**Abnormal Uterine Bleeding**

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SHORT title of paper: Abnormal Uterine Bleeding

**STRUCTURED ABSTRACT** of no more than 150 words.

Introduction: It is not uncommon for a woman to suffer from abnormal uterine bleeding (AUB) or heavy menstrual bleeding (HMB) at some point during her lifetime. Once pathology is excluded, in practice, management needs to be individualised, taking into account the improvement of the woman’s symptoms and quality of life.

Sources of data: Peer-reviewed journals, governmental and professional society publications.

Areas of agreement: There is now agreement on a structured, universal approach to the diagnosis of AUB, with the aide memoirs PALM (polyps, adenomyosis, leiomyoma, malignancy) and COEIN (coagulopathies, ovulatory dysfunction, endometrial, iatrogenic, not otherwise classified). Once malignancy and significant pelvic pathology have been ruled out, medical treatment is an effective first line therapeutic option, with surgery, including endometrial ablation and hysterectomy, offered when medical management has failed to resolve symptoms and fertility is no longer desired.

Areas of controversy: There remains controversy around the management of the types and subtypes of adenomyosis and leiomyoma, and understanding their impact on clinical reproductive outcomes.

Areas currently under development: Standardised assessment tools for measuring outcomes of AUB are being developed.

Areas timely for developing research: Novel diagnostic and monitoring tools should be developed to help stratify treatment for women with AUB, particularly relating to ‘unclassified’ and ‘endometrial’ causes.

**KEY WORDS:** menstruation, abnormal menstrual bleeding, dysfunctional menstrual bleeding, heavy menstrual bleeing

**Introduction**

‘There can be no other disease or condition that affects so many people on such a regular basis with consequences, at both the individual and societal levels, which is not prioritised in some way by health professionals or policy makers.’(1)

AUB describes a range of symptoms, such as heavy menstrual bleeding (HMB, bleeding above the 95th centile of the normal population), inter-menstrual bleeding, and a combination of both heavy and prolonged menstrual bleeding. This terminology was established by the International Federation of Gynecology and Obstetrics (FIGO) Menstrual Disorders Working Group in 2011 and has been gaining global acceptance. The diagnosis of AUB can be made when conditions within the acronym PALM-COEIN are implicated (Figure 1) - PALM (polyps, adenomyosis, leiomyoma, malignancy) and COEIN (coagulopathies, ovulatory dysfunction, endometrial, iatrogenic, not otherwise classified) (2). Menstrual disorders, previously portrayed as dysfunctional uterine bleeding (DUB) and menorrhagia, are now better described as abnormal uterine bleeding (AUB) (3). The terms DUB and menorrhagia should be discarded (4). (5)

The volume of menstrual flow is influenced in part by uterine contractions, vascular tone and haemostatic function. Normal menstruation can range from a frequency of between 24 and 38 days, a duration between 4.5 and 8 days, and a volume of blood loss between 5 and 80 mL per cycle (6). The experience of menstruation is different for every woman. Therefore, defining what constitutes ‘abnormal’ menstrual bleeding is a subjective assessment for patients and their clinicians. The definition of heavy menstrual bleeding (HMB) in the research setting relates to blood loss of more than 80 mL per cycle (7). This level of blood loss increases the risk of iron deficiency anaemia (8).

Despite its relative frequency, AUB continues to be a significant and at times unmet clinical need. Standardising assessment tools for measuring outcomes of AUB is the focus of current work being developed through the Crown Initiative (Core Outcomes in Women’s and Newborn Health), aiming to address the widespread, unwarranted variation in reporting of women’s health outcomes (9).

**Abnormal uterine bleeding across the life course**

AUB may first manifest at the onset of the menarche (10). It is particularly prevalent in women of reproductive age, but continues to be a common problem until menopause. As such, the clinico-pathological spectrum of uterine diseases that may be involved, and the management strategy adopted, depends very much on the risk profile of individual at the time of presentation.

Menstrual problems are common in adolescence with many suffering from unpredictable, prolonged or heavy bleeding soon after menarche. Adolescents frequently have irregular and/or painful periods, but occasionally experience unpredictable, prolonged or excessive bleeding that may present as a medical emergency (11). Anovulation is likely to be the most common reason for HMB in this age group (12) but other causes, such as an underlying bleeding disorder, are essential to exclude.

In the reproductive years, AUB and its subgroup HMB affects about 14-25% of women and impacts significantly on physical, social, emotional and psychological aspects of the quality of life (13). Two national audits in England and Wales (14, 15) reported that, at one year post referral, only a third of women (including those who underwent surgery) were ‘satisfied’ (or better) at the prospect of current menstrual symptoms continuing for the next 5 years. A postal survey of 4610 women (aged 25–44 years) in Scotland found that 30–35% of women reported “menorrhagia”, and one-fifth of these women felt that their periods were a problem. Reporting period problems was directly proportional to the incidence of dysmenorrhoea and heaviness of the flow (16). The management of AUB in this group of women, many of whom wish to retain fertility, often poses a challenge, as current effective treatments for AUB often render the patient infertile. Specific considerations therefore have to be made in this group to balance the woman’s desire for fertility against the need for symptomatic treatment of AUB.

During the premenopausal phase, the menstrual cycles are shortened, often anovulatory and irregular. The irregular pattern of bleeding may be exacerbated by ‘Luteal Out of Phase Events’ (LOOP), where the mid-cycle oestradiol peak is followed by a second or even third peak that is yet higher. The last oestradiol peak and subsequent rise progesterone after flow starts in the following cycle, determines the presence of menstrual symptoms. Hale estimated that a third of cycles during the menopausal transition have LOOP characteristics (17). The increased frequency of anovulatory cycles, and consequent exposure of the endometrium to unopposed oestrogen, increases the risk of endometrial hyperplasia and endometrial carcinoma in peri-menopausal and post-menopausal women with AUB.

Whilst the management of AUB should be disease-specific and address underlying pathology, individualising treatment strategies and management of patient expectations are crucial for a successful outcome. In the sections below, we examine the clinical approach to patients with AUB and review the evidence-based medical and surgical treatment options.

**The clinical approach to abnormal uterine bleeding**

The first step in the diagnostic workup is to assess the ‘quantity’ of menstrual blood loss and the impact on the patient. Various charts, questionnaires and disease-specific patient-reported outcome measures (PROMs) are available. However, these are not commonly used in the clinic as there is limited evidence that they alter patient outcomes. Whilst research is being conducted to develop clinically useful validated PROMs and bleeding scores (18, 19), in practice, the clinician must rely on individual assessment to investigate AUB.

The clinical approach to assessing a patient with AUB can be taken in several steps.

1. History
2. History of menstrual cycle(20):
   * 1. menstrual cycle length (frequent <24days; normal 24-38 days; infrequent >38days)
     2. variability, duration (prolonged >8 days; normal 4.5-8.0; shortened <4.5)
     3. volume of flow and quantify the blood loss (heavy >80mls; normal 5-80mls; light <5mls)
        + Rate of change of sanitary protection during peak flow days;
        + need to change sanitary protection overnight;
        + the presence and size of clots that are passed;
        + the occurrence of a ‘flooding’ sensation;
        + and the existence of iron deficiency.
3. Impact of symptoms on quality of life and wellbeing:
   * 1. enquire about the impact of the menstrual pattern on social life (e.g. work and school attendances, ability to carry out activities of daily living, impact on sex life)
     2. emotional life (including symptoms of depression and distress)
     3. health-seeking behavior (including interactions with other healthcare professionals).
4. Sexual and reproductive history
5. Symptoms suggestive of systemic causes of bleeding such as hypothyroidism, hyperprolactinaemia, polycystic ovary syndrome, adrenal or hypothalamic disorders
6. Coagulation disorders  
   History of i) excessive menstrual bleeding since menarche, *or ii)* one of the following—postpartum haemorrhage, surgery-related bleeding, or bleeding associated with dental work, *or iii)* two or more of the following— bruising greater than 5 cm once or twice a month, epistaxis once or twice a month, frequent gum bleeding, family history of bleeding symptoms (21). The presence of a significant clinical history, together with abnormalities in investigation results (Table 2), will warrant a referral to haematology colleagues.
7. Explore related symptoms
   * 1. Pelvic pain and/or pressure symptoms (Pressure and bladder symptoms may suggest the presence of a pelvic mass)
     2. Mood changes
     3. Fatigue
8. A family history of inherited coagulation disorders, PCOS, or endometrial or colon cancer should also be sought, as well as any co-morbid conditions, such as hormonally-dependent tumours, thromboembolic disease, or cardiovascular problems that would influence treatment options.
9. Physical examination

A physical examination should be carried out to exclude underlying pathology. For example, petechiae, purpura, ecchymoses or gum bleeding might suggest a bleeding disorder. However, the clinical history is a much stronger predictor of an underlying bleeding disorder and the absence of such physical exam signs does not rule out the presence of a bleeding disorder. General examination should focus on excluding systemic disorders such as thyroid disease, hyperandrogenism or Cushing’s. Abdominal and pelvic examination is usually recommended to assess for pelvic tumours and other specific pathologies.

1. Investigations

Table 1 shows a list of investigations that may be useful in the context of AUB.

**General management strategies**

In practice, if there is an obvious pathology identified, the key management strategy will be aimed at treating the cause through medical or surgical treatment (Figure 3). Women with severe symptoms (those with severe pain or pressure symptoms) may require treatment that results in a swifter resolution and clinicians may lean towards a surgical approach if an effective strategy is available. Table 3 (14) lists the recommended treatments for AUB with and without identifiable treatable pathology. For more detailed reviews on the individual topics, please refer to the following references (22-24). Where no obvious pathology has been identified, the abnormal bleeding is likely to be attributed to local endometrial causes. However, currently, there are no ideal diagnostic or monitoring tools to help stratify treatment for women with AUB related to ‘endometrial’ causes (25, 26).

Medical treatment is tailored to the individual woman’s therapeutic goals, desire for pregnancy or contraception, underlying medical conditions, and tolerance of side effects will encourage compliance and maximize the likelihood of treatment success.

Medical options, besides the treatment of iron deficiency anaemia (Table 2), the management of AUB can be divided into non-hormonal and hormonal therapies. Non-hormonal treatments, including anti-fibrinolytics and non-steroidal anti-inflammatory drugs (NSAID) can reduce menstrual blood loss by up to a 50% (27, 28). These are appropriate first-line options for women who wish to conceive or avoid hormonal side effects. In addition, they also confer the benefit of a degree of analgesia. Anti-fibrinolytics and NSAIDs may also be used in conjunction. However, they are less likely to be effective in the presence of significant pathology, such as uterine fibroids.

The choice of hormonal treatment very much depends on the patients’ preferences. With regard to hormonal treatments, the combined oral contraceptive pill (COCP) is widely used to regulate bleeding and reduce blood loss, although there are minimal data from randomized trials to demonstrate clinical benefit. Treatment consecutively for 3 months without a pill free week may be of value (29). Oral progestogens may be used to stop an acute heavy bleed, to manage irregular or heavy bleeding or to control the timing of the onset of menstruation, although side effects may limit longer term use (30).

In women with HMB who presented to primary care providers, the levonorgestrel intrauterine system (LNG-IUS) was reported to be more effective than other first line medical treatments in reducing the impact of HMB on quality of life (31). However, insertion of the intrauterine system into the uterus may prove difficult, particularly in the presence of lesions such as large submucous fibroids, or fibroids that alter the structure of the uterine cavity.

In addition to providing effective contraception, injectable progestogens (such as depot medroxyprogesterone acetate DMPA) cause amenorrhoea in up to 50% of users (32), though this approach may also be associated with troublesome breakthrough bleeding.

Gonadotrophin releasing hormone agonists (GNRHa) are known to induce amenorrhoea in up to 90% of women. This treatment is often used in women with fibroids, effectively shrinking the size of fibroids and reducing operative blood loss if surgery is subsequently undertaken (33-35). However, side effects due to the associated hypo-oestrogenic state may be significant. Use is usually limited to 6 months prior to elective surgery. If longer-term treatment is contemplated, ‘add-back’ hormone replacement therapy may be prescribed to reduce side effects and protect against osteoporosis.

Selective progesterone receptor modulators (SPRMs) are a newer group of pharmacological agents possessing tissue-specific progesterone antagonistic effects on the endometrium and myometrium. With good treatment compliance, clinical trials have demonstrated control of HMB in women with fibroids in over 90% of cases and amenorrhoea in over 70%. There is good evidence that the SPRM, ulipristal acetate (UPA), compares well with GnRHa for pre-surgery treatment of uterine fibroids, and is better tolerated (36). Repeated 12-week courses of daily oral ulipristal acetate (5 and 10mg) have recently been shown to control bleeding and pain, reduce fibroid volume, and restore quality of life in patients with symptomatic fibroids (37). The investigators concluded that the 5mg dose of ulipristal acetate approved for pre-operative use would be appropriate for long term symptom management, although the data available thus far are only based on up to 4 repeated courses.

Administration of all SPRMs is associated with a “class-effect” on the endometrium known as ‘progesterone receptor modulator associated endometrial changes’ (PAEC) (38). This unique morphology, encompassing endometrial glandular changes with architectural irregularity with cystic dilatation and with the glandular epithelium appearing inactive, with no physiological secretary appearance, requires recognition by gynaecologists and gynaecological pathologists. These features have not been associated with significant pathology to date and appear to be reversible.

**Surgical treatment**

A detailed discussion about the surgical management of malignancy, fibroids, adenomyosis, uterine anomalies and polyps is beyond the scope of this review but suggested references include the following (22, 39-42).

Surgical management, in the absence of underlying pathology (i.e. surgical management of HMB) takes the form of either endometrial destruction or hysterectomy. Endometrial destruction is only applicable when the patient’s family is complete or she utilises a permanent/highly reliable method of contraception. The endometrium may be removed by surgical resection (first-generation hysteroscopic techniques), or through controlled application of energy (second-generation techniques, e.g. heat, cold, microwave), to produce full thickness necrosis. Risks of endometrial ablation include uterine perforation, infection, hemorrhage, and bowel or bladder injury. Other risks of hysteroscopic techniques are fluid overload, especially when hypotonic solutions (e.g. 1.5% glycine) leading to symptoms of hyponatraemia and post-ablation syndrome, often present as cyclical pain, as a result of haematometra.

A summary of the current RCTs comparing the surgical management of HMB is outlined in Figure 2. A recent Cochrane systematic review found that success rates and complication profiles of newer techniques of ablation compare favourably with hysteroscopic techniques (43). In comparison with hysterectomy, endometrial destruction techniques have a shorter operation time and hospital stay, quicker recovery, fewer postoperative complications and similar satisfaction rates. Hence, in practice, most clinicians initially perform endometrial ablation using one of the second-generation techniques unless a polyp or fibroid need to be removed, when a hysteroscopic resection technique will be more appropriate. Ongoing reliable contraception is essential for sexually active women after endometrial ablation/destruction. Although fertility is usually significantly impaired, conception is possible and is associated with an increased risk of serious complications, including abnormal placentation and major haemorrhage.

The review also compared endometrial resection with medical treatments (hormonal and non-hormonal). Endometrial resection was more effective in controlling bleeding at four months (RR 2.66, 95% CI 1.94 to 3.64, one RCT, 186 women, moderate quality evidence) and at two years (RR 1.29, 95% CI 1.06 to 1.57, one RCT, 173 women, low quality evidence) although no difference was seen at five years (RR 1.14, 95% CI 0.97 to 1.34, one RCT, 140 women). Indeed, the satisfaction with treatment achieved at 2 years was not maintained at 5 years. Regrettably, there were insufficient data to perform a meaningful head-to-head comparison between specific types of surgery and individual medical treatments.

In the same review, when hysterectomy was compared with the LNG-IUS, the hysterectomy group was more likely to have objective control of bleeding at one year (RR 1.11, 95% CI 1.05 to 1.19, one RCT, 223 women, moderate quality evidence). There was no difference in quality of life between the groups at 5 or 10 years, but a significant proportion of women (46%) assigned to the LNG-IUS had undergone hysterectomy by 10 years.

Predictably, for most trials, it was not possible to recruit women who had never had any form of medical treatment. Hence, this was a significant confounder in favour of surgery over medical therapies.

Clearly, the decision for conservative or major surgery versus any form of medical treatment is dependent on the patient’s fertility aspirations, fitness and preference. Surgery carries complications such as the injury to viscera, bleeding, venous thromboembolism and infection. In some patients, these risks may be not insignificant. Women should ideally try less invasive treatments with the lowest complication rates as first-line therapy.

**Conclusion**

The management of the patient with AUB requires a step-by-step approach, where treatment is customised to the individual’s needs, addressing any underlying pathology and taking into account the desire, or not, for preservation of fertility. There is however, in addition to the introduction of new treatments, a need for the development of novel tools to help diagnose, monitor and quantify the severity of the disorder. But let us not forget that no therapeutic discovery will ever eliminate the need for good judgment, sensitive communication and the art of managing expectations.

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Figure 1. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding (AUB).

**Table 1. Recommended investigations and tests**

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| Investigations | Rationale |
| Full blood count | Exclude anaemia; consider ferritin measurement. |
| Transvaginal ultrasound scan | General assessment of uterine shape, size and presence or absence of fibroids, polyps, adenomyosis. Uterine anomalies, such as uterine didelphys, can present with AUB.  Can visualize appearances suggestive of polycystic ovaries.  Exclude endometrial pathology such as polyps and/or malignancy. |
| MRI | Useful for women suspected of having fibroids, helping assessment prior to myomectomy, fibroid embolisation and possible malignancy. |
| Hysteroscopy | Evaluate the endometrial cavity for the presence of polyps and/or endometrial cancer.  Polyp removal and endometrial biopsy can be performed simultaneously. |
| Endometrial sampling | Exclude endometrial hyperplasia and/or cancer. |
| Coagulation disorders screen | Especially in the adolescent, diagnose/exclude bleeding disorders.  PT, APTT, fibrinogen and thrombin time to investigate factor deficiencies  VWD panel testing (VW factor (VWF) antigen (Ag), VWF: ristocetin (RCo) co-factor activity and VWF multimer) and factor levels depending on clinical and family history. |
| Thyroid function | Hypothyroidism can be excluded but only indicated if symptoms and signs suggest. |

**Prothrombin time (PT), activated partial thromboplastin time (APTT); Von Willebrand (VW)**

**Table 2. Medical treatments – mode of action**

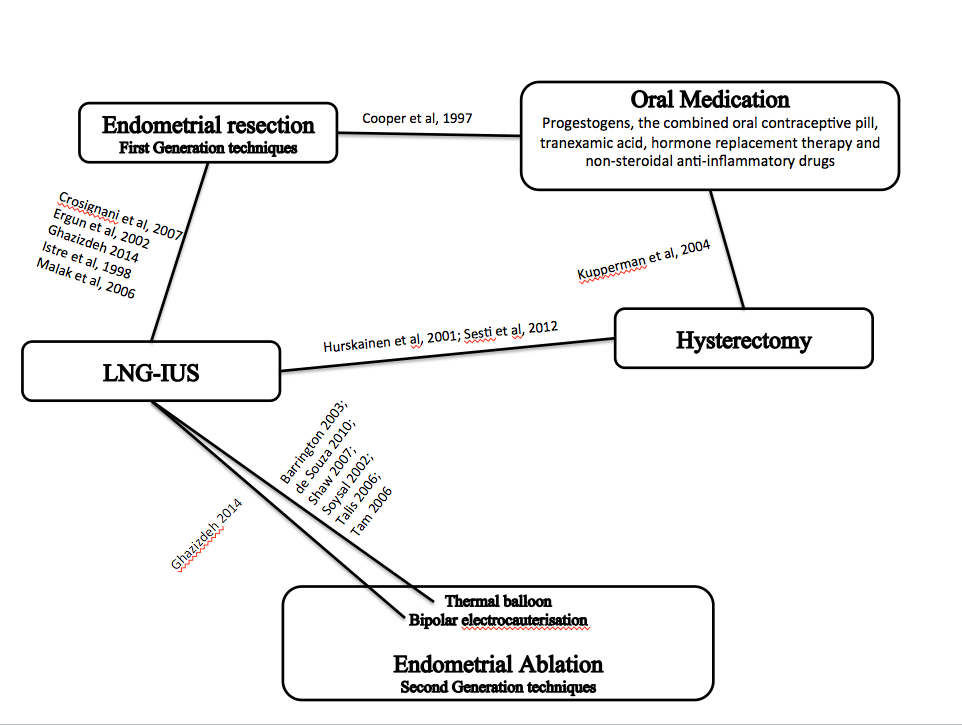
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| --- | --- | --- | --- |
| Drug | How it works | How to prescribe | Side effects & contraindications |
| Iron therapy | Replacement of iron (44) | Intravenous Fe:  At least as effective as oral iron. e.g. Iron Sucrose 200mg IV in 200mls N/Saline minimum of 30 minutes three times/week. Total dose is determined by Ganzoni calculation. Total iron deficit (mg) = body weight (kg) x (target Hb – actual Hb) x 0.24 + depot iron (mg). Other forms of Iron preparation are also now available e.g. Ferinject (ferric carboxymaltose;) (50 mg iron/mL solution for injection/infusion.  No test dose is required. may be administered by slow intravenous injection at a rate of 1ml undiluted solution per minute and not exceeding 10ml (200mg iron) per injection. Patients should be observed carefully during the infusion and for at least 30 minutes after completion.  Oral Iron  e.g. FeSO4 200mg b.d. orally, taken between meals and check FBC and Fe levels monthly (where patients take iron supplements effectively, Hb should rise by 2g/l every three weeks). Lower doses are better tolerated (start daily and build up dosing). Ascorbic acid (vitamin C) in combination may help absorption. | Mainly gastrointestinal side effects  Contraindications:  Known hypersensitivity to intravenous iron  anaemias not caused by iron deficiency  iron overload  First trimester of pregnancy.  Precautions include:  asthma, eczema or other atopic allergy  liver dysfunction  acute or chronic infection hypotension |
| Antifibrinolytics e.g. tranexamic acid | Anti-fibrinolytic – counteracts the over activation of the fibrinolytic system | 1 gm tds or qds during the days of menstruation | Mainly gastrointestinal symptoms |
| NSAIDS e.g. mefenemic acid | Anti-inflammatory effect through inhibition of cyclooxygenase | 500gm tds | Mainly gastrointestinal symptoms  Contraindicated in patients with bleeding disorders. |
| Levonorgestrel-releasing intrauterine system (LNG-IUS) | Slowly released from the IUS to act on the local endometrial  environment preventing proliferation. It may  also impact on the frequency of ovulation. | 20mcg LNG (average released daily – intrauterine route -for the duration of use) | Contraindications: pregnancy,  unexplained vaginal bleeding and uterine sepsis.  Side effects: unscheduled bleeding, infection (increased in the first 3 weeks after insertion), expulsion (higher in nulliparous women), perforation (1/1000 cases) |
| Combined oral contraceptive pill (COCP) | Supresses ovulation, regulates menstruation with ‘pill free’ week | Daily pill for 21 days each month  “Tri-cycling” may be considered  Useful to refer to medical eligibility criteria MEC:  http://www.fsrh.org/ukmec/. | Mood changes; headaches; nausea; fluid retention; breast tenderness;  deep vein thrombosis; stroke; heart attacks |
| Injectable progestogen e.g.  depot medroxyprogesterone  acetate | Inhibition of follicle stimulating  hormone (FSH) release from the anterior  pituitary and prevention of ovulation | Every 12 weeks to maintain progestogen exposure and ensure contraceptive efficacy | Weight gain, greasy skin  and hair, acne and bloating  Long term use associated with decrease in bone mineral density, restored on cessation of use |
| Oral progestogens e.g. norethisterone | Induces predictable bleeding and may inhibit ovulation in high doses | 5mgs tds days 5-26 of cycle | Those common to all progestogen use |
| Gonadotropin-releasing hormone agonists (IM, SC or intranasal) +/- add-back | Induces a profound  hypogonadal state | IM every 3-6 monthly with add-back for longer term use | Menopause­like symptoms (such as hot flushes, increased sweating, vaginal dryness)  osteoporosis, particularly trabecular bone loss with longer than 6 months’ use |
| Ulipristal Acetate (UPA) | Licensed for use in clinical practice, 3 months’ pretreatment of fibroids prior to surgical removal or repeated 12 week courses \* | 5mg once daily preoperatively or  repeated 12 week courses of daily oral ulipristal acetate (5 mg) \* | Fertility preserving.  Patients and clinicians need to be aware of  progesterone receptor modulator associated endometrial changes (PAEC) |

\* 5mg daily; current data available on up to 4 courses

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| --- | --- |
| AUB Sub-classification | Specific treatment |
| Polyp | Resection |
| Adenomyosis | Surgery: hysterectomy; adenomyomectomy (not frequently performed) |
| Malignancy (endometrial cancer / leiomyosarcoma) | Surgery +/- adjuvant treatment  High-dose progestogens (if surgery not possible)  Palliation (including radiotherapy) |
| Coagulopathy | Tranexamic acid  DDVAP (Desmopressin) |
| Ovulation | Lifestyle modification  Cabergoline (if hyperprolactinaemia)  Levothyroxine (if hypothyroid) |
| Endometrial | Specific therapies await further delineation of underlying mechanisms |
| Iatrogenic | Refer to Faculty of Sexual and reproductive Healthcare Clinical Effectiveness Unit (FSRH CEU) guidance on problematic bleeding with hormonal contraception |
| Not otherwise classified | e.g. Antibiotics for endometritis; embolisation of AV malformation |

**Table 3. Specific treatment options for individual PALM-COEIN causes of AUB**

**Figure 2. RCT comparisons on the surgical treatment of HMB.**

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**Figure 3. General management pathway for AUB (FBC: Full blood count; TSH: Thyroid stimulating hormone; TAS/TVS: transabdominal/transvaginal scan); MRI: Magnetic resonance imaging)**

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