Abnormal Uterine Bleeding

7

Patricia Geraghty

7.1 Normal Menstrual Parameters and Abnormal Uterine Bleeding (AUB) Overview

The International Federation of Gynecology and Obstetrics (FIGO) has defined two systems, System 1 for the nomenclature of symptoms of normal and abnormal bleeding (AUB), and System 2 for the classification of the etiologies of abnormal bleeding [1]. The revision of previous menstrual terminology, first introduced in 2007, and revised in 2018, has increased the precision and uniformity of assessment of AUB across the lifespan for use in clinical practice and research (Table 7.1). Menses are assessed on the dimensions of regularity, frequency, duration, and volume. Regular or normal is roughly defined by the menstrual pattern experienced by 90% of the population, similar to the definition of norms in other health parameters. Despite the elegance of this system, adoption has been slow in many diagnostic compendiums [2, 3].

It is likely to be the first change in cycles, not necessarily the most dramatic change, that leads a woman to seek advice and treatment. The clinician must be aware of the possibility of other causes of HMB superimposed on the expected age-related cycle changes. Women in the LRS often report menstrual patterns outside of the norms for regularity, frequency, duration, and volume and these women should be evaluated. The clinician must be alert to differentiating patterns of menstrual and anovulatory bleeding. Women may consider all vaginal bleeding a menstrual period and report it as such, but a true menstrual bleed implies follicular development and ovulation, followed by menstrual flow. Heavy menstrual bleeding is no longer

P. Geraghty (✉)
Women's Health, Patricia Geraghty FNP, WHNP A Nurs Corp, Walnut Creek, CA, USA
e-mail: patricia@eachwomanshealth.com

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Table 7.1 International Federation of Gynecology and Obstetrics (FIGO) menstrual cycle terminology. (Based on Fraser et al. 2007 [2], Munro et al. [1]. Used with permission of John Wiley and Sons Publishing)

Dimension	Descriptive categories			
Regularity cycle-to-cycle over 12 months	***Regular***		***Irregular*** (typical variation >7–9 days between longest/shortest interval)	
Frequency	***Absent***	***Infrequent*** (>38 days)	***Normal***	***Frequent*** (<24 days)
Duration			***Normal***	***Prolonged*** (>8 days)
Volume (patient determined)	***Light***		***Normal***	***Heavy*** (interferes w/ activity)
Intermenstrual	***Random***			
	Cyclic		***Early Cycle Intermenstrual*** ***Mid Cycle Intermenstrual*** ***Late Cycle Intermenstrual***	
Unscheduled bleeding on gonadal steroids (hormonal contraception)	***Not applicable***		Not on gonadal steroids	
	None		Using gonadal steroids and having no bleeding	
	Present			

defined quantitatively, which was difficult to implement in the clinical setting, but as bleeding that interferes with the women's physical, emotional, and material quality of life. The NICE Guidelines also state that any woman who perceives her cycles to interfere with daily activity or to deviate from her established pattern should be evaluated. All assessments of menstrual bleeding should include a discussion on the impact of bleeding on a woman's life [4–6].

The second FIGO system organizes the approach to diagnosis of AUB. Even though pregnancy is an increasingly unlikely etiology for AUB in the fifth decade, complications of pregnancy should always be considered and eliminated as a first step to diagnosis. Remaining etiologies are organized into the PALM-COEIN classifications [5] (see Fig. 7.1). The PALM categories are structural or neoplastic in nature, including AUB-P endometrial or cervical polyps, AUB-A adenomyosis or endometriosis, AUB-L leiomyoma, and AUB-M malignancy and hyperplasia. The COEIN categories are systemic or endocrinological, including AUB-C coagulopathy, AUB-O ovulatory dysfunction, AUB-E endometrial, AUB-I iatrogenic due to a medication including anti-coagulation therapy, medical device, or medical procedure, and AUB-N not otherwise classified [1]. Systemic or endocrinological conditions associated with AUB may become apparent for the first time in the late reproductive and perimenopause stages or may be superimposed on the cycle changes expected in these life stages. The very nature of the menopause transition is increasing irregular anovulation. Otherwise, neoplastic etiologies are the more likely sources of abnormal bleeding in the late reproductive to perimenopause stage.

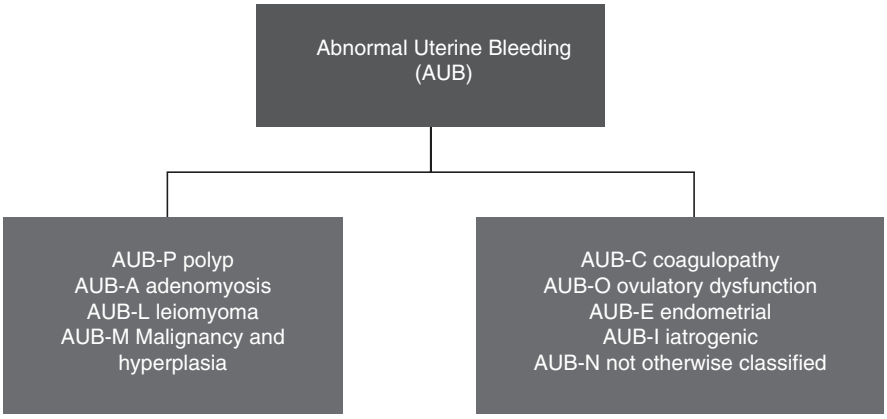

Fig. 7.1 FIGO PALM-COIEN classification of abnormal uterine bleeding. (Based on Munro et al. [1]. Used with permission of John Wiley and Sons Publishing)

7.1.1 Epidemiology of AUB

AUB is a common presentation in the clinical setting, accounting for 30% of gynecological visits in the United States. The reported population incidence worldwide varies from 3% to 30% of women. As many as 50% of women with AUB do not seek treatment, regardless of access to care, with a resulting lack of precision in epidemiological estimates [1, 7]. A study in rural India comparing women's reports of menstrual disorders to the incidence detected upon examination found that only 5% of women reported heavy menstrual bleeding with an examination detected incidence three times higher [8]. Menstrual disorders are not included in the global burden of disease. Most surveys in low and middle low resource countries, dating back to the 1970s through 2002, are hampered by lack of definitions, varied interpretations of menstrual disorders, and methodological inconsistencies [9].

Conditions such as leiomyomata and coagulation disorders demonstrate variable racial/ethnic and geographic patterns of distribution. This variability stems from the combined influences of genetics, consanguineous cultural marriage patterns, modifiable risks, and gaps in data. One classification of AUB may not be independent of other classifications.

Twin studies of uterine leiomyomata (UL) indicate heritability [10]. A genome-wide association scan (GWAS) of 35,474 UL cases and 267,505 controls in females of European ancestry identified numerous loci associated with risk of UL, with four loci specifically associated with HMB and four loci overlapping with risk of endometriosis. An epidemiological meta-analysis across 402,868 women suggests at least a doubling of risk for UL diagnosis among women with a history of endometriosis [11]. Women of African ancestry in the United States report 2–3 times more

diagnosed leiomyomata, experience onset at a younger age, and are more likely to undergo surgery than women of European ancestry. In a prospective universal ultrasound screening of premenopausal women, the difference in prevalence narrowed, while still remaining significantly higher in women of African ancestry [cumulative incidence of tumors by age 50 >80% Black and almost 70% white] [12]. A GWAS identified unique loci of heritability among women of African ancestry. The attempt to replicate a dense set of tag single nucleotide polymorphisms at different loci associated with UL in Japanese women failed to replicate the associations in women of African ancestry. This indicates that genetic variation for heritability of UL may differ among populations [13]. Differential exposure to epigenetic triggers must also be considered.

Von Willebrand Disease (VWD) is the most common inherited coagulation disorder with a general population prevalence estimated to be 1% and with a prevalence of 11–16% among women with HMB [14]. The incidence of VWD appears to be underreported in low resource regions based on the increased percentage of the severe form identified and the low ratio of the less severe VWD to Hemophilia A prevalence. Heritability appears influenced by culture with an increased incidence of VWD in cultures with high prevalence of consanguineous marriage [15]. This pattern is similar to the prevalence of the more rare autosomal recessive bleeding disorders such as combined Factor V and Factor VIII deficiency [16]. In summary, the varied influences of culture and care resources, or lack thereof, lead to gaps in our understanding of the epidemiology and impact of AUB.

7.2 Management of Acute Heavy Bleeding

Acute heavy bleeding is an episode of bleeding requiring management of bleeding before considering management of the underlying etiology [1]. Assessment of hemodynamic stability and possible pregnancy determine initial triage. A hemodynamically unstable woman should be seen in an acute care setting. Management of acute HMB in the hemodynamically stable woman may occur in the outpatient or ambulatory setting. Women should be evaluated with a complete blood count. When possible, the investigation of acute heavy uterine bleeding starts with a transvaginal ultrasound to assess the endometrial thickness.

7.2.1 Combined Estrogen and Progestin in Acute HMB

In the presence of a normal endometrial thickness, proceed with an oral monophasic combined hormonal contraceptive (CHC) formulation of 20–25 μg ethinyl estradiol (EE) and progestin in a multi-dose regimen. See Table 7.2. The initial dose is one tablet four times daily. This serves to reduce bleeding, typically within

Table 7.2 Management of acute heavy menstrual bleeding in the hemodynamically stable woman

Protocol	Initial management	After bleeding subsides
Estrogen and Progestin with Transvaginal ultrasound to assess endometrium prior to management	**Normal endometrial thickness**: Monophasic oral **CHC 20–25 mg EE/progestin** 4 times daily	**CHC** 3 times daily for 7 days then **CHC** 2 times daily for 7 days then **CHC** daily for 7 days Expect withdrawal bleeding after completion
	Thin endometrium: Oral **CEE** 2.5 mg 4 times daily	**CEE** 2.5 mg/day plus **MPA** 5–10 mg/day for 7–10 days
Progestin	**MPA** 20 mg 3 times daily for 7 days	**MPA** 20 mg/day for 21days
Anti-fibrinolytic	**Tranexamic acid** 1.3 g orally 3 times daily for 5 days	

EE ethinyl estradiol, *CHC* combined hormonal contraceptive, *CEE* conjugated equine estrogen, *MPA* medroxyprogesterone acetate
Based on Taylor et al. [17], James et al. [18], American College of Obstetricians and Gynecologist [4]

48 h. Once a reduction of bleeding has occurred, continue the CHC three times daily for a week, tapering to twice daily for a week and then once daily for a week. The CHC should be continued for 1 week after bleeding stops. The patient may need an anti-emetic at the higher dose and she should be counseled that bleeding is likely to return after completion of the protocol [17].

In the denuded endometrium, start with conjugated equine estrogen (CEE) 2.5 mg four times daily to restore epithelium and stabilize lysosomal enzymes [17]. Administer an anti-emetic with the CEE. Consider the woman's risk of venous thromboembolism (VTE) with this regimen. Pulmonary embolus has been reported in high dose intravenous estrogen [19]. Once bleeding has tapered, proceed with tapering the CEE to 2.5 mg/day and adding a progestin such as medroxyprogesterone acetate (MPA) 5–10 mg/day for 7–10 days [17].

7.2.2 Progestin Only in Acute HMB

Management with high dose progestin is appropriate, particularly when there are concerns for VTE such as a history of VTE, obesity, or reduced activity. Women with migraine with aura are advised against use of estrogen containing contraceptives [20]. There are no guidelines regarding emergency use of estrogen as in this scenario. Inability to access sonographic evaluation of the endometrium in a timely manner may also influence management decisions. The clinician may use expert judgement and shared decision making with the individual woman in determining treatment protocol. MPA 20 mg is given three times daily for 7 days, then daily for 3 weeks. See Table 7.2. A trial of EE with norethindrone acetate (NETA) compared to MPA alone demonstrated equal median days to bleeding cessation (3 days), with 76% cessation of bleeding and 100% avoidance of surgery in the MPA group and

88% cessation of bleeding and 95% avoidance of surgery in the EE/NETA group. Satisfaction was equal and high in both groups [21].

7.2.3 Antifibrinolytics in Acute HMB

Antifibrinolytics block lysine sites on plasminogen, preventing degradation of fibrin, and reducing bleeding. Tranexamic acid is widely used in Europe and is approved for use in the United States for HMB. Use has been adopted for acute bleeding due to trauma and postpartum hemorrhage [22, 23]. Tranexamic acid meets the European and ACOG guidelines for acute HMB [4, 18]. Treatment is 1.3 g orally every 8 h for 5 days. See Table 7.2. There is concern about risk of VTE due to the mechanism of action of tranexamic acid. The actual risk of VTE is controversial. An observational population based study over a 19-year period with 238,000 women-years treatment with tranexamic acid had no occurrence of VTE [24]. A nested case-control study in Sweden found increased risk for VTE with tranexamic acid that failed to reach statistical significance, partially due to the low overall incidence of VTE and to the presence of VTE in other treatment groups for HMB. The authors concluded that anemia, as a proxy for HMB, may be an independent risk for VTE [25]. Use of tranexamic acid is contraindicated with acquired impaired color vision impairment and current thrombotic or thromboembolic disease. Caution should be used with history of thrombosis and with concurrent combined hormonal contraceptive (CHC) use [26].

7.3 Chronic Heavy Menstrual Bleeding Presentations in Midlife

Chronic HMB is defined as heavy bleeding that most often occurs in the preceding 6 months or cycles [1]. Many women experience heavy menstrual bleeding for the first time or an exacerbation of previously moderately heavy flow in the transition from late reproductive stage to early perimenopause. The first changes may be related to flow and to subtle, less than 7 days variability, cycle length alterations. With increased aromatization leading to increased estradiol in some but not all cycles, menstrual flow varies from cycle to cycle [27] (see Chap. 4). Hale et al. measured blood loss in ovulatory and anovulatory cycles across mid-reproductive to late perimenopause stages. In ovulatory cycles, blood loss increased only slightly from mid to late reproductive age, then almost doubled in early perimenopause. The heaviest blood flow occurred in the rare ovulatory cycles of late perimenopause [28]. Life stage is the most common contributing factor to ovulatory dysfunction, possibly resulting in HMB. This may occur as much as a decade prior to the final menses [27].

7.3.1 AUB-O: Ovulatory Dysfunction

Polycystic ovarian syndrome (PCOS) is the most common menstrual endocrinopathy with an international incidence of up to 20% and a population of more than 10 B women worldwide [29]. Geographical prevalence varies widely, reported as low as 3% in some areas. Lack of surveillance, inadequate diagnosis, and challenges in resources to achieve diagnosis contribute to gaps in epidemiological data by race and region [30].

Chronic ovulatory dysfunction, as in PCOS, is characterized by irregular bleeding with heavy or variable flow. With PCOS, there is increased peripheral aromatization of androgens to estrogen, decreased SHBG with increased free testosterone and estrogen, and increased peripheral insulin resistance leading to increased insulin and increased ovarian production of androgens. This contributes to an estrogen/androgen dominant physiology. The unopposed estrogen and hyperandrogenism cause heavy but unstable endometrium. Bleeding may be heavy without typical premenstrual symptoms, mixed with light bleeding or spotting due to partial endometrial sloughing [17, 29, 31].

There is no single diagnostic measurement to identify PCOS. The international consensus of the Rotterdam criteria identify four phenotypes of PCOS. Phenotype A, representing 75% of the population with PCOS, includes clinical and/or biochemical hyperandrogenism (HA), oligomenorrhea/infrequent menses (OA), and polycystic ovarian morphology (PCOM) on ultrasound (ovarian volume >10 mL or ≥25 follicles of 2–9 mm size). The remaining phenotypes involve any combination of two of these findings. Phenotype B (HA, OA) along with phenotype A is considered "classic" PCOS, while phenotype C (HA, PCOM) is sometimes called "ovulatory" PCOS, and phenotype D (OA, PCOM) is "nonhyperandrogenic" PCOS [31, 32]. Many studies show a normalization of menstrual cycling in women with PCOS as menopause approaches [33–35]. The age-related decline in inhibin B and AMH may allow for dominant follicle selection and ovulation in the woman with PCOS despite reduced gonadotropins [33–35].

7.3.2 AUB-A: Adenomyosis

Endometriosis, the implantation of endometrial tissue external to the endometrial lining, and the subtype adenomyosis, the presence of endometrial tissue within the uterine wall, is a disease of estrogen dependent inflammation typically presenting with some combination of heavy painful menses, pain with intercourse, and nonmenstrual pelvic pain. The clinical course is variable with symptoms worsening with time, spontaneous remission of symptoms, or late onset of symptoms. There is little to no correlation between the extent of endometrial implants identified surgically and symptom profile. Women with endometriosis and adenomyosis typically have symptoms for many years prior to diagnosis. It is feasible that a woman with

AUB-A may first present with new or worsening painful and heavy menses in the late reproductive stage [17, 36]. In a recent shift from the reliance on invasive uterine biopsy or costly imaging, two-dimensional ultrasonography has been shown to be as sensitive as MRI for detecting adenomyosis. The exact criteria of ultrasound detected morphological findings for a diagnosis are in development [1].

7.3.3 AUB-L: Leiomyoma/Uterine Fibroids

Uterine leiomyomata (UL), commonly called "fibroids," are benign neoplasms of fibrous connective tissue. FIGO has classified leiomyomata according to location. Most leiomyomata are without symptoms and most are discovered incidentally. Ultrasound evidence of UL was detected in 51% of perimenopausal women without a previous clinical diagnosis [12]. Actual prevalence is difficult to assess without universal ultrasound screening [37]. Symptoms, when present, may include infertility, heavy menstrual bleeding, and "bulk" symptoms such as pain, abdominal distention, and urinary or bowel changes. Presence and severity of symptoms is correlated to tumor size and uterine mass rather than leiomyoma location [37]. A 25 year review of hospitalizations for UL in South Nigeria found the women treated had a median uterine size 15 ± 9.7 weeks. Presenting complaints were menstrual irregularities (47.7%), abdominal swelling (39.1%), and infertility (31.9%) [38]. Similar presentations were seen in a second review, demonstrating that Nigerian leiomyomata data follows patterns similar to other parts of the world [39]. Uterine mass due to leiomyomata increases over the reproductive life stages under the influence of reproductive hormones. Heavy bleeding may require attention only in the late reproductive or early perimenopause stages. In the United States, peak hospitalization for UL occurs in the fifth decade [40].

7.3.4 AUB-I: Iatrogenic

Iatrogenic heavy menstrual bleeding is caused directly or indirectly by a medication or medical device. The copper IUD initially increases menstrual blood flow duration and volume by up to 50% over baseline though flow may return to baseline with continued use [41, 42]. The number of medical diagnoses increases with age. Women in late reproductive and perimenopause stages are more likely to be using medications that can influence menstrual bleeding. Women on anti-coagulant therapy who are still menstruating experience HMB. In one study, rivaroxaban demonstrated a twofold increase in HMB over vitamin K antagonist anticoagulants. There were more interruptions in therapy in the rivaroxaban group, possibly related to bleeding events, and a subsequent increased incidence of recurrent VTE [43]. Selective serotonin reuptake inhibitors (SSRIs) interact with gonadal steroids and are associated with increased gastrointestinal bleeds. A review found scant data on the interaction with menstrual bleeding [44].

Table 7.3 Screening for inherited coagulopathy in heavy menstrual bleeding

Presence of:	Heavy menstrual bleeding since menarche			
Presence of one of:	History postpartum hemorrhage	Surgery-related bleeding	Bleeding associated with dental work	
Presence of two or more:	Bruising 1–2 times monthly	Epistaxis 1–2 times monthly	Frequent gum bleeding	Family history of bleeding symptoms

Based on Kouides et al. [46]

7.3.5 AUB-C: Coagulopathy

Inherited coagulopathy presents with a lifelong history of HMB. It would seem feasible that the diagnosis of AUB-C would then occur in adolescence or early adulthood. However, 47% of women presenting with HMB were found to have a hemostatic disorder and the prevalence of new diagnosis of AUB-C did not vary by age groups of <20 years, 21–44 years, and >44 years [45]. An international collaboration of professional hematological societies are developing guidelines on detection and management of the most common bleeding disorder, Von Willebrand disease. Currently appropriate screening using a structured history accurately identifies 90% of women with AUB-C and directs further investigation. See Table 7.3 [46]

7.3.6 AUB-E: Endometrial

AUB-E is indicated in regular heavy menses with a structurally normal uterus and exclusion of coagulopathy and ovulatory dysfunction. The events leading to endometrial sloughing, repair, and regrowth are triggered by hormonal changes and mediated via prostaglandins, plasminogen hypoxia-inducible factor 1, and local glucocorticoid metabolism, all of which have been implicated in AUB-E [47]. There are no clinical tests for AUB-E at this time so it remains a useful category in research and a diagnosis of exclusion in the clinical setting [48].

7.4 Approach to the Assessment of Chronic Heavy Menstrual Bleeding

The approach to the investigation of chronic heavy menstrual bleeding in the late reproductive stage starts with a structured history and physical examination. The history will identify related medical disorders, medications, and lifestyle influences and dictate the need for inherited coagulopathy screening [1]. All women should have a complete blood count (CBC). Further laboratory assessment may include thyroid studies in the presence of infrequent heavy menses. Hormone studies are not helpful in determining AUB-O in the late reproductive stage or perimenopause stage woman outside of an infertility assessment. A single lab value does not

adequately reflect the highly variable state of reproductive hormone levels in this age group [1, 17, 49]. The European and FIGO guidelines do not recommend serum ferritin in the initial workup [1, 6]. If she is screen positive for hemostatic disorder, first-level laboratory investigation of suspected coagulopathy includes CBC with platelets, ferritin, partial thromboplastin time and prothrombin time as well as ristocetine cofactor activity and antigen (Von Willebrand Factor) and factor VIII [50].

Following the initial clinical assessment, the most productive direction is to rule out neoplasms with a uterine assessment. Transvaginal ultrasound is first-line imaging for UL. If obtaining the imaging via a separate institution, making specific requests for noting endometrial thickness, ovarian size and morphology, and uterine wall texture assists both referring and imaging clinicians in achieving a proper diagnosis. In the absence of other clear etiologies, the diagnosis of HMB is related to AUB-O or AUB-E [1].

7.4.1 Medical Management of Chronic Heavy Menstrual Bleeding

Empiric treatment should begin based on the index of suspicion even while waiting for pending test results. Many treatment modalities achieve similar results regardless of etiology. Most national guidelines consider medical management as first-line therapy [51]. The clinician should discuss all available options with the individual woman, considering her desire for future fertility and her cultural concerns [52].

7.4.1.1 Estrogen and Progestogen or Progestogen Alone in Chronic HMB

Although widely used for reducing menstrual blood flow, there is little empirical evidence that combined hormonal contraception is effective for this purpose. A trial of two combined hormonal agents and two prostaglandin inhibiting agents demonstrated a 40% reduction in blood flow with the EE and progestin [53]. Combined hormonal agents have the additional benefit of providing high quality contraception and bleeding regularity. Midlife women are more likely to have medical conditions such as hypertension or tobacco use, precluding use of estrogen containing contraceptives [20].

Progesterone or a progestin alone was once the most common medical treatment for HMB. Anti-estrogenic activity suppresses blood volume, but increases irregularity of bleeding. Depot medroxyprogesterone acetate (DMPA) provides contraceptive benefits but short and long course cyclic progestin do not. Short course (MPA or norethisterone for 7–10 days, starting cycle Day 15 or 19 of cycle) was inferior to other medical treatments in measures of reduction in blood flow and number of days bleeding. Long course (MPA 10 mg - 20 mg or norethisterone 5 mg three times/day) daily from Day 5 to Day 26 of the menstrual cycle was inferior to LNG-IUS or tranexamic acid and equal to combined hormonal vaginal ring in reduction of bleeding. Patient satisfaction was equal to the combined hormonal vaginal ring. There is no patient satisfaction comparison data for LNG-IUS or tranexamic acid [54].

7.4.1.2 Nonsteroidal Anti-inflammatory in Chronic HMB (NSAID)

Prostaglandins control the volume of menstrual flow. PGE2 causes vasodilation and inhibits platelet aggregation while PGE2α stimulates vasoconstriction and, with thromboxane, promotes platelet aggregation [17]. Both prostaglandins increase near menses with the ratio of PGE2α:PGE2 increasing with menstrual flow, stimulating tapering and cessation of flow. Women with HMB have both increased levels of prostaglandin and prostacyclin in menstrual flow and more PG receptors in the endometrium [17]. NSAID initiation prior to onset of menstrual flow and used continuously to maintain serum levels for 3–5 days reduces menstrual blood flow by 30%. No single NSAID regimen is superior to any other. This management has the advantage of no exposure to exogenous hormones but does not provide contraception for the woman desiring fertility control. NSAIDs are less effective to treat HMB than antifibrinolytics or LNG-IUS [55].

7.4.1.3 Levonorgestrel Intrauterine System (LNG-IUS) in Chronic HMB

The LNG-IUS suppresses endometrial development via progestin action and provides ongoing highly reliable contraception for the woman who desires fertility control. The 52 mg levonorgestrel intrauterine system is the most effective medical management for heavy menstrual bleeding. Not all doses or brands of LNG-IUS have been evaluated or approved for this use. Menstrual pain and menstrual blood loss are reduced by 97% in 6 months of use. Patient satisfaction is superior to any other medical management for HMB and is equal to satisfaction in endometrial ablation [56]. HMB in the presence of leiomyomata requires special consideration. Distortion of the uterine cavity may preclude device placement. Efficacy of blood loss reduction has been demonstrated in small studies, but may be hampered by fibroid mass interference with the uterine muscle contracture involved in menstrual flow tapering and cessation [57].

7.4.1.4 Antifibrinolytics in Chronic HMB

Antifibrinolytics inhibit plasminogen activator with a 40–60% reduction in menstrual blood loss [56]. Tranexamic acid 1.3 g orally three times daily for up to 5 days during menses is approved for this use. Tranexamic acid, due to its mechanism of action, is contraindicated for use in the patient with a history of VTE and with concomitant use of CHC. See further discussion under management of acute HMB [26].

7.4.1.5 GnRH Modulation for HMB

First-line medical management of HMB in the presence of leiomyoma includes the potential benefits and limitations of the methods previously discussed. GnRH analogs have been used as second-level intervention to reduce fibroid size but the hypoestrogenic bone loss limits treatment to 6 months. These medications are typically used prior to surgery or adjuvant with surgery [58]. A GnRH antagonist elagolix with add back estrogen and progestin, is indicated for HMB associated with fibroids. Elagolix rapidly and dose dependently reduces gonadal steroid production via competitive binding with GnRH receptors of the pituitary leading to inhibition

of release of follicle stimulating hormone and luteinizing hormone. The approved protocol for management of HMB in the presence of UL is 300 mg elagolix twice daily with add back hormones (1 mg estradiol/0.5 mg norethindrone acetate) once daily for up to 12 months. In clinical trials, elagolix compared to placebo demonstrated reduced blood loss volume to ≤80 mL (72.2% vs. 9.3%), mean change in menstrual blood loss (−172.5 mL vs. −0.8 mL), amenorrhea (50.4% vs. 4.5%), reduced symptom severity (−37.1 vs. −9.2), and improved health-related quality of life score (39.9 vs. 8.9) [59]. A second GnRH antagonist, relugolix, combined with estradiol and norethindrone acetate is also approved for this indication. Elagolix is effective for alleviation of endometrial pain using 150 mg daily for 24 months or 200 mg twice daily for six months. While clinical trials in this population also demonstrated reductions in menstrual bleeding, this was not a study endpoint and reduction of HMB is not the approved indication in endometriosis [60]. Elagolix and relugolix are contraindicated for use in severe liver dysfunction. They must be used with contraception and hormonal contraception may interfere with therapeutic results. Hypoestrogenic side effects include vasomotor symptoms (6.9% hot flush and 3.2% night sweats) along with headache (5.5%) and nausea (4.1%) in elagolix clinical trials. Treatment duration is limited by bone mineral density decrease [61].

7.4.1.6 Selective Progesterone Receptor Modulation for HMB in Uterine Leiomyoma

Selective progesterone receptor modulators (SPRM) act to suppress the progesterone receptor gene, counteracting the progesterone and estrogen growth promoting effects upon leiomyoma. Several SPRM products have been developed. Dosing and regimens vary widely with no clear superiority of any product or protocol [58]. Ulipristal 5 mg, approved in Europe in 2012, but not in the United States, is the most widely used. Ulipristal was studied in women with UL with HMB as a series of 5 and 10 mg oral daily doses for 12 weeks, followed by a drug holiday to induce menses and then repeated for up to eight consecutive courses of treatment. Reduction in pain, bleeding, and tumor size were significant [62]. Benign endometrial changes occurred with a trend toward resolution at completion of therapy [63]. In 2018 reports of liver failure and death in women using ulipristal acetate 5 mg resulted in the European Medicines Agency reviewing the medication, with the conclusion that causal relationship could not be established but also limiting use to 3 months duration as adjuvant to surgery [64–66].

7.4.2 Minimally Invasive Procedural and Surgical Options in Chronic HMB

Endometrial ablation is indicated for women with a normal endometrial cavity who have not had satisfactory outcome using medical therapy, have no desire for future fertility, and have highly reliable contraception. In women with high risk factors for endometrial carcinoma such as obesity, complex atypical endometrial hyperplasia, diabetes, and hypertension, strongly consider establishing normal endometrial

histology prior to the procedure or select a different treatment method [52]. The procedure may be performed in an office setting with minimal analgesia and has shorter recovery time than hysterectomy. Endometrial ablation has been widely adopted in middle and high resource countries. Currently there are five methods of endometrial ablation utilizing techniques of thermal balloon, heated free fluid, cryoablation, radio-frequency, and two microwave devices.

Compared to hysterectomy, only 11% fewer women with endometrial ablation perceived improved bleeding symptoms at 1 year (RR 0.89, CI 0.85–0.93; four studies, 650 women). This gap persisted but narrowed over 4 years follow-up. Compared to LNG-IUS, endometrial ablation had equal patient satisfaction, quality of life, and treatment failure in 8-year follow-up [67]. Younger women (mean age ≤42 years) who received endometrial ablation were more likely to experience subsequent need for hysterectomy than women who received LNG-IUS (RR = 5.26, 95% CI 1.21–22.91, $p = 0.03$, I2 = 0%, three studies, 189 women) [68].

Late onset endometrial ablation failure (LOEAF) presents with persistent or recurrent vaginal bleeding, cyclic pelvic pain, or the inability to assess the endometrium as needed. Etiology of intractable bleeding involves both insufficient initial ablation and endometrial regrowth. Unsuspected adenomyosis and intrauterine scarring contribute both to bleeding and pain [69]. Of a group of 377 women undergoing endometrial resection, 22% had diagnosis of adenomyosis following the procedure [69]. Age at initial procedure is the predominant risk for LOEAF, as well as uterine anatomical distortion including leiomyomata and septum. Women under age 45 years at time of ablation are 2 times more likely and women under age 36 years are 3 times more likely to require subsequent hysterectomy [69, 70].

Two minimally invasive procedures, uterine artery embolization (UAE) and MRI guided high-frequency ultrasound, to reduce tumor bulk and decrease HMB are available for HMB with UL. Uterine artery embolization (UAE) is a minimally invasive interventional radiology procedure performed via femoral artery catheterization and embolization of the bilateral uterine arteries. This leads to necrosis of the leiomyoma while preserving the uterus. The first large trial of 305 women with uterine fibroids undergoing selective uterine artery embolization (UAE) demonstrated satisfactory control of HMB of 86% at 3 months post-procedure and 92% at 12 months [71]. Outcomes with UAE are similar to those obtained following myomectomy, with a subsequent intervention rate at 5 years of 20–30% [72]. A Cochrane Review found no difference in UAE patient satisfaction when compared to hysterectomy and to myomectomy at 2 and 5 years post-procedure. Post-procedure risk of major complications was equal in all procedures with a slightly higher risk of minor complications in UAE and more likelihood of subsequent surgery in UAE (15–32% vs. 7%) [73]. Though healthy pregnancies have occurred after UAE, effects on fertility and subsequent adverse events are not well defined [74].

MRI guided focused ultrasound thermal ablation technique results in coagulative necrosis at the target site [58]. Damage to surrounding tissue has been documented and future fertility may be compromised. Cost may be prohibitive. There is, as yet, no large body of outcome data [62].

7.5 Infrequent Bleeding

Infrequent bleeding is an expected bleeding pattern of the menopause transition. It is a defining criteria of the late perimenopause stage [75]. The gradual age-related loss of ovarian follicular mass and reduced follicular sensitivity to follicle stimulating hormone (FSH) are initially compensated by the gradual decline in Antimullerian hormone (AMH), decrease in inhibin, and age-related increase in aromatase, maintaining normal 17β-estradiol and ovulation [76 77]. With transition into the late perimenopause stage, a critically low threshold of follicles leads to decreased folliculogenesis and decreased follicular size when ovulation does occur, resulting in limited progesterone production. Cycles are irregular and interspersed with durations of ≥60 days without bleeding. Estrogen dominance may lead to endometrial hyperplasia [78] (see Chap. 4).

Infrequent bleeding at an age not within the norm for the menopause transition should be evaluated as an endocrinopathy (see Chap. 4). Health conditions developed in midlife may directly affect menstrual pattern. Thyroid, liver, and chronic kidney disease are all associated with infrequent menses [17]. There may also be increased health conditions with treatment induced menstrual changes. The most frequent source of iatrogenic (AUB-I) infrequent menses is exogenous hormone use [48]. Drug induced hyperprolactinemia and infrequent or absent menses may result from multiple classes of frequently used pharmaceuticals: anti-psychotics, antidepressants including tri-cyclic antidepressants, SSRI, SNRI, and MAO-I, as well as antihypertensives verapamil, α-methlydopa, reserpine, and labetolol (intravenous only) and the pro-kinetic agents metoclopramide and domperidone. There is question if H2-receptor blockers cimetidine and ranitidine contribute to hyperprolactinemic infrequent menses. Finally recreational drugs have been implemented in hyperprolactinemic infrequent menses including marijuana, heroin, methadone, cocaine, and alcohol [79].

To protect from endometrial hyperplasia, women who have a uterus must always be prescribed with a progestogen when estrogen is initiated, regardless of menstrual status [80]. Numerous studies have compared protocols for progestogen. Continuous use of 100 mg oral daily micronized progesterone, 1 mg norethisterone, or 1.5 mg MPA or sequential use 10–14 days per month of 200 mg oral daily micronized progesterone are effective for preventing endometrial hyperplasia in the presence of exogenous estrogen [81, 82]. Bjarnason et al. [83] comparing long cycle sequential progesterone (10 days every 12 weeks) to monthly sequential progesterone demonstrated increase in neoplasia in the long cycle group (see Chap. 6). In another study, the LNG-IUS was more effective in endometrial suppression than sequential MPA, but was comparable to other forms of systemic progestogen [84].

The clinical challenge is to determine which women in the perimenopause stages with infrequent bleeding require further investigation into endometrial status. A careful history is necessary to uncover iatrogenic and health-related causes beyond the expected age-related changes in menstrual pattern. Consider ultrasound evaluation for women with:

- Atypical age for perimenopause
- Symptoms or signs consistent with acquired comorbidity: thyroid endocrinopathy, liver and kidney disease
- Use of drug-inducing hyperprolactinemic agents
- Presence of additional risk factors for complex hyperplasia and endometrial carcinoma: obesity, PCOS, family history of endometrial cancer or genetic cancer syndrome such as HNPCC [85]

Management of an ultrasound measured endometrial stripe that is >4 mm or of irregular profile follows the assessment protocol as in postmenopause bleeding. A woman presenting with infrequent menses and <6 months without bleeding, may be considered for a progestogen withdrawal in the presence of a uniform endometrial stripe of >4 mm on ultrasound. Micronized progesterone 200 mg/day or MPA 10 mg/day for 10–12 days should stimulate a sloughing of the endometrium. Ultrasound re-assessment of the endometrial stripe should be done on Day 3–7 of withdrawal bleeding. If the endometrium remains >4 mm, endometrial sampling is warranted [17, 86].

Management of infrequent bleeding in the absence of endometrial hyperplasia in perimenopause is largely expectant. Ongoing management of the woman with infrequent menses and no additional risk factors for endometrial hyperplasia and carcinoma is directed at protection from the influence of unopposed estrogen in anovulatory cycles. She may use continuous low dose 1.5 mg MPA or 100 mg micronized progesterone, or cyclic progestogen for 12–15 days of 10–15 mg MPA or 200 mg micronized progesterone, or combined hormonal contraception, particularly if contraception is desired [17].

7.6 Postmenopause Bleeding

The largest risk for endometrial hyperplasia is exposure to unopposed estrogen. The time frame of exposure typically occurs in the ages of the early 50s, with progression to endometrial atypia in the early 60s, and peak incidence of carcinoma in the 70s [87]. Postmenopause bleeding may be a result of exogenous hormone use, benign neoplasms such as endometrial or endocervical polyps, endometrial atrophy, or endometrial hyperplasia or carcinoma [88]. Selective estrogen receptor modulators (SERMs), particularly tamoxifen, demonstrate endometrial activity and stimulation leading to risk of endometrial hyperplasia. Raloxifene, bazedoxifene, and ospemifene show no increase in endometrial activity over placebo [81].

There is only very limited evidence of endometrial safety for women using compounded bioidentical progesterone (cBHT). The National Academies of Sciences, Engineering, and Medicine [89], in a report on cBHT focusing on the United States, included only three studies of compounded progesterone cream, two of which were pharmaceutically formulated products. None of the studies were of sufficient power

or duration to determine long-term endometrial safety. Additionally cBHT products typically lack oversight in production ensuring uniformity of dosage and delivery. Many women may be unsure of formulations in current or previous use (see Chap. 6).

Any patient with postmenopause bleeding, whether on MHT, SERM, or no medication, and regardless of flow volume or duration, requires investigation. Even though only 1–14% of such patients will actually prove to have endometrial cancer, with peak age of incidence over 60 years, the clinician must assume an etiology of endometrial carcinoma until proven otherwise [90]. The initial step in evaluation is ultrasound imaging [88]. A uniform endometrial thickness of ≤4 mm has a greater than 99% negative predictive value for endometrial carcinoma [91].

In the presence of thickened endometrium, blind endometrial sampling is an appropriate next step and may be accomplished as an office procedure. With an irregular endometrial profile on ultrasound or persistent bleeding despite normal endometrial stripe and negative blind sampling, hysteroscopy and targeted biopsy is indicated [86, 88, 91]. This woman, and any woman with endometrial atypia or carcinoma on blind endometrial sampling, should be referred to gynecological oncology specialty if available or to gynecology for management.

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