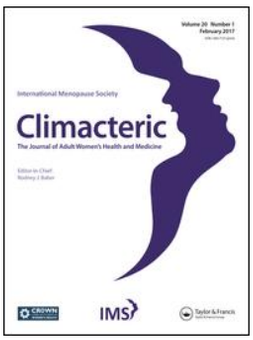

Climacteric

ISSN: 1369-7137 (Print) 1473-0804 (Online) Journal homepage: http://www.tandfonline.com/loi/icmt20

Abnormal uterine bleeding in perimenopause

S. R. Goldstein & M. A. Lumsden

To cite this article: S. R. Goldstein & M. A. Lumsden (2017): Abnormal uterine bleeding in perimenopause, Climacteric, DOI: 10.1080/13697137.2017.1358921

To link to this article: http://dx.doi.org/10.1080/13697137.2017.1358921

Published online: 07 Aug 2017.

CLIMACTERIC, 2017
https://doi.org/10.1080/13697137.2017.1358921

Taylor & Francis
Taylor & Francis Group

REVIEW

Abnormal uterine bleeding in perimenopause

S. R. Goldstein[a] and M. A. Lumsden[b]

[a]Professor of Obstetrics and Gynecology, New York University School of Medicine, New York, NY, USA; [b]Professor of Medical Education and Gynaecology, Lead for Reproductive and Maternal Medicine, School of Medicine, University of Glasgow, Glasgow, UK

ABSTRACT

Abnormal uterine bleeding is one of the commonest presenting complaints encountered in a gynecologist's office or primary-care setting. The wider availability of diagnostic tools has allowed prompt diagnosis and treatment of an increasing number of menstrual disorders in an office setting. This White Paper reviews the advantages and disadvantages of transvaginal ultrasound, blind endometrial sampling and diagnostic hysteroscopy. Once a proper diagnosis has been established, appropriate therapy may be embarked upon. Fortunately, only a minority of such patients will have premalignant or malignant disease. When bleeding is sufficient to cause severe anemia or even hypovolemia, prompt intervention is called for. In most of the cases, however, the abnormal uterine bleeding will be disquieting to the patient and significantly affect her 'quality of life'. Sometimes, reassurance and expectant management will be sufficient in such patients. Overall, however, in cases of benign disease, some intervention will be required. The use of oral contraceptive pills especially those with a short hormone-free interval, the insertion of the levonorgestrel intrauterine system, the incorporation of newer medical therapies including antifibrinolytic drugs and selective progesterone receptor modulators and minimally invasive treatments have made outpatient therapy increasingly effective. For others, operative hysteroscopy and endometrial ablation are proven therapeutic tools to provide both long- and short-term relief of abnormal uterine bleeding, thus avoiding, or deferring, hysterectomy.

ARTICLE HISTORY
Received 7 July 2017
Revised 11 July 2017
Accepted 13 July 2017
Published online 7 August 2017

KEYWORDS
Abnormal uterine bleeding; perimenopause; intermenstrual bleeding; heavy menstrual bleeding; menorrhagia; metrorrhagia

Introduction

Perimenopause is defined as 'the period around the onset of menopause that is often marked by various physical signs such as hot flushes and *menstrual irregularities*'[1] [italics added]. Perhaps another way to think of this is that perimenopause is the mirror image of adolescence, which is the coming on to the reproductive years, while perimenopause is the coming off from the reproductive years. Although the median age of menopause, at least in North America, is 51 years[2], the perimenopause is often highly variable in its age of onset, duration and bleeding patterns.

Regular menstrual cycles are associated with ovulation and production of progesterone in the luteal phase. Anovulatory cycles can be highly variable in their bleeding patterns. The definition of abnormal uterine bleeding (AUB) is 'flow outside of normal volume, duration, regularity or frequency'[3]. One-third of patient visits to the gynecologist are for AUB and it accounts for more than 70% of all gynecological consults in the perimenopausal and postmenopausal years[4]. A thorough evaluation of patients is important for two main reasons: (1) to exclude serious pathology such as carcinoma or complex atypical hyperplasia, and (2) to identify the cause of bleeding so that proper therapy (which, in some cases, may be expectant management) can be embarked upon. A classification of the causes of AUB is shown in Figure 1.

Diagnosis in women presenting with abnormal uterine bleeding

AUB is an umbrella term that encompasses heavy menstrual bleeding (HMB, previously referred to as menorrhagia) and intermenstrual bleeding (IMB, previously referred to as metrorrhagia). The goal of diagnosis is to distinguish women with anatomic causes (cancer, hyperplasia, polyps, leiomyomas) from women with normal anatomy where the cause may be ovulatory dysfunction, adenomyosis without endometrial abnormalities, and, less likely, coagulopathic or iatrogenic reasons.

As with all good medical practice, diagnosis begins with a thorough history and physical examination followed by appropriate laboratory and imaging tests as indicated (see Figure 2).

History should include a relevant family history including underlying bleeding disorders, and use of medications or herbal preparations that might affect bleeding such as ginseng, ginkgo, motherwort, contraceptives, non-steroidal anti-inflammatory drugs (NSAIDs), and warfarin or heparin or their derivatives[5,6].

Physical examination should include assessment of body mass index, thyroid examination, a pelvic examination including speculum findings to rule out cervical or vaginal causes, and bimanual pelvic assessment including size and contour of the uterus.

CONTACT Professor S. R. Goldstein steven.goldstein@nyumc.org New York University School of Medicine, 530 First Avenue, Suite 10N, New York, NY 10016, USA

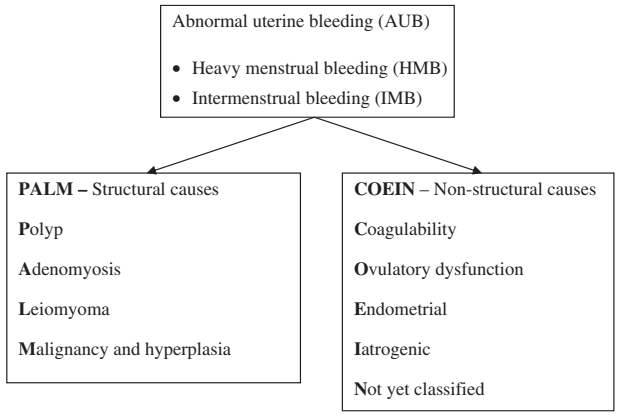

Figure 1. FIGO classification of abnormal uterine bleeding. Adapted from Munro M, *et al. Int J Gynaecol Obstet* 2011;113:3–13.

- General assessment
  - History and bleeding pattern
  - Physical, pelvic and speculum examination
- Laboratory tests including:
  - Full blood count, iron studies, thyroid, hCG
  - Disorders of hemostasis
- Determine ovulatory status
- Evaluate pelvic organs and endometrium
  - Role of transvaginal ultrasound
  - Role of endometrial biopsy
  - Role of hysteroscopy

Figure 2. Assessment of abnormal uterine bleeding.

Laboratory assessment should include a full blood count and iron studies as well as tests for bleeding disorders if suspected or indicated. Pregnancy testing and thyroid screening may also be appropriate.

Although many women may be unsure of how often or how long they bleed, a careful history of bleeding patterns, frequency and heaviness is critical and will often assist with diagnosis. For instance, cyclic HMB without IMB would be unlikely to be carcinoma or even hyperplasia. The commonest cause of irregular bleeding is anovulatory uterine bleeding. Most often, anovulatory bleeding is not associated with anatomical abnormalities. One study of 443 women used transvaginal ultrasound and saline infusion sonohysterography (SIS) as the first step in triage and reported that 79% of women between 35 years old and menopause with AUB had no anatomic pathology[7]. Some women with AUB may have an enlarged cavity with increased surface area due to increasing parity, uterine hypertrophy secondary to leiomyoma with no submucous component, or adenomyosis without endometrial abnormality. Of course, some women with anovulatory bleeding will have endometrial pathology, and proper endometrial evaluation will be essential in triaging patients to those with and without pathology and furthermore into those with focal or global pathological processes. Historically, dilatation and curettage was the primary diagnostic test. In fact, it was the most common surgical procedure in women during much of the 20th century. More recently, endometrial biopsy in an outpatient setting has gained greater currency.

Shortcomings of endometrial biopsy

After a single study by Stovall and colleagues[8], blind endometrial sampling with disposable suction piston devices became the standard approach to patients with AUB. Stovall performed such an outpatient biopsy on 40 patients with known carcinoma in the week prior to their hysterectomy and obtained endometrial carcinoma in 39 of the 40 samples, thus reporting a 97.5% accuracy. This was widely publicized, marketed and promoted and was rapidly accepted as 'standard of care'. In a similar study, Guido and colleagues performed blind endometrial sampling in 65 patients with known carcinoma in the operating room just prior to their hysterectomy[9]. They missed 11/65 cancers (sensitivity only 83%) but, upon opening all those uteri, they reported that, when the cancers occupied 50% or more of the endometrial surface, the biopsy was 100% accurate. Others did similar studies. In women with known carcinomas, the sensitivity of blind sampling was only 84%[10] and 68%[11], yielding a false-negative rate of 16% and 32%, respectively. These studies involved blind biopsies done on women with *known* carcinoma. In trying to understand why such biopsies failed in non-global pathology, one needs to look no further than the pre-hysterectomy study by Rodriguez and colleagues[12] in which a popular sampling device sampled an average of 4% of the endometrial surface area (range 0–12%).

In 2012, the American College of Obstetricians and Gynecologists (ACOG), in their Practice Bulletin[3], acknowledged 'the primary role of endometrial sampling in patients with AUB is to determine if carcinoma or pre-malignant lesions are present.' The Bulletin goes on to state that endometrial biopsy has 'high overall accuracy in diagnosing endometrial cancer *when an adequate specimen is obtained and when the endometrial process is global.* If the cancer occupies less than 50% of the surface area of the endometrial cavity, the cancer can be missed by blind endometrial biopsy. Therefore, these tests are only an endpoint when they reveal cancer or atypical complex hyperplasia.' This has tremendous ramifications for clinical practice. Certainly, health-care providers, especially in low-resource areas, can begin the evaluation with a blind biopsy but, if the results do not indicate cancer or atypical hyperplasia, the evaluation is not adequate, especially if bleeding persists. Thus, the concept of distinguishing 'global' from 'focal' pathologies is becoming increasingly understood and important.

Imaging techniques

The primary imaging test of the uterus for the evaluation of AUB is transvaginal ultrasound. However, not all uteri lend themselves to a meaningful ultrasound examination such as in cases of co-existing myomas, previous surgery, marked obesity, axial uterus or adenomyosis. In such cases, another alternative is SIS (the installation of fluid or gel into the

endometrial cavity to further delineate endometrial anatomy). SIS can virtually always distinguish the presence or absence of actual anatomic pathology. SIS can also distinguish between global and focal abnormalities.

Hysteroscopy as a diagnostic tool may also be employed, although it is more expensive, requires more anesthesia and, if performed, is preferably done in an office setting[3]. Newer disposable hysteroscopes make this recommendation easier to follow.

Transvaginal ultrasonography

The vaginal probe provides a degree of image magnification as if we were doing ultrasound through a low-power microscope and can be considered a form of 'sonomicroscopy'[13]. We see things with the vaginal probe that we could not see with our naked eye, if we could hold the structure in our hand at arm's length and squint at it.

Early observational studies and subsequent large multicenter trials, mostly from Western Europe, clearly established the fact that, in postmenopausal women with bleeding, a thin distinct endometrial echo is indicative of a lack of significant tissue and has higher negative predictive value for endometrial cancer than blind endometrial sampling[13]. This caused ACOG in February 2009 to change its committee opinion to state that, when an endometrial echo less than or equal to 4 mm on transvaginal ultrasound is obtained, an endometrial biopsy is not required[14].

There are less data collected on perimenopausal women with AUB. Perimenopausal women have cycling of the endometrium based on the erratic estrogen production of perimenopausal ovaries. Thus, the use of transvaginal ultrasound in such patients must be timed to the end of a bleeding episode when the endometrial echo will be as thin as one would expect throughout the whole month. This protocol prevents misinterpretation of endometrial moguls, which can occur because of the heterogeneity of the topography of the functionalis as it proliferates. As previously discussed, not all uteri lend themselves to meaningful ultrasound examination. In a study of 433 perimenopausal patients aged 37–54 years, 10.2% required sonohysterography because the unenhanced transvaginal ultrasound done at the end of a bleeding cycle was inadequate effectively to characterize and measure the endometrium[15]; 64.7% of patients had an endometrial thickness less than or equal to 5 mm, while 25.1% had an endometrial thickness greater than 5 mm and, therefore, underwent SIS to characterize global versus focal changes. Final diagnosis of the entire cohort revealed 79% had dysfunctional anovulatory bleeding, 13% had polyps, 3.5% had hyperplasia, and 5.3% had submucous myomas (although 33% had sonographic evidence of myomas, only the 5.3% were submucous).

Hysteroscopy is certainly an alternative approach, although issues of operator dependence, cost, analgesia/anesthesia concerns, and availability of the resource must be considered.

In summary, the diagnostic evaluation is paramount to successful therapeutic decision-making and will have important ramifications for triage for appropriate therapies, particularly surgical versus medical versus expectant management.

- Expectant
- Non-hormonal medical treatments
  - Non-steroidal anti-inflammatory drugs
  - Anti-fibrinolytic agents
- Hormonal medical treatments
  - Cyclical or long-acting progestogens
  - Combined oral contraceptives
  - GnRH analogs (fibroid-associated)
  - Selective progesterone receptor modulators (fibroid-associated)
- Levonorgestrel intrauterine system (LNG-IUS)
- Endometrial ablation
- Uterine artery embolization (fibroid-associated)
- Hysterectomy

Figure 3. Management of abnormal uterine bleeding.

Treatment of perimenopausal bleeding

Therapy must always be directed by proper diagnosis. After pregnancy and malignancy have been excluded, for women with no anatomic abnormality (e.g. anovulatory dysfunction, use of contraceptives, adenomyosis or simply an enlarged cavity surface area), treatment may be approached in a variety of ways (see Figure 3). Treatment goals for patients with AUB include regulation of menstrual cycles, minimization of blood loss and improvement in quality of life. For heavy menstrual periods, treatment aims to prevent worsening of anemia and reduce the need for blood transfusion. For many patients who are not anemic, the bleeding is more of a 'quality of life' issue rather than of medical significance. Thus, for some, the knowledge that there is no serious problem and, especially for patients with dysfunctional anovulatory bleeding, the knowledge that this is a normal part of the transition from the reproductive to the non-reproductive years may be sufficiently reassuring to manage them expectantly.

Pharmacologic therapy

Hormonal treatments

According to a recent survey conducted among ACOG members, the most commonly selected first-line choice for AUB treatment in the United States was combined oral contraceptives (COCs). The levonorgestrel intrauterine system (LNG-IUS) was the next most frequently selected option[16]. COCs can correct menstrual irregularities resulting from oligo-ovulation or anovulation and make menstruation more predictable. They can also reduce excessive menstrual bleeding in most affected women and are considered a reasonable option for initial management of HMB. The COC is less effective for the treatment of heavy menstrual periods in women with organic pathology, although the response can be variable. Menstrual blood loss is reduced by about 50% in women using COCs,

and the reduction is most apparent during the first 2 days of the menstrual flow. Extended-cycle or continuous COCs with the 20 μg ethinylestradiol/100 μg levonorgestrel formulation, with either 84/7 regimens that shorten the hormone-free interval and decrease the number of days of bleeding per year, or the 365-day regimen designed to eliminate bleeding altogether, are associated with significant reduced bleeding when compared with cyclic COCs. Shortening of the hormone-free interval from 7 to 4 days significantly decreases the number of withdrawal bleeding days in each cycle and increases the amenorrhea rate.

Many patients who are already on COCs experience what we refer to as 'breakthrough bleeding'. Usually, adjustment of the dose or type of pill can overcome this, although persistent bleeding of such a nature should trigger further diagnostic evaluation in case some co-existing organic pathology is also present.

For those women with a contraindication to estrogen therapy, progesterone therapy or the LNG-IUS can be an alternative. Because of the effect of levonorgestrel on the endometrium, the duration and amount of menstrual bleeding are reduced. This effect may begin during the first menstrual cycle after the placement of the device, and bleeding becomes progressively less over time. Many of the progesterone-only, long-acting, reversible contraceptive methods have been used for the treatment of HMB. Patients should be counseled about the inconvenience of breakthrough bleeding observed during the initial months of treatment. The timing of complete suppression of the menstrual cycle is variable depending on the method. Amenorrhea occurs in approximately 30–40% and 20–80% in 12 months after the single-rod progestin contraceptive implant and the LNG-IUS, respectively[17]. Use of depot medroxyprogesterone acetate results in relatively high rates of amenorrhea by the fourth dose (approximately as high as 90% in some studies) and has traditionally been used extensively to suppress menses.

Non-steroidal anti-inflammatory drugs

NSAIDs reduce prostaglandin synthesis. Prostaglandins may have a role in aberrant neovascularization leading to dysfunctional uterine bleeding. Oral NSAIDs are an excellent treatment to reduce HMB. When compared with placebo, they decrease menstrual cramping and reduce menstrual blood loss by 33%[18]. There is no evidence of a difference between individual NSAIDs in reducing HMB. Mefenamic acid 500 mg three times a day for 5 days and ibuprofen 600 mg every 6 h or 800 mg every 8 h are commonly prescribed during the first 3 days of the menstrual cycle to reduce blood loss and menstrual cramping.

Tranexamic acid

Tranexamic acid reversibly blocks lysine-binding sites on plasminogen, preventing plasmin and fibrin polymer interaction and resulting in fibrin degradation, the stabilization of clots, and reduction of bleeding. It is contraindicated in women with increased risk for thromboembolism. It has been routinely used for many years to reduce blood loss and the need for blood transfusion during and after surgical procedures. It has been used for the treatment of HMB outside of the United States for several decades. Its therapeutic effect is superior to placebo, and results in significant reduction in objective measurement of idiopathic HMB[19]. Tranexamic acid has no effect on the duration of bleeding or in relieving unscheduled bleeding. In all studies analyzed, only mild to moderate side-effects were reported, mostly gastrointestinal, and there were no reports of thromboembolic events[20]. The FDA has approved tranexamic acid at a *per oral* dosage of 1300 mg (two 650-mg tablets) three times daily for 5 days each menstrual cycle[20]. The oral bioavailability of tranexamic acid is only about 35%, which makes frequent administrations necessary. The disadvantages of frequent administrations include decreased patient compliance and increased risk of gastrointestinal side-effects, most commonly nausea, vomiting and diarrhea.

To summarize for the patients described above:

(1) Virtually always begin with medical treatment before considering surgery unless you have a strong reason to do so.
(2) Not all uterine bleeding needs treatment; expectant management can be carried out after serious pathologies have been ruled out.
(3) Any therapeutic options should take into consideration a patient's desire for future fertility and her cultural background.
(4) Empiric treatment should be initiated, based on index of suspicion, if waiting for a pending test result or a definite diagnosis cannot yet be established.
(5) Many therapeutic modalities lead to a similar outcome, so be sure to discuss the risk, benefits and alternatives of available options.

Non-medical approaches to abnormal uterine bleeding

Endometrial ablation

Endometrial ablation is a minimally invasive alternative for the treatment of HMB and is associated with a high level of patient satisfaction. It is usually reserved for patients refractory to medical treatment and who wish to avoid definitive treatment with hysterectomy. Although endometrial ablation is a less invasive surgical alternative to hysterectomy, it does not eliminate surgical risk and is followed by further surgery within 4 years in up to 38% of the women who undergo this treatment[21]. Endometrial ablation should be considered as an alternative to hysterectomy, especially in older women who have opted to retain their uterus and not in women with a desire for future fertility. Patient age is an important predictor of treatment success. In contrast to the original resectoscopic endometrial ablation, several new ablation devices offer the advantage of being performed in an office setting. A discussion of the various devices is beyond the scope of this White Paper; however, a word about patient selection is crucial. Careful patient selection seems to be the key to decrease the occurrence of endometrial cancer after ablation. In a recent systematic review where 22

post-ablation endometrial cancer cases were reviewed[22], time to diagnosis of endometrial cancer ranged from 2 weeks to 10 years following endometrial ablation. Most patients had symptoms of persistent bleeding or pain after the procedure. Eighty-six percent of the cancer patients presented with risk factors for endometrial cancer such as obesity, complex atypical endometrial hyperplasia, diabetes, hypertension and postmenopausal status. Thus, endometrial ablation should be restricted to premenopausal women who have low risk factors for endometrial cancer and who have documented normal endometrial histopathologic features at pre-ablation evaluation.

Uterine fibroids

Uterine fibroids occur in 25% of women of reproductive age and are often associated with abnormal uterine bleeding, particularly irregular and/or heavy bleeding. Although hysterectomy remains a common treatment for uterine fibroids, other treatments should be discussed in order that women are able to make an informed choice.

A combination of presenting clinical symptoms, fibroid size and location, and the patient's desire for fertility will influence the choice of therapeutic modality offered and accepted by a woman to treat her symptomatic fibroids.

Treatments for fibroids

Non-surgical treatment

There is no medical treatment that can cure fibroids but several treatments are available that provide symptom relief. In perimenopausal women, such therapies are employed with the goal of satisfactorily alleviating symptoms until the menopause.

Tranexamic acid and mefenamic acid. Tranexamic acid (discussed above) has been used as first-line treatment for HMB and is frequently used for those with small fibroids despite little evidence of efficacy[23]. However, the safety and efficacy of the modified-release variant have been proven in women with fibroids when compared to placebo.

Mefenamic acid is a NSAID that is commonly used for dysmenorrhea and leads to a modest reduction in HMB in women without fibroids, although it is less effective than tranexamic acid. There have been no trials to date to show the benefits of NSAIDs in women with fibroids[18].

Levonorgestrel-releasing intrauterine system. The LNG-IUS is used for treatment of HMB[24,25]. Studies on women with fibroids have demonstrated relief of menstrual symptoms and a non-significant effect on volume. The overall incidence of spontaneous expulsion of the LNG-IUS is 9.6% over a 3-year period. This is increased to 15.8% in the presence of fibroids.

Gonadotropin-releasing hormone agonists. Gonadotropin-releasing hormone (GnRH) agonists may be used prior to fibroid surgery since they reduce both uterine volume and fibroid size[26]. They correct pre-operative iron deficiency anemia and reduce intra-operative blood loss. If uterine size is such that a mid-line incision is planned, this can be avoided in many women with the use of GnRH agonists. However, some argue that they render myomectomy more difficult because they destroy tissue planes, increase the risk of recurrence, and are associated with side-effects in situations where they confer no benefit, or where alternative cheaper drugs with fewer side-effects are available. Add-back therapy may be initiated at the same time as the treatment with a GnRH agonist to reduce the hypoestrogenic side-effects such as vasomotor symptoms and loss of bone mineral density, if use for more than 6 months is anticipated in those who do not desire surgery.

Selective progesterone receptor modulators. Ulipristal acetate (UPA) is currently the only selective progesterone receptor modulator (SPRM) clinically available in some countries. UPA induced amenorrhea in 63.1% of women and controlled menstrual bleeding in 91% in a dose of 5 mg/day and in 71.3% and 92%, respectively, in a dose of 10 mg/day, although irregular bleeding often occurs in those with submucous fibroids. UPA also has some effect on fibroid size, although less than GnRH agonists[27].

The potential long-term effects of UPA on the endometrium are under study due to an unusual histological pattern of benign, 'non-physiologic' endometrial change which occurred in many UPA-treated women. These are referred to as PAEC (progesterone modulator-associated endometrial changes). Common side-effects of its use are headaches, nasopharyngitis, abdominal pain and hot flushes.

The anti-progesterone properties of mifepristone have also been utilized for the treatment of fibroids and have been shown to be effective in reducing fibroid size and improving the quality of life at low doses.

Other medical treatments. Other medical treatments can be used, although frequently they are less effective in the presence of fibroids. Those that induce amenorrhea such as the oral contraceptive pill and norethisterone acetate may be valuable, and studies have been undertaken with aromatase inhibitors, although the side-effect profile of the latter may diminish long-term use for this indication.

Radiological treatment: uterine artery embolization

Uterine artery embolization (UAE), performed by an appropriately trained interventional radiologist, is a minimally invasive treatment option for uterine fibroids. A catheter is inserted through the femoral artery in the groin under local anesthetic and directed towards the uterine arteries using fluoroscopy. The uterine artery is blocked on each side using an appropriate embolic agent. The objective of UAE is completely to infarct all the fibroid tissue while preserving the uterus, ovaries and surrounding pelvic structures.

UAE was used initially for massive obstetric hemorrhage. It is indicated for symptomatic fibroids and is an alternative to myomectomy, since it allows conservation of the uterus and only involves a short hospital stay. The most common

problem associated with UAE is post-procedure pain which can usually be controlled by analgesics. Expulsion of a necrotic fibroid, chronic vaginal discharge and premature ovarian failure are less common effects associated with UAE.

A recently published Cochrane review concluded that UAE is a safe and effective treatment for fibroid-related menstrual disorders. Major complications were rare and reported not to be more common than after surgery. Since the effects on fertility and pregnancy are still unclear, it is a good option for most perimenopausal women[28,29].

UAE is also associated with some decrease in ovarian function in women older than 45 years which may lead to menopause[30].

Surgical treatment

Hysterectomy. Hysterectomy is the established surgical treatment for women who no longer plan to give birth and have completed their family. Although hysterectomy is a major surgical procedure for women with fibroids, it results in resolution of most symptoms, particularly when related to menstrual disorders, and has a high satisfaction rate[31].

Myomectomy. Myomectomy is a surgical procedure to remove uterine fibroids and reconstruct the uterus. It is used as a fertility-sparing option. Myomectomy can be associated with considerable bleeding, risk of hysterectomy, prolonged postoperative stay, postoperative adhesion formation and recurrence of the fibroids[32,33].

Myomectomy can be performed as an open procedure and by laparoscopy or hysteroscopy, depending on the position of the fibroids and the skill of the surgeon. It may also depend on the size and number of fibroids that can be treated laparoscopically, and the skills required are often only available in specialist units[34]. These constraints also apply to vaginal myomectomy. Hysteroscopic myomectomy is most suitable for fibroids under 5 cm in diameter and where a majority of the fibroid is within the uterine cavity[35,36]. Submucosal or pedunculated fibroids distort the endometrial cavity and may be covered with vessels that break down, thus leading to irregular bleeding. Those less than about 5 cm in diameter can be removed hysteroscopically, a procedure now facilitated by the development of new instrumentation that has increased the safety and ease of the procedure. If larger than 5 cm in diameter, then a two-step procedure might be utilized and/or with prior administration of a drug such as a GnRH agonist or a SPRM that will shrink the fibroid.

Malignant and premalignant disease

Endometrial polyps

Endometrial polyps are usually removed as their malignant potential is uncertain and they may cause irregular bleeding. Removal can often be carried out under a local anesthetic.

Although a wide range of benign gynecological problems present with abnormal bleeding, it is also a common presenting symptom of endometrial cancer, endometrial hyperplasia, cervical cancer and, less commonly, cancer of the vagina or even vulva.

Treatments for endometrial hyperplasia

Endometrial hyperplasia of low malignant potential

Often cases of endometrial hyperplasia of low malignant potential, previously referred to as simple or complex hyperplasia without atypia, may be handled with conservative management and appropriately timed endometrial resampling to check for regression. More often, however, progestogens, administered either orally or by LNG-IUS, are employed. A systematic review of progestogens for treatment of hyperplasia concluded that the LNG-IUS is a good treatment for non-atypical hyperplasia, with both high success and high compliance rates[37]. Definitive therapy in selected cases may utilize hysterectomy.

Atypical hyperplasia

Cases of atypical hyperplasia are usually treated with total hysterectomy and bilateral salpingo-oophorectomy. In selected cases, especially fertility-sparing, high-dose progestogens are utilized.

Gynecologic malignancies resulting in abnormal uterine bleeding

A detailed account of the treatment of gynecological malignancies is beyond the scope of this article. Most often, this will involve referral to appropriate specialists/consultants.

Conclusion

In summary, abnormal uterine bleeding in perimenopausal patients is a common and important part of clinical practice for health-care providers of women. Fortunately, the majority of cases do not involve malignancy or advanced premalignant conditions, although these should be carefully excluded in the diagnostic work-up. Sometimes, the amount of bleeding can result in significant blood loss resulting in anemia and, in extreme cases, hypovolemia or shock. These will be medical issues requiring prompt interventions. Most often, however, the bleeding is worrisome and mostly has a negative impact on quality-of-life issues. The pros and cons of various diagnostic tests as well as medical and surgical treatments have been reviewed above, keeping in mind that, once appropriate diagnosis is arrived at, the most appropriate treatment for that individual patient can be successfully carried out.

Conflict of interest Steven Goldstein has acted as Consultant for Cook OB/GYN, Cooper Surgical and Philips Ultrasound; and as a member of the Gynecologic Advisory Board for Allergan Pharmaceuticals. Mary Ann Lumsden reports no conflict of interest. The authors alone are responsible for the content and writing of this paper.

Source of funding Nil.

References

1. Available: https://www.meriam-webster.com/dictionary/perimenopause. Accessed on March 20, 2017
2. Grady D. Clinical practice management of menopausal symptoms. *N Engl J Med* 2006;355:2338–47
3. American College of Obstetrics and Gynecology. Practice Bulletin No. 128, Diagnosis of abnormal uterine bleeding in reproductive aged women. *Obstet Gynecol* 2012;120:197–206
4. Spencer CP, Whitehead MI. Endometrial assessment re-visited. *Br J Obstet Gynaecol* 1999;106:623–32
5. Basila D, Yuan CS. Effects of dietary supplements on coagulation and platelet function. *Thromb Res* 2005;117:49–53
6. Wittkowsky AKA. Systematic review and inventory of supplemental effects on warfarin and other anticoagulants. *Thromb Res* 2005;117:81–6
7. Goldstein SR. Modern evaluation of the endometrium. *Obstet Gynecol* 2010;116:168–76
8. Stovall TG, Photopulos GJ, Poston WM, Ling FW, Sandlers LG. Pipelle endometrial sampling in patients with known endometrial carcinoma. *Obstet Gynecol* 1991;77:954–6
9. Guido RS, Kanbour-Shakir A, Rulin MC, Christopherson WA. Pipelle endometrial sampling. Sensitivity in the detection of endometrial cancer. *J Reprod Med* 1995;40:553–5
10. Larson DM, Krawisz BR, Johnson KK, Broste SK. Comparison of the Z-Sampler and Novak endometrial biopsy instruments for in-office diagnosis of endometrial cancer. *Gynecol Oncol* 1994;54:64–7
11. Ferry J, Farnsworth A, Webster M, Wren B. The efficacy of the pipelle endometrial biopsy in detecting endometrial carcinoma. *Aust N Z J Obstet Gynaecol* 1993;33:76–8
12. Rodriguez MH, Platt LD, Medearis AL, Lacarra M, Lobo RA. The use of transvaginal sonography for evaluation of postmenopausal size and morphology. *Am J Obstet Gynecol* 1988;159:810–14
13. Goldstein SR, Pregnancy. 1. Embryo. *Endovaginal Ultrasound*, 2nd ed. New York (NY): Wiley-Liss, Inc, 1991
14. American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 440: the role of transvaginal ultrasonography in the evaluation of postmenopausal bleeding. *Obstet Gynecol* 2009;114:409–11
15. Goldstein SR. Use of ultrasonohysterography for triage of perimenopausal patients with unexplained uterine bleeding. *Am J Obstet Gynecol* 1994;170:565–70
16. Matteson KA, Anderson BL, Pinto SB, *et al*. Practice patterns and attitudes about treating abnormal uterine bleeding: a national survey of obstetricians and gynecologists. *Am J Obstet Gynecol* 2011;205:321.e1–8
17. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 121. Long-acting reversible contraception: implants and intrauterine devices. *Obstet Gynecol* 2011;118:184–96
18. Lethaby A, Augood C, Duckitt K, *et al*. Nonsteroidal anti-inflammatory drugs for heavy menstrual bleeding. *Cochrane Database Syst Rev* 2007;(4):CD000400
19. Lethaby A, Farquhar C, Cooke I. Antifibrinolytics for heavy menstrual bleeding. *Cochrane Database Syst Rev* 2000;(4):CD000249
20. Barbieri RL. A new (to the US) first-line agent for heavy menstrual bleeding (Editorial). *OBG Management* 2010;22:9–12
21. Lethaby A, Shepperd S, Cooke I, *et al*. Endometrial resection and ablation versus hysterectomy for heavy menstrual bleeding. *Cochrane Database Syst Rev* 2000;(2):CD000329
22. AlHilli MM, Hopkins MR, Famuyide AO. Endometrial cancer after endometrial ablation: systematic review of medical literature. *J Minim Invasive Gynecol* 2011;18:393–400
23. Lumsden MA, Wedisinghe L. Tranexamic acid therapy for heavy menstrual bleeding. *Expert Opin Pharmacother* 2011;12:2089–95
24. Gupta JK, Daniels JP, Middleton LJ, ECLIPSE Collaborative Group, *et al*. A randomised controlled trial of the clinical effectiveness and cost-effectiveness of the levonorgestrel-releasing intrauterine system in primary care against standard treatment for menorrhagia: the ECLIPSE trial. *Health Technol Assess* 2015;19:1–118
25. Senol T, Kahramanoglu I, Dogan Y, Baktiroglu M, Karateke A, Suer N. Levonorgestrel-releasing intrauterine device use as an alternative to surgical therapy for uterine leiomyoma. *Clin Exp Obstet Gynecol* 2015;42:224–7
26. Lumsden MA, West CP, Thomas E, *et al*. Treatment with the gonadotrophin releasing hormone-agonist goserelin before hysterectomy for uterine fibroids. *Br J Obstet Gynaecol* 1994;101:438–42
27. Donnez J, Tatarchuk TF, Bouchard P, *et al*. Ulipristal acetate versus placebo for fibroid treatment before surgery. *N Engl J Med* 2012;366:409–20
28. Gupta JK, Sinha A, Lumsden MA, Hickey M. Uterine artery embolization for symptomatic uterine fibroids. *Cochrane Database Syst Rev* 2014;(12):CD005073
29. Manyonda IT, Bratty M, Horst JS, Banu N, Gorti M, Belli AM. Uterine artery embolization versus myomectomy: impact on quality of life–results of the FUME (Fibroids of the Uterus: Myomectomy versus Embolization) Trial. *Cardiovasc Intervent Radiol* 2012;35:530–6
30. Rashid S, Khaund A, Murray LS, *et al*. The effects of uterine artery embolization and surgical treatment on ovarian function in women with uterine fibroids. *BJOG* 2010;117:985–9
31. McPherson K, Metcalfe MA, Herbert A, *et al*. Severe complications of hysterectomy: the VALUE study. *BJOG* 2004;111:688–94
32. LaMote AI, Lalwani S, Diamond MP. Morbidity associated with abdominal myomectomy. *Obstet Gynecol* 1993;82:897–900
33. Kongnyuy EJ, Wiysonge CS. Interventions to reduce haemorrhage during myomectomy for fibroids. *Cochrane Database Syst Rev* 2014;(2):CD005355
34. Palomba S, Zupi E, Falbo A, *et al*. A multicenter randomized, controlled study comparing laparoscopic versus minilaparotomic myomectomy: reproductive outcomes. *Fertil Steril* 2007;88:933–41
35. Bosteels J, Kasius J, Weyers S, *et al*. Hysteroscopy for treating subfertility associated with suspected major uterine cavity abnormalities. *Cochrane Database Syst Rev* 2015;(2):CD009461
36. Varma R, Soneja H, Clark TJ, Gupta JK. Hysteroscopic myomectomy for menorrhagia using Versascope bipolar system: efficacy and prognostic factors at a minimum of one year follow up. *Eur J Obstet Gynecol Reprod Biol* 2009;142:154–9
37. Orbo A, Arnes M, Hancke C, Vereide AB, Pettersen I, Larsen K. Treatment results of endometrial hyperplasia after prospective D-score classification: a follow-up study comparing effect of LNG-IUD and oral progestins versus observation only. *Gynecol Oncol* 2008;111:68–73