.6 Hysteroscopy is better at identifying polyps than ultrasound.6 Hysteroscopy allows direct visualization of the endometrial cavity and, importantly, directed endometrial sampling of any suspicious areas.

Hysteroscopy can also be therapeutic, allowing the removal of endometrial polyps, submucous fibroids or the endometrium.

Magnetic resonance imaging

Evidence shows that magnetic resonance imaging has no advantage over ultrasound as a first-line investigation for menorrhagia, but may be reserved for problem solving where ultrasound provides indeterminate results.6

SUMMARY

Abnormal uterine bleeding is common and encompasses the presentations of menorrhagia, PCB, IMB and PMB. The causes are varied and include complications of pregnancy, benign and malignant lesions, systemic causes and DUB. Although a large proportion of these women will require nothing more than reassurance, these symptoms must be taken seriously as they may have a major impact on a woman’s quality of life, and to ensure that the minority of women with significant underlying pathology are identified.

Investigations should be chosen carefully to distinguish between these diagnoses in as safe and efficient a manner as possible. Where appropriate, structural and histological abnormalities should be identified so that therapies can be directed accordingly.

To maximize the success of the therapeutic encounter, the woman’s ideas, concerns, expectations and needs must be explored and used to guide investigations and treatment. Good counselling and adequate explanation of all procedures and results is paramount for successful management of abnormal uterine bleeding.
**Practice points**

- anaemia needs to be assessed and treated in women with abnormal uterine bleeding
- women with abnormal uterine bleeding and risk factors for endometrial carcinoma should be investigated thoroughly to exclude endometrial hyperplasia and carcinoma
- where a woman has a abdominally-palpable uterus, a pelvic mass on vaginal examination or where pharmacological treatments have failed, imaging should be employed to investigate structural abnormalities
- if on reviewing the history from a woman with abnormal uterine bleeding, there are no features suggestive of serious pathology, pharmacological treatments may be commenced without the need for examination or investigation
- any abnormal uterine bleeding that does not improve with simple pharmacological measures needs investigation
- thyroid function and clotting tests should only be performed if the history or examination findings are suggestive of systemic abnormalities

**Research agenda**

- investigation of the impact of abnormal menstrual bleeding on quality-of-life parameters of affected women
- development of increasingly accurate non-invasive investigative techniques in order to minimize morbidity from invasive procedures

**REFERENCES**


