TECHNICAL NOTE

Diagnostic Hysteroscopy and Saline Infusion Sonography in Abnormal Uterine Bleeding

Amardeep Gupta[1]

Authors' Affiliation: [1]Sarvepalli Radhakrishnan University, Bhopal, India
Corresponding author: Dr. Amardeep Gupta**, Email:** dramardeep0913@gmail.com

ABSTRACT

One of the commonest reasons for women seeking gynecological advice is Abnormal uterine bleeding (AUB). Most common anatomical causes of abnormal uterine bleeding in women are endometrial polyps, sub mucosal fibroids and endometrial hyperplasia. Hysteroscopy is an effective procedure but is more expensive than Saline Infusion Sonography (SIS). Direct visualization of uterine cavity is possible by hysteroscopy, but it does not give any information about myometrium and adnexa. Saline infusion sonography is effortlessly accepted by most patients as it can be an outpatient procedure. This article present summary of salient features of the procedure which will help the practitioner to take informed decision.

Keywords: Hysteroscopy, Saline infusion, Sonography, Abnormal uterine bleeding, AUB

INTRODUCTION

One of the commonest reasons for women seeking gynecological advice is Abnormal uterine bleeding (AUB).[1] Intrauterine abnormalities are the leading cause of AUB after dysfunctional uterine bleeding (DUB). Intrauterine abnormalities are reported in more than 40% of affected women with AUB.[2]

Most common anatomical causes of abnormal uterine bleeding in women are endometrial polyps, sub mucosal fibroids and endometrial hyperplasia. Endometrial cancer causes 10% to 15% of postmenopausal vaginal bleeding so a detailed examination should be carried out to assess these symptoms.[3] 2D and 3D ultrasound is the most common procedure performed on women with abnormal uterine bleeding[4] since many years commonest recognized approach for the managing of abnormal uterine bleeding has been 2D TV scan. It has been followed by hysteroscopy with a histological examination of the obtained specimen.[5]

Trans-vaginal sonography (TVS) is the initial investigation since it is rapid, easy, and cost effective. But this technique cannot differentiate intrauterine pathology with total confidence. [6] Diagnostic hysteroscopies together with a histological examination of endometrial aspiration or biopsyis the gold standard investigation for the diagnosis of intrauterine abnormalities. Hysteroscopy is time consuming, invasive, involves anesthesia and reasonably expensive. Hysteroscopy is too accompanying risks like ascending genitourinary infection and uterine perforation.[7]

In comparison to hysteroscopy, Saline infusion sonography (SIS) is cheaper, less invasive and doesn't require anesthesia. Saline infusion sonography consistently assesses adhesions, uterine contour, and focal pathologies. Moreover, in Saline infusion sonography, clear visualization of the inner surface of both sides of the endometrium is seen after distending the cavity with saline. In most cases, sub mucous fibroid can be distinguished from the endometrial polyp based on the imaging characteristics.[8] Diffuse and focal and abnormalities can be distinguished. Polyps are classically smooth in outline, round and are generally echogenic in comparison to the endometrium or may be isoechoic to it. The original endometrial-myometrial interface is conserved.[9]

The occurrence of a vascular pedicle has a PPV - positive predictive value around eight percent. Fibroids are more hypoechoic, homogeneous and endometrial-myometrial interface loss is also seen. Intra-cavitary portions of the submucous fibroids can be evaluated by Saline infusion sonography (SIS). Furthermore, the intramural fibroids distorting the cavity can be differentiated from the submucous fibroids. Therefore, by expanding the inner walls of endometrium, diffuse and focal lesions can be recognized, along with size of the pathology and the location, with reasonable precision.[10,11]

Saline infusion sonography is effortlessly accepted by most patients as it can be an outpatient procedure. With SIS, complications are rare. During balloon inflation and instillation of saline, the patient may have discomfort, anxiety, and mild lower abdominal cramps. Though, symptoms subside soon after the finish of the procedure. Vaginal spotting is also known to occur for 1 or 2 days after the procedure. Infection in the form of endometritis was reported in only 1% to 2% of patients. This procedure is normally well-tolerated. [6]

Hysteroscopy is an effective procedure but is more expensive than Saline Infusion Sonography (SIS). Direct visualization of uterine cavity is possible by hysteroscopy, but it does not give any information about myometrium and adnexa.[8]

Abnormal uterine bleeding (AUB) describes a range of symptoms, such as heavy menstrual bleeding (HMB, bleeding above the 95th centile of the normal population), intermenstrual 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 (Fig. 1)—PALM (polyps,

adenomyosis, leiomyoma, malignancy) and COEIN (coagulopathies, ovulatory dysfunction, endometrial, iatrogenic, not otherwise classified). [12] Menstrual disorders, previously portrayed as dysfunctional uterine bleeding (DUB) and menorrhagia, are now better described as abnormal uterine bleeding (AUB).[12] The terms DUB and menorrhagia should be discarded. In clinical practice, HMB is defined as 'excessive menstrual blood loss leading to interference with the physical, emotional, social and material quality of life of a woman'. Hence, treatment success ultimately depends on the improvement of the woman's symptoms and quality of life. [13]

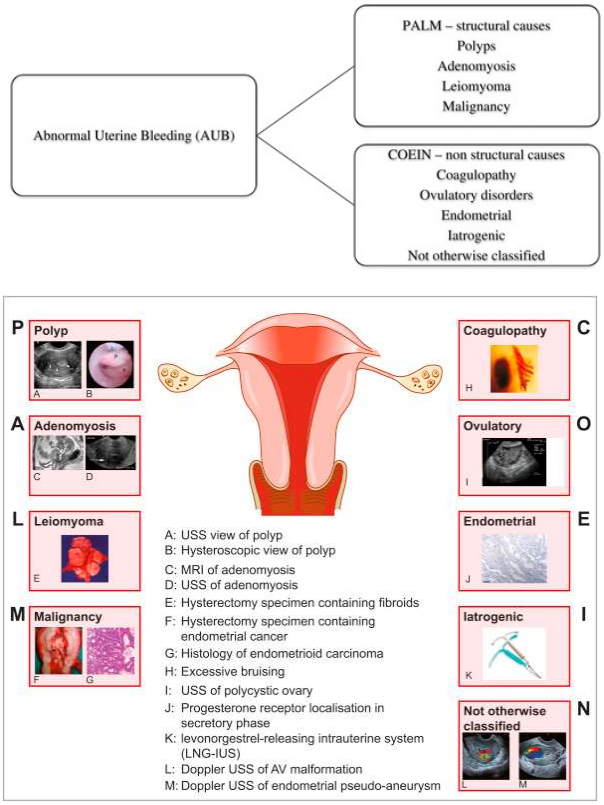

Figure 1: FIGO classification of cause of AUB: 'PALM-COEIN'

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. 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 HMB in the research setting relates to blood loss of more than 80 ml per cycle. This level of blood loss increases the risk of iron deficiency anaemia. [14]

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. [15]

Definitions

AUB was redefined by Fédération International de Gynécologie et d'Obstétrique (FIGO) in 2009 by the FIGO Menstrual Disorders Group (FMDG). This was in order to standardise definitions, nomenclature and the underlying categories of aetiology. It was hoped that this would facilitate ease of investigation and comparison of similar patient populations and thereby aid research and improve evidence-based care; this would also be a practical tool for assessing contributing aetiologies. [12]

Chronic AUB was defined as 'bleeding from the uterine corpus that is abnormal in volume, regularity and/or timing that has been present for the majority of the last 6 months.

With regard to volume, however, both the Royal College of Obstetricians and Gynaecologists (RCOG) and American College of Obstetricians and Gynecologists (ACOG) prefer the patient-centred definition of HMB, 'excessive menstrual blood loss which interferes with a woman's physical, social, emotional and/or material quality of life', as an indication for investigation and treatment options. As such, objective measurements of volume are usually the preserve of research studies and surrogates such a pictorial blood-loss assessment chart (PBAC) scores are not recommended in routine clinical practice. [12]

FIGO classification of cause: 'PALM-COEIN'

Once bleeding is defined as being abnormal, the acronym PALM-COEIN is now being increasingly used for categorising causes: **P**olyp, **A**denomyosis, **L**eiomyoma, **M**alignancy (and hyperplasia), **C**oagulopathy, **O**vulatory disorders, **E**ndometrial, **I**atrogenic and **N**ot otherwise classified . The 'PALM' are assessed visually (imaging and histopathology) and the 'COEIN' are non-structural (Fig. 2).

Depending on the site, leiomyoma (fibroids) are further subdivided into submucosal (SM) and other (O) and then into nine tertiary categories adapted from the Wamsteker classification. [16]

ABNORMAL UTERINE BLEEDING ACROSS THE LIFE COURSE

AUB may first manifest at the onset of the menarche. 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. [17]

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. Anovulation is likely to be the most common reason for HMB in this age group but other causes, such as an underlying bleeding disorder, are essential to exclude. [18]

In the reproductive years, AUB and its subgroup HMB affects ~14–25% of women and impacts significantly on physical, social, emotional and psychological aspects of the quality of life. Two national audits in England and Wales[19]

reported that, at 1 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. 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. [20]

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 of 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. 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. [21]

While 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.

CONTRIBUTION OF FIBROIDS (LEIOMYOMA) TO AUB

The relationship between AUB and fibroids remains incompletely understood. The obvious paradox is that many women have fibroids but also have entirely normal bleeding patterns. Fibroids are also highly prevalent in women presenting with AUB.

Previous postulated theories include an increased endometrial surface area and the presence of fragile and engorged vasculature in the perimyoma environment. [22] The increase in vascular flow observed along with these enlarged vessels can overcome platelet action. There is increasing knowledge regarding the complex cellular and molecular changes found in association with fibroids, with impact on angiogenesis, alteration in vasoactive substrates and growth factors as well as alteration in coagulation. The effect of fibroids on endometrial function is now thought to represent a field change within the uterine cavity rather than limited to regions overlying the myoma(s). Some of these changes may have an impact on endometrial receptivity and implantation as well as AUB. [23]

Matrix metalloproteinase (MMP) 2 and 11 levels are increased in fibroids (with MMP 1 and 3 unchanged), but the impact on endometrial bleeding is unclear. Expression of vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), heparin-binding epidermal growth factor, platelet-derived growth factor (PDGF), parathyroid hormone-related protein (PTHrP) and prolactin is altered in women with fibroids. VEGF, bFGF, PDGF and PTHrP all have potential angiogenic effects but their specific role within the endometrium in women with fibroids has yet to be determined. [23]

There is alteration of plasminogen modulators and this may impact on endometrial haemostasis and repair. Transforming growth factor beta(TGF-β) is produced in excess in the endometrium in women with fibroids and is associated with reduced levels of plasminogen activator inhibitor-1 (PAI-1), thrombomodulin and antithrombin III, both in vivo and in endometrial stromal cells treated in vitro with TGF-β. This may represent a putative mechanism for some cases of AUB observed in the context of fibroids and may in the future offer a potential therapeutic target. [24]

In women with fibroids, alterations in the blood plasma levels of circulating interleukin (IL)-13, IL-17 and IL-10 have been reported. Whether these variations affect immune function and inflammation implicated in endometrial breakdown and repair remains unknown.

With regard to the location of fibroids, it was previously thought that those women with SM fibroids, particularly with those distorting the cavity, were more likely to present with HMB. There is current debate that women with significant cavity distortion represent additional therapeutic challenges. [22]

OTHER CAUSES OF AUB

The PALM-COEIN classification system accepts that women may have more than one underlying aetiology and also that often in the case of structural abnormalities, many women may in fact be asymptomatic.

Polyps (AUB-P)

Endometrial polyps are epithelial proliferations arising from the endometrial stroma and glands. The majority are asymptomatic. The contribution of polyps to AUB varies widely ranging from 3.7% to 65%, but it is widely accepted. The incidence of polyps as with fibroids increases with age and both pathologies may frequently co-exist, or suspected polyps visualised on transvaginal ultrasound scanning (TV-USS) may be mistaken for SM fibroids and vice-versa. [25]

Adenomyosis (AUB-A)

The relationship between adenomyosis and AUB remains unclear, particularly with regard to wide variations in histopathological diagnosis reflecting variations in criteria used and also improved radiological diagnosis. Typically, adenomyosis is associated with increasing age and may co-exist with fibroids. Furthermore, adenomyosis may be both focal and diffuse and it may be harder to establish diagnosis if fibroids are also present. [26]

Malignancy (AUB-M)

Endometrial cancer is the most common gynaecological malignancy in the western world. Historically, endometrial cancer has rarely occurred in premenopausal women; however, with increasing obesity and rising prevalence of the metabolic syndrome, the endocrine-driven subset of endometrial malignancy has markedly increased in frequency. Between 1992–1994 and 2009–2011, the European age-standardised rates of uterine cancer in the UK have

increased by 48%. With the reclassification by the WHO from hyperplasia to endometrial intraepithelial neoplasia (EIN), the current prevalence of premalignant disease is unknown. The evaluation of the endometrium may be affected by distortion of the uterine cavity by fibroids, and as such, the co-existing pathology may delay diagnosis.

The diagnosis of cervical cancer should be considered, particularly with persistent intermenstrual bleeding, and rarely ovarian cancer may present with AUB.

Uterine sarcoma have been reported as rare (3–7/100,000 in the USA) but maybe a cause of AUB-M. A recent meta-analysis reported that leiomyosarcoma are unexpectedly diagnosed following surgery for anticipated 'benign' myomas in 2.94 per 1000 women (one in 340 women). Race is the only commonality between leiomyosarcoma and leiomyoma with black women having an approximately twofold increased risk. The risk of development of leiomyosarcoma is reported to increase with age with <1 case per 500 among women aged under 30 years to one in 98 among women in the age range 75–79 years . Other risk factors for uterine leiomyosarcoma include the long-term use of tamoxifen, previous pelvic radiation therapy and rare inherited disorders such as hereditary leiomyomatosis and renal cell carcinoma (HLRCC). [27]

Interestingly, the previously held view was that a rapidly enlarging uterus would raise the suspicion for malignancy. This is now no longer held to be true as benign fibroids can grow rapidly and sarcomas grow slowly. However, more objective investigations are still lacking. Both ultrasound scanning (USS) and magnetic resonance imaging (MRI) do not as yet have robust criteria to accurately predict differentiation between leiomyoma and leiomyosarcoma.[28] The lack of a robust pre-surgical predictor/biomarker has recently altered surgical practice because morcellation of an unsuspected leiomyosarcoma increases dissemination. [29]

If malignancy or premalignancy is found along with AUB classification, the pathology should be described and staged utilising the appropriate WHO/FIGO systems.[30]

Coagulopathy (AUB-C)

Coagulopathies are reported to affect 13% of the women presenting with HMB. The majority of these women suffer from Von Willebrand disease. Systemic disorders of haemostasis may be identified in 90% of women using a structured history. [31] (Table 1).

Table 1. Structured history for coagulopathy screen. Adapted from Koudies et al. [32] .

Criteria
1. Heavy bleeding since the menarche
2. One of the following:
Postpartum haemorrhage
Surgical-related bleeding
Bleeding associated with dental work
3. Two or more of the following:
Bruising 1–2 times/month
Epistaxis 1–2 times per/month
Frequent gum bleeding
Family history of bleeding problems

If 1, 2 or 3 (see Table 1) is ascertained, it indicates positive screen, and further referral for appropriate investigation should be considered.

Anticoagulant and antiplatelet therapy hitherto has been considered as a part of 'AUB-C' (rather than AUB-I). Compression caused by a large fibroid uterusmay lead to venous thromboembolism (VTE). Bleeding previously deemed as AUB-L may be exacerbated by subsequent anticoagulation and presents additional management challenges.

Ovulatory (AUB-O)

Anovulatory cycles may contribute to AUB by unopposed oestrogen effects on the endometrium causing marked proliferation and thickening resulting in HMB along with an altered frequency of menstruation. This is observed at the extremes of reproductive age; however, impact on the HPO axis along with endocrinopathies is also present. The latter include polycystic ovarian syndrome (PCOS), hyperprolactinaemia, hypothyroidism as well as factors such as obesity, anorexia, weight loss, mental stress and extreme exercise. Typically, women in this group have menstrual cycles that fall out with 38 days or have a variation of >21 days. Drugs that affect dopamine levels, with their attendant effects on the HPO axis, also currently fall under this category rather than AUB-I. In women with fibroids, the co-existing ovulatory dysfunction may exacerbate menstrual loss.

The FIGO AUB classification system is a dynamic system with feedback and contemporary debate informing future revisions. The position of drug therapies affecting AUB is currently under review with regard to whether anticoagulant/antiplatelet therapies and drugs affecting the HPO axis may be better placed in 'AUB-I'. [12]

Endometrial (AUB-E)

AUB that occurs in the context of a structurally normal uterus with regular menstrual cycles without evidence of coagulopathy is likely to have an underlying endometrial cause. Endometrial function in the context of menstruation and its disorders is still not fully understood and remains an area of active scientific enquiry, particularly the complexities of the sequence of events triggered by progesterone withdrawal (due to demise of the corpus luteum in the absence of pregnancy). Hypoxia, inflammation, haemostasis and angiogenesis all play crucial roles in the shedding and subsequent scarless repair of the functional upper layer of the endometrium. Perturbation of local glucocorticoid metabolism, aberrant prostaglandin synthesis and excessive plasminogen (resulting in premature clot lysis) have all been implicated in AUB. [33]

AUB-E may be implicated in many women with AUB, but a lack of clinically available specific tests or biomarkers means that practical testing for such disorders is not yet feasible. As such, diagnosis depends on careful history taking and exclusion of other contributors. The high prevalence of potential endometrial dysfunction means that it is highly likely that those with AUB-L will often have an element of AUB-E contributing to increased/aberrant menstrual blood loss with its attendant implication for therapy.

Iatrogenic (AUB-I)

Iatrogenic causes of AUB include exogenous therapy than may lead to unscheduled endometrial bleeding. This is typically associated with continuous oestrogen or progestin

therapy (systemic or intrauterine delivery routes) or those interventions that act on ovarian steroid release such as gonadotropin-releasing hormone (GnRH) agonists and aromatase inhibitors. Selective oestrogen receptor modulators (SERMs) and more rarely selective progesterone receptor modulators (SPRMs) may cause AUB through direct action on the endometrium.

The use of an intrauterine device (IUD) may cause a low-grade endometritiswhich may also contribute to AUB.

Not otherwise classified (AUB-N)

It is inevitable that there will be pathologies that are either rare or poorly defined that do not easily fit within the categories described earlier. Examples include arteriovenous malformations, endometrial pseudoaneurysms, myometrial hypertrophy and chronic endometritis (not precipitated by an IUD). All of these can co-exist with AUB-L.[12]

The planned regular review of the FIGO PALM-COEIN classification system every 3–5 years through FIGO will allow reassessment, in particular, of this category. Further areas considered for future sub-classification include AUB-P and AUB-A.

DIAGNOSTIC HYSTEROSCOPY

Hysteroscopy is confirmed as the gold standard in the assessment of AUB in menopause, permitting the elimination of the false-negative results of blind biopsy through direct visualization of the uterine cavity and the performance of targeted biopsy in case of doubt. It permits full visualization of the endocervix, endometrial cavity and tubal ostia, allowing visual diagnosis of focal endometrial lesions that are missed with endometrial sampling, TVS or SIS. [34] In addition, vaginoscopic approach to perform AH can also be used for careful evaluation of any vaginal pathology that may be a culprit for AUB. Besides, this approach reduces discomfort in all patients, including those with moderate stenosis of the internal cervical os and can be successfully used in virginal older women who otherwise would need general anesthetic. The high accuracy, sensitivity and specificity of hysteroscopy are well studied. [35,36] With miniaturization of hysteroscopes and newer treatment modalities such as bipolar devices and hysteroscopic morcellators, outpatient hysteroscopy is no longer just a simple diagnostic test but can offer "see-and-treat" approach to these women presenting with AUB.

AH has been widely recommended with substantial evidence to prove its safety, efficacy and acceptability, but it is a mini-invasive procedure and can be associated with complications including severe pain.34,35 Although major complications are extremely rare. [37] Hysteroscopy may be unnecessary when a normal endometrial cavity has been optimally visualized using simple TVS or COH. Like other methods, hysteroscopy is also beset by limitations, especially in premenopausal women. Some of these include phase of the menstrual cycle, presence of copious bleeding and mistaking uneven surfaces as pathologic. Excessive uterine distension can affect the detection of disease.40 There are several studies regarding the accuracy of ultrasound and hysteroscopy in the diagnosis of endometrial disease. [38]

Cooper et al[39] published an analysis of cost-effectiveness of different strategies for investigating AUB and concluded that outpatient hysteroscopy appeared to be the most cost-effective first-line investigation for women with HMB referred to secondary care after failed medical interventions, including levonorgestrel intrauterine system (LNG-IUS). In conclusion, the above investigations should be used to complement each other depending on available resources to achieve an accurate diagnosis that would then help the clinician to optimize the management of women presenting with AUB.

After excluding malignancy, the treatment goals for management of women with AUB include reduction of blood loss, improvement in quality of life and the treatment of any structural abnormality that appears to be contributing to the AUB. Pharmacological treatment for regulation of the menstrual cycles and reduction of monthly bleeding should ideally be the first-line treatment offered in primary care prior to considering referral of these women with AUB to secondary care. This involves the non-hormonal and hormonal treatment options, including the LNG-IUS, in suitable cases.

AH is instrumental in the management of AUB (HMB, IMB and PMB), particularly when structural pathologies diagnosed by AH are suitable for immediate treatment as a one-stop see-and-treat approach.

SALINE INFUSION SONOGRAPHY

Transvaginal sonography (TVS) is used as an initial investigation because it is easy, rapid and cost effective, but it is unable to differentiate intrauterine pathology with complete certainty.5 The gold standard for diagnosis of intrauterine abnormalities is diagnostic hysteroscopy combined with a histological examination of endometrial aspiration or biopsy. Hysteroscopy is invasive, reasonably expensive, time consuming, and involves general anesthesia. Hysteroscopy is also associated with risks like uterine perforation and ascending genitourinary infection. [40]

Three-dimensional saline infusion sonography (3D SIS) in comparison to hysteroscopy is less invasive, cheaper, and does not require general anesthesia. [41] 3D SIS reliably evaluates uterine contour, adhesions, and focal pathologies. Furthermore, in 3D SIS, after distending the cavity with saline, there is clear visualization of the inner surface of both sides of the endometrium.[5] Focal and diffuse abnormalities can be distinguished, and in most cases an endometrial polyp can be differentiated from the submucous fibroid based on the imaging characteristics. The polyps are typically round in shape, smooth in outline, and are generally echogenic, compared to the endometrium or are isoechoic to it. The underlying endometrial-myometrial interface is preserved (**Figures 3, 4**). [42]

The presence of a vascular pedicle has a positive predictive value of up to 81.3%. Fibroids are more inhomogeneous, hypoechoic, and there is a loss of endometrial- myometrial interface. The percentage of the intracavitary portions of the submucous fibroids can be assessed by 3D SIS (**Figure 5**). In addition, the sub- mucous fibroids can be differentiated from the intramural fibroids that are distorting the cavity (**Figure 6**). Thus by distending the inner walls of the endometrium, focal and diffuse lesions can be identified,

along with the location and size of the pathology, with reasonable accuracy. [43]

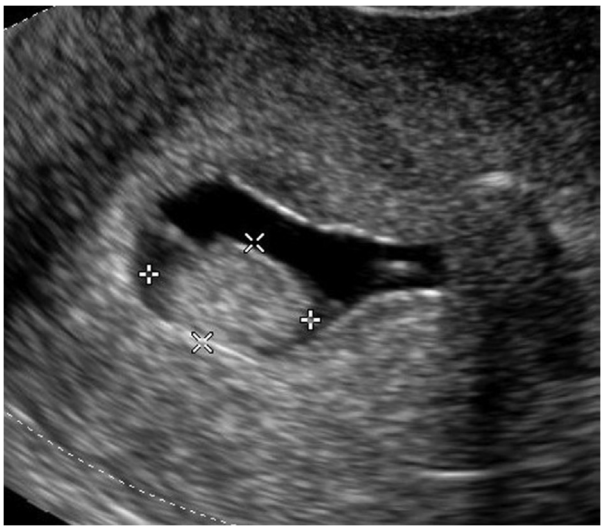

Figure 3. Saline infusion sonography demonstrating posterior wall uterine polyp, protruding into the cavity, measuring 15×10 mm

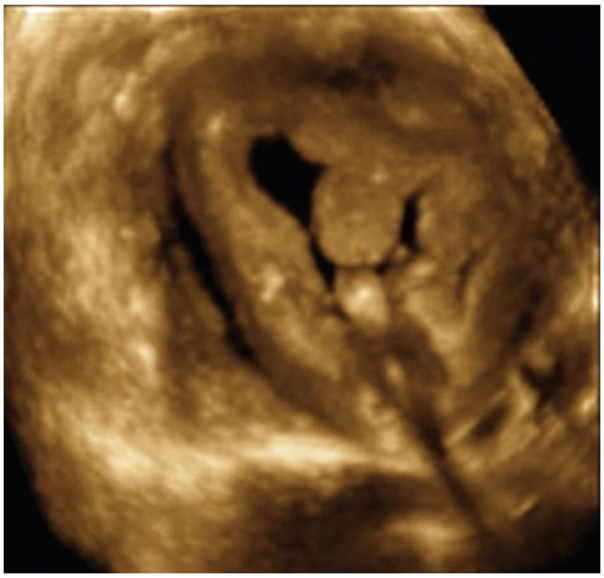

Figure 4. Saline infusion sonography demonstrating a 13×11 mm uterine polyp arising from the left fundal uterine wall.

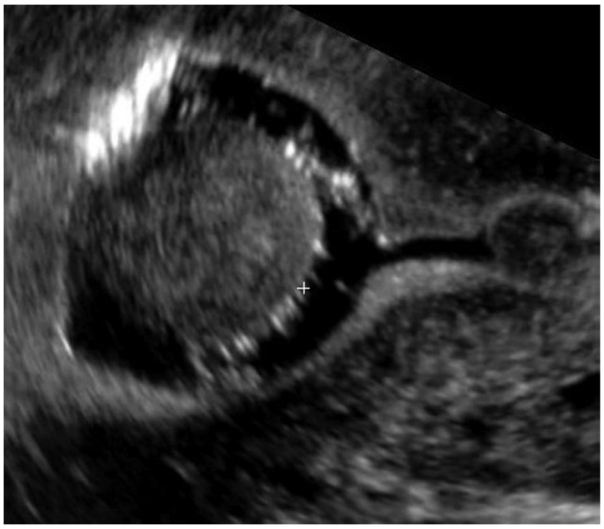

Figure 5: Saline infusion sonography demonstrating a 30×30 mm intrcavitary uterine fibroid, protruding from the fundus.

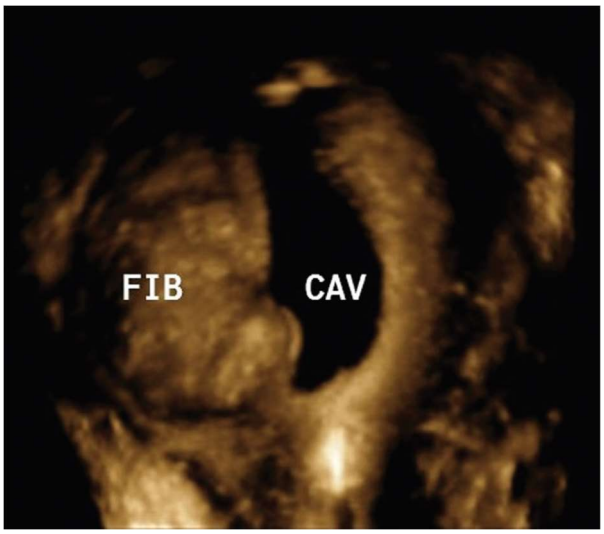

Figure 6. Saline infusion sonography demonstrating a 34×35 mm intramural fibroid distorting the cavity.

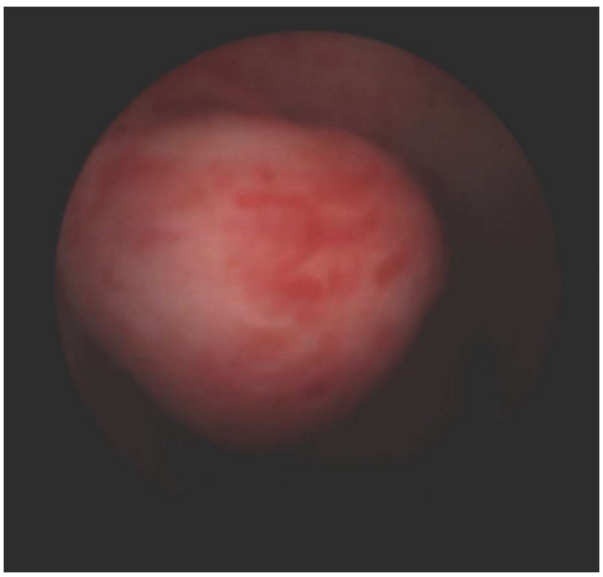

Figure 7. Endometrial polyp by office hysteroscopy.

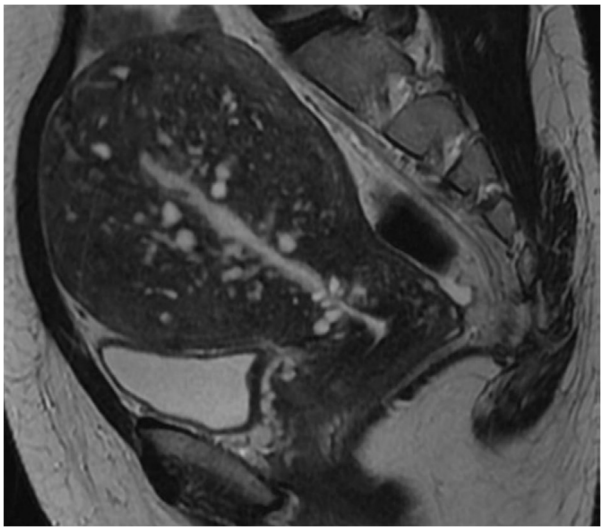

Figure 8. Adenomyosis of the uterus by magnetic resonance imaging.

3D SIS is easily accepted by most patients as an outpatient procedure. Complications are rare with 3D SIS. The patient may experience anxiety, discomfort, and mild lower abdominal cramps during balloon inflation and instillation of saline. However, the symptoms abate soon after the end of the procedure. Vaginal spotting may also occur for one or two days after the procedure. Only 1% to 2% infection was reported, mostly as endometritis. [44]

The procedure is usually well-tolerated. The purpose of the study was to assess whether three-dimensional saline infusion sonohysterography (3D SIS) can replace diagnostic hysteroscopy (DH) for the diagnosis of endometrial pathology in patients with abnormal uterine bleeding. [45]

EVALUATION AND DIAGNOSIS OF CAUSES OF AUB

Polyps

Intermenstrual bleeding or AUB may occur in up to 67% of premenopausal women with endometrial polyps. Polyps may be single or multiple, measuring from a few millimeters to centimeters, and may be sessile or pedunculated. They are localized hyperplastic overgrowths of endometrial glands and stroma around a vascular core forming a projection often from the uterine fundus and extending toward the internal os. The exact cause of polyps is unknown, but possible etiologies include genetic, biochemical, and hormonal factors. The prevalence of polyps ranges from 7.8% to 34.9% of women and seems to increase with age. [46] Most endometrial polyps are benign, but a large review of more than 10,000 women suggests that the incidence of malignancy is 1.7% in premenopausal women, whereas the risk in postmenopausal women is 5.4%.[47]

Risk factors for developing polyps include age, tamoxifen use, increased levels of endogenous or exogenous estrogen, obesity, and Lynch syndrome (hereditary nonpolyposis colorectal cancer). Endometrial polyps can be accurately diagnosed using transvaginal ultrasound (TVUS) (sensitivity, 91%; specificity, 90%), saline infusion sonohysterography (SIS) (sensitivity, 95%; specificity, 92%), diagnostic hysteroscopy (sensitivity, 90%; specificity, 93%), and hysterosalpingography (sensitivity, 98%; specificity, 35%).[46] The benefits of TVUS or SIS include the ability to visualize the adnexa, whereas polypectomy can be performed with hysteroscopy (Figure 3). Asymptomatic polyps greater than 1.5 cm and symptomatic polyps should be considered for excision and sent for pathologic examination. [46]

Cervical polyps occur most often in the reproductive years, especially after age 40 years. They generally arise from the endocervix potentially from inflammation and hormonal factors. Cervical polyps are rarely larger than 3 cm, are usually non-malignant, generally are easily removable in the office, and should be sent for pathologic examination. Importantly, cervical polyps may coexist with endometrial intraepithelial neoplasia (EIN) or endometrial hyperplasia and endometrial polyps and may be mistaken for prolapsing leiomyoma. [49]

Adenomyosis

Adenomyosis is a disorder in which endometrial glands and stroma are present focally or globally through the uterine musculature, causing hypertrophy of the surrounding myometrium. Prevalence is predicted to be 5% to 70% of women. Most cases occur in multiparous women in the fourth to fifth decades of life.[50] Whereas adenomyosis is asymptomatic in one-third of cases, women may present with HMB, irregular bleeding, dysmenorrhea, or dyspareunia. Evidence supports that the pathologic features of adenomyosis are related to abnormal gene expression, increased angiogenesis and proliferation, decreased apoptosis, impaired cytokine expression, local estrogen production, resistance to progesterone, increased nerve density, and immunologic oxidative stress. [51]

Definitive diagnosis is by histologic examination at hysterectomy; however, specific TVUS and magnetic resonance imaging (MRI) criteria help establish the diagnosis. Transvaginal ultrasound may include echogenic striations, myometrial cysts, globular uterus configuration or asymmetrical thickening of the myometrium, and heterogeneity of the myometrium leading to poor definition of the endometrialmyometrial interface (sensitivity, 89%; specificity, 89%). Given that adenomyosis increases uterine vascularity, a pattern of penetrating vessels can be seen at color Doppler ultrasound. T2-weight MRI findings may show diffuse or focal endometrialmyometrial junctional zone widening of 12 mm or more, islands of heterotopic endometrial tissue, cystic dilation of heterotopic glands, and punctate hyperintense foci of hemorrhage (sensitivity, 86%; specificity, 86%)21 (Figure 8). [52]

In a systematic review by Pontis et al, effective medical therapies for adenomyosis include suppressive hormonal treatments such as continuous contraceptive hormones, high-dose progestins, selective estrogen receptor modulators (SERMs), selective progesterone receptor modulators (SPRMs), the 52-mg LNG IUS, aromatase inhibitors, danazol, and temporary use of gonadotropin receptor hormone (GnRH) agonists. The review concluded that if amenorrhea was achieved, there was no statistically significant difference between medical therapies in terms of pain relief. However, adverse effects and costs vary widely between various treatments. The most promising medical therapy per the authors is the LNG IUS, given its effectiveness and low profile adverse effects. [53]

When endometrial ablation has been performed, adenomyosis is a predictor of treatment failure due to bleeding, with

a failure rate of 20%. In nonrandomized studies, uterine artery embolization (UAE) and MRI-guided focused ultrasound (MgFUS) seem to be promising treatments for adenomyosis, although they were approved by the Food and Drug Administration primarily for leiomyoma therapy. Taran et al[54] reported improved symptoms in 50% to 90% of women in several small studies undergoing UAE followed for 1 or more years. Use of MgFUS resulted in a 25% to 66% reduction in bleeding over 12 months in women with adenomyosis. Hysterectomy remains definitive therapy for women failing medical treatments.

Leiomyoma

Leiomyomas (also called myomas or fibroids) are benign monoclonal tumors arising from smooth muscle cells of the myometrium that develop during the reproductive years. They are the most common pelvic tumors, with an estimated lifetime prevalence of 70% in white women and more than 80% in black women. [55]

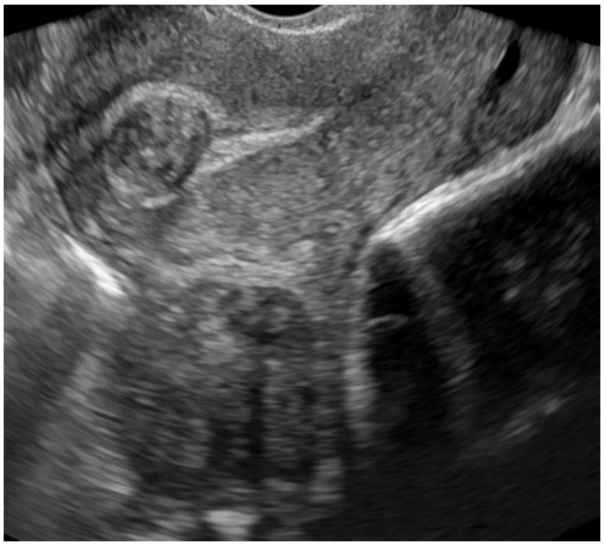

Figure 9. Uterine leiomyoma, intrauterine and subserosal-posterior uterus, by transvaginal pelvic ultrasound

Risk factors for developing leiomyomas include African American race, early menarche, early oral contraceptive use, low parity, obesity, diet (increased consumption of meats, increased glycemic index or load, consumption of alcohol), hypertension, and family history. Symptoms include painful menses or HMB and bulk-related symptoms such as pelvic pressure, urinary frequency, bowel symptoms, or reproductive dysfunction (infertility or obstetrical complications such as adverse outcomes related to leiomyoma location).[55]

Clinical diagnosis may be based on results of pelvic examination (although normal findings do not exclude the presence of submucosal leiomyoma as a cause of AUB), with pelvic ultrasound as the standard confirmatory test. The FIGO classification of leiomyoma location helps define the relationship of leiomyomas in reference to the endometrium or the visceral peritoneum (serosal layer) (Figure 9). Submucous (subendometrial) or types 0, 1, and 2 leiomyomas can be diagnosed by using either SIS or hysteroscopy. [56] In addition, MRI can show the relationship of leiomyomas to both the endometrium and the visceral peritoneum. The use of gadolinium can identify devascularized (degenerated) leiomyomas, and MRI can also be used to determine whether uterine-sparing treatments are an option. Although MRI may demonstrate features concerning for leiomyosarcoma, no preoperative testing can definitively rule out this rare malignancy. [55]

The many treatment options for leiomyomas can help individualize therapy to symptoms. Asymptomatic leiomyomas usually do not need to be treated, except in some cases associated with fertility treatments. When HMB is the only symptom, medical therapies may be highly effective, including tranexamic acid, nonsteroidal anti-inflammatory drugs (NSAIDs), contraceptive hormones, danazol, GnRH agonists, aromatase inhibitors, SERMs, and SPRMs. In a review by Talaulikar, tranexamic acid reduced bleeding by 30% to 60%, and the LNG IUS significantly decreased bleeding while increasing ferritin and hematocrit levels. [57]

A uterus with leiomyomas is at increased risk for expulsion of the LNG IUS, and the LNG IUS may be challenging to place in women with larger leiomyomas. The GnRH agonists can be used preoperatively to reduce leiomyoma volume, correct anemia, and reduce intraoperative blood loss. A review of SPRMs shows them to be beneficial for improving quality of life, decreasing HMB, and creating amenorrhea, but they are not available in the United States currently for leiomyomas. For submucous leiomyomas, hysteroscopic myomectomy may be the best therapeutic option for AUB. Endometrial ablation can be performed in women with leiomyomas who have a normal uterine cavity or in conjunction with hysteroscopic myomectomy to reduce HMB; ablation is reserved for women who have completed childbearing. [44]

For women with bulk symptoms with or without HMB, the goal is to decrease bleeding and shrink leiomyomas. Uterine-sparing options include myomectomy, UAE, MgFUS, or laparoscopic radiofrequency ablation. All of these treatment options have been shown to improve symptoms. In comparing treatments, reintervention risk after 36 months was 1.2% for abdominal myomectomy, 7.4% for UAE, 34.7% for high intensity focused ultrasound (includes both MRI and ultrasound guided), and 3.2% for hysteroscopic myomectomy. Oral SPRMs seem to be promising as medical therapy that lowers bleeding and decreases leiomyoma size; 1 SPRM is available outside of the United States. [58] Additional long-term medical treatments are anticipated in the future. Hysterectomy remains the treatment for leiomyoma symptoms after childbearing is completed and when other options fail.

Malignancy and Premalignant

Conditions Malignancy of the vagina or uterus (including the cervix) can cause abnormal bleeding. Thus, it is important to discern the etiology of any AUB through examination of the vulva, vagina, and cervix with Pap test screening or tissue sampling, as indicated by the American College of Obstetricians and Gynecologists guidelines. In older premenopausal and menopausal women, AUB may be secondary to EIN (subtype: simple or benign hyperplasia vs [the more worrisome] subtype: atypical hyperplasia with progression to or concurrent with endometrial malignancy). [59] Fortunately, 70% of cases are found at an early stage given that most women (75%- 90%) with malignancy present with AUB. Endometrioid (adenocarcinoma) is the most common type of malignancy; papillary serous, clear

cell, mucinous, and carcinosarcoma are rarer but more aggressive endometrial cancers. The risks for EIN and malignancy include unopposed estrogen with an intact uterus, obesity, diabetes mellitus, hypertension, nulliparity, and tamoxifen use.[60] Women with Lynch syndrome have a 27% to 71% lifetime risk of endometrial cancer and, thus, require close endometrial surveillance until risk-reducing hysterectomy.

The American College of Obstetricians and Gynecologists recommends that all women with AUB older than 45 years and women younger than 45 years who have additional risk factors for EIN undergo endometrial sampling. [61] The sensitivity for endometrial cancer by endometrial sampling using the Pipelle device in premenopausal women is 91%, and the sensitivity for diagnosis of EIN (subtype: atypical endometrial hyperplasia) is 81%. In a systematic review of hysteroscopy for the diagnosis of endometrial cancer, sensitivity was 86% and specificity was 99%; in the diagnosis of EIN, sensitivity was 78% and specificity was 96%. Endometrial intraepithelial neoplasia (subtype: benign hyperplasia without atypia) can be treated with oral progestins or LNG IUS and followed with endometrial surveillance; EIN (subtype: atypical) and endometrial malignancy are best treated with hysterectomy.[59]

Coagulopathy

Inherited bleeding disorders, especially von Willebrand disease (vWF), are identifiable in 5% to 24% of women with HMB. Coagulopathy should be considered in women with heavy, prolonged menses from an early reproductive age; a history of frequent bruising, epistaxis, gum/dental bleeding, postpartum hemorrhage, and severe surgical bleeding; and a family history of these issues. Heavy menses may be seen with factor deficiencies (factors VIII and IX are most common, factors VII and XI are less frequent) and platelet disorders. An acquired coagulopathy should be considered in the setting of leukemia, aplastic anemia, renal or liver disease/failure, sepsis, and disseminated intravascular coagulopathy and in women taking drugs that affect coagulation or platelet function, such as NSAIDs and herbal remedies, anticoagulants, and chemotherapeutic agents. [62]

Evaluation should begin with a history to assess symptoms and risk factors for a coagulopathy, followed by confirmatory testing. Evaluation for a suspected coagulopathy should begin with a complete blood cell count or platelet count for thrombocytopenia, prothrombin (prothrombin time/international normalized ratio), activated partial thromboplastin time followed by, when indicated, plasma vWF antigen, plasma vWF activity (ristocetin cofactor activity, vWF:RCo and vWF collagen binding), factor VIII, and other factor testing. Inherited coagulopathies and HMB can be treated with factor replacement and desmopressin acetate as well as hormone therapy as follows.40 Medical therapy for acquired coagulopathies with HMB may include intravenous (IV) conjugated equine estrogens (Premarin; Pfizer Inc) 25 mg every 4 to 6 hours for 24 hours, combined oral contraceptives (monophasic continuous pills containing 35 mg of ethinyl estradiol) 3 times daily for 7 days (then daily thereafter), or medroxyprogesterone acetate 20 mg orally 3 times daily for 7 days (then daily for 3 weeks). [63]

Tranexamic acid may be considered for acute AUB using 10 mg/kg IV (maximum of 600 mg per dose) or 1.3 g orally 3 times daily for 5 days. Intrauterine tamponade using a 26F Foley catheter infused with 30 mL of saline solution may control bleeding. In women treated with IV Premarin for HMB, 72% had controlled bleeding; in women taking oral contraceptive pills (OCPs) as above, 88% had controlled bleeding compared with 76% using medroxyprogesterone acetate. For chronic bleeding, NSAIDs, the 52-mg LNG IUS, combined OCPs (monthly or extended cycle), progestin therapy (oral, intramuscular, or subdermal), or tranexamic acid with menses may be useful. When medical therapies fail for coagulopathies, endometrial ablation or hysterectomy may be warranted after childbearing is completed. [64]

Ovulatory Dysfunction

Ovulatory dysfunction includes not ovulating on a regular basis or infrequently, which may lead to amenorrhea but more likely results in irregular bleeding. Anovulation occurs most commonly in the early reproductive years and later perimenopausal years. Episodes of bleeding range from light and infrequent for 2 or more months to episodes of unpredictable and extreme HMB requiring intervention.[21]

When HMB is associated with anovulation, the loss of luteal progesterone results in persistent proliferative endometrium, which seems to be associated with reduced local levels of prostaglandin F2a, a necessary factor for efficient endometrial hemostasis. A different disorder, generally manifesting in the later reproductive years, can occur in ovulatory women: the luteal-out-of-phase event. These women ovulate but recruit follicles early in the luteal phase, resulting in high circulating estradiol levels and associated HMB. Although there is no identifiable cause, ovulatory dysfunction can occur with polycystic ovarian syndrome, obesity, hypothyroidism, hyperprolactinemia, anorexia, extreme exercise, and significant weight loss. In women with AUB consistent with ovulatory dysfunction, evaluation should be directed toward identifying treatable causes, which may include thyroid function testing. Human chorionic gonadotropin, prolactin, and follicle-stimulating hormone testing should be considered for prolonged amenorrhea in younger women. Follicle-stimulating hormone levels can fluctuate daily. In obese women, prolonged amenorrhea due to anovulation and exposure to unopposed endogenous estrogen increases the risk of EIN and endometrial cancer; consideration for endometrial sampling/assessment is important.[59]

Endometrial Disorders

Endometrial disorders are due to primary dysfunction of local endometrial hemostasis.3 Women present with predictable and cyclic menses suggestive of normal ovulation but have HMB. Etiology is not completely defined, but there are likely deficiencies in vasoconstriction (endothelin-1, prostaglandin F2a) and excessive production of plasminogen, leading to accelerated lysis of clot. This latter phenomenon may be improved using tranexamic acid given its antifibrinolytic action. Other therapies for HMB include NSAIDs, oral/ring or patch combined contraceptives (monophasic, monthly, or extended cycle), progestins (oral, intramuscular, subdermal), the 52-mg LNG IUS, and danazol, with surgical interventions such as endometrial ablation or hysterectomy when warranted. [64]

In addition, endometrial inflammation or endometritis may play a role, as seen in Chlamydia trachomatis or ureaplasma

infections. Sources of infection are easily treated after cultures with appropriate antibiotic regimens. [61]

Iatrogenic

The most common iatrogenic causes of AUB are due to hormone therapy such as OCPs or intramuscular, intrauterine, or subdermal contraceptives, which can cause BTB.3 Corticosteroid-related drugs that may cause BTB are GnRH agonists, aromatase inhibitors, SERMS, and SPRMs. Systemic agents (ie, antidepressants) that contribute to disorders of ovulation, such as those that interfere with dopamine metabolism or cause hyperprolactinemia, may also lead to AUB. Anticoagulants (warfarin, heparin, and direct oral anticoagulants) may cause HMB, prolonged menses, and postmenopausal bleeding. Treatment may not be necessary for minor BTB due to hormones. Breakthrough bleeding may initially be seen when estrogen containing OCPs are used in a continuous manner without inert pills taken or in the first 4 to 6 months of OCP or LNG IUS use; only reassurance may be required. Use of the subdermal implant has more associated BTB than other hormonal contraceptives and may improve with low-dose estrogen when not contraindicated (oral estradiol 1 mg daily for 10 days), short-course NSAIDs, or doxycycline 100 mg twice daily for 10 days. [65]

BIBLIOGRAPHY

1. Moschos E, Ashfaq R, McIntire DD, Liriano B, Twickler DM. Saline infusion sonography endometrial sampling compared with endometrial biopsy in diagnosing endometrial pathology. Obstet Gynecol 2009;113:881-7.
2. de Kroon CD, Jansen FW. Saline infusion sonography in women with abnormal uterine bleeding: An update of recent findings. Curr Opin Obstet Gynecol 2006;18:653-7.
3. Ryu J, Kim B, Lee J, Kim S, Lee S. Comparison of transvaginal ultrasonography with hysterosonography as a screening method in patients with abnormal uterine bleeding. Korean J Radiol 2004;5:39-46.
4. Susanna I. An imaging algorithm for evaluation of abnormal uterine bleeding: Does sonohysterogrphy play a role? Menopause 2007;14:823-5.
5. Glanc P, Betel C, LevToaff A. Sonohysterography: Technique and clinical applications. Ultrasound Clin 2008;3:427-31.
6. Khan F, Jamaat S, Al-Jaroudi D. Saline infusion sonohysterography versus hysteroscopy for uterine cavity evaluation. Annals of Saudi medicine. 2011 Jul;31(4):387-92.
7. Daniilidis A, Pantelis A, Dinas K, Tantanasis T, Loufopoulos PD, Angioni S, Carcea F. Indications of diagnostic hysteroscopy, a brief review of the literature. Gynecological Surgery. 2012 Feb 1;9(1):23-8.
8. Draz MH, El-Sabaa TM, El Shorbagy SH. Saline infusion sonography versus hysteroscopy in the evaluation of uterine cavity in women with unexplained infertility. Tanta Medical Journal. 2017 Jul 1;45(3):155.
9. Sue W, Sarah SB. Radiological appearances of uterine fibroids. The Indian journal of radiology & imaging. 2009 Aug;19(3):222.
10. Rani RP, Lakshmikantha G. Transvaginal Sonography (TVS) and Saline Infusion Sonohysterography (SIS) in the evaluation of Abnormal Uterine Bleeding (AUB). J Obstet Gynecol India. 2010;60(6):511-5.
11. Goyal AS, Chaudhari SJ, Shrivastava AR, Verma RN. Comparison of transvaginal sonography and saline infusion sonohysterography for the diagnosis of causes of abnormal uterine bleeding: a diagnostic accuracy study. IJRCOG. 2016;5:1566-70.
12. Munro MG, Critchley HO, Broder MS, et al. Disorders FWGoM. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int J Gynaecol Obstet 2011;113:3–13.
13. Fraser IS, Critchley HO, Munro MG, et al. Writing Group for this Menstrual Agreement P. A process designed to lead to international agreement on terminologies and definitions used to describe abnormalities of menstrual bleeding. Fertil Steril 2007;87:466–76.
14. Hallberg L, Hogdahl AM, Nilsson L, et al. Menstrual blood loss – a population study. Variation at different ages and attempts to define normality. Acta Obstet Gynecol Scand 1966;45:320–51.
15. Royal College of Obstetrician and Gynaecologist. http://www.crown-initiative.org 2016.
16. Wamsteker K, Emanuel MH. Transcervical hysteroscopic resection of submucous fibroids for abnormal uterine bleeding: results regarding the degree of intramural extension. Obstetrics and Gynecology. 1993 Nov;82(5):736-40.
17. Bahamondes L, Ali M. Recent advances in managing and understanding menstrual disorders. F1000Prime Rep 2015;7:33.
18. Benjamins LJ. Practice guideline: evaluation and management of abnormal vaginal bleeding in adolescents. J Pediatr Health Care 2009;23:189–93.
19. Bansi-Matharu L National Heavy Menstrual Bleeding (HMB) Audit. HQIP ESQH European National Clinical Registries and Audit Summit April 2012.
20. Palep-Singh M, Prentice A. Epidemiology of abnormal uterine bleeding. Best Pract Res Clin Obstet Gynaecol 2007;21:887–90.
21. Hale GE, Hughes CL, Burger HG, et al. Atypical estradiol secretion and ovulation patterns caused by luteal out-of-phase (LOOP) events underlying irregular ovulatory menstrual cycles in the menopausal transition. Menopause 2009;16:50–9.
22. Munro MG. Classification of menstrual bleeding disorders. Reviews in Endocrine and Metabolic Disorders. 2012 Dec 1;13(4):225-34.
23. Doherty L, Mutlu L, Sinclair D, Taylor H. Uterine fibroids: clinical manifestations and contemporary management. Reproductive sciences. 2014 Sep;21(9):1067-92.
24. Sinclair DC, Mastroyannis A, Taylor HS. Leiomyoma simultaneously impair endometrial BMP-2-mediated decidualization and anticoagulant expression through secretion of TGF-β3. The Journal of Clinical Endocrinology & Metabolism. 2011 Feb 1;96(2):412-21.
25. Van den Bosch T, Ameye L, Van Schoubroeck D, Bourne T, Timmerman D. Intra-cavitary uterine pathology in women with abnormal uterine bleeding: a prospective study of 1220 women. Facts, views & vision in ObGyn. 2015;7(1):17.
26. Hulka CA, Hall DA, McCarthy K, Simeone J. Sonographic findings in patients with adenomyosis: can sonography assist in predicting extent of disease?. American Journal of Roentgenology. 2002 Aug;179(2):379-83.
27. Launonen V, Vierimaa O, Kiuru M, Isola J, Roth S, Pukkala E, Sistonen P, Herva R, Aaltonen LA. Inherited susceptibility to uterine leiomyomas and renal cell cancer. Proceedings of the National Academy of Sciences. 2001 Mar 13;98(6):3387-92.
28. Valentin L. Imaging techniques in the management of abnormal vaginal bleeding in nonpregnant women before and after menopause. Best Pract Res Clin Obstet Gynaecol. 2014;28:637–654
29. FDA. UPDATED Laparascopic Uterine Power Morcellation in Hysterectomy and Myomectpmy: FDA Safety Communication 2014. Available at: http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm424443.htm.
30. Denny L., Quinn M., Hacker N. FIGO Cancer Report 2012. Int J Gynaecol Obstet. 2012;119(Suppl. 2):S89.
31. Kadir RA, Economides DL, Sabin CA, Owens D, Lee CA. Frequency of inherited bleeding disorders in women with menorrhagia. The Lancet. 1998 Feb 14;351(9101):485-9.
32. Kouides PA, Conard J, Peyvandi F, Lukes A, Kadir R. Hemostasis and menstruation: appropriate investigation for underlying

disorders of hemostasis in women with excessive menstrual bleeding. Fertility and sterility. 2005 Nov 1;84(5):1345-51.

33. Critchley HO, Maybin JA. Molecular and cellular causes of abnormal uterine bleeding of endometrial origin. InSeminars in reproductive medicine 2011 Sep (Vol. 29, No. 05, pp. 400-409).

34. Grimbizis GF, Tsolakidis D, Mikos T, et al. A prospective comparison of transvaginal ultrasound, saline infusion sonohysterography, and diagnostic hysteroscopy in the evaluation of endometrial pathology. Fertil Steril. 2010;94(7):2720–2725.

35. Angioni S, Loddo A, Milano F, Piras B, Minerba L, Melis GB. Detection of benign intracavitary lesions in postmenopausal women with abnormal uterine bleeding: a prospective comparative study on outpatient hysteroscopy and blind biopsy. J Minim Invasive Gynecol. 2008;15(1):87–91.

36. van Dongen H, de Kroon CD, Jacobi CE, Trimbos JB, Jansen FW. Diagnostic hysteroscopy in abnormal uterine bleeding: a systematic review and meta-analysis. BJOG. 2007;114(6):664–675.

37. Stankova T, Ganovska A, Stoianova M, Kovachev S. [Complications of diagnostic and operative hysteroscopy – review]. Akush Ginekol. 2015;54(8):21–27.

38. Soguktas S, Cogendez E, Kayatas SE, Asoglu MR, Selcuk S, Ertekin A. Comparison of saline infusion sonohysterography and hysteroscopy in diagnosis of premenopausal women with abnormal uterine bleeding. Eur J Obstet Gynecol Reprod Biol. 2012;161(1):66–70.

39. Cooper NA, Barton PM, Breijer M, et al. Cost-effectiveness of diagnostic strategies for the management of abnormal uterine bleeding (heavy menstrual bleeding and post-menopausal bleeding): a decision analysis. Health Technol Assess. 2014;18(24):1–201, v–vi.

40. Erdem M, Bilgin U, Bozkurt N, Erdem A. Comparison of transvaginal ultrasound and saline infusion sonohysteroscopy in evaluating the endometrial cavity in pre- and postmenopausal women with abnormal uterine bleeding. Menopause 2007;14:846-52.

41. Alfhaily F, Ewies A. The first-line investigation of postmenopausal bleeding: Transvaginal ultrasound scanning and endometrial biopsy may be enough. Int J Gynecol Cancer 2009;19:892-5.

42. Li Ong C. Saline infusion sonohysterography. Ultrasound Clin 2007;2:121-3.

43. Salim R, Lee C, Davies B, Jolaoso E, Ofuasia E, Jurkovic D. A comparative study of three-dimensional saline infusion sonohysterography and diagnostic hysteroscopy for the classification of submucous fibroids. Hum Reprod 2005;20:253-7

44. Li Ong C. Saline infusion sonohysterography. Ultrasound Clin 2007;2:121-3.

45. Hamilton JA, Larson AJ, Lower AM, Hasnain S, Grudzinskas JG. Routine use of saline hysterosonography in 500 consecutive, unselected, infertile women. Hum Reprod 1998;13:2463-73

46. Salim S, Won H, Nesbitt-Hawes E, et al. Diagnosis and management of endometrial polyps: a critical review of the literature. J Minim Invasive Gynecol. 2011;18(5):569-581.

47. Lee SC, Kaunitz AM, Sanchez-Ramos L, Rhatigan RM. The oncogenic potential of endometrial polyps: a systematic review and meta-analysis. Obstet Gynecol. 2010;116(5):1197-1205

48. Ferrazzi E, Zupi E, Leone FP, et al.Howoften are endometrial polyps malignant in asymptomatic postmenopausal women? a multicenter study. Am J Obstet Gynecol. 2009;200(3):235.e1-235.e6.

49. Spiewankiewicz B, Stelmachow J, Sawicki W, Cendrowski K, Ku_zlik R. Hysteroscopy in cases of cervical polyps. Eur J Gynaecol. 2003;24(1):67-69.

50. Levy G, Dehaene A, Laurent M, et al. An update on adenomyosis. Diag Interv Imaging. 2013;94(1):3-25.

51. Benagiano G, Brosens I, Habiba M. Structural and molecular features of the endomyometrium in endometriosis and adenomyosis. Hum Reprod Update. 2014;20(3):386-402.

52. CunninghamRK,HorrowMM,Smith RJ, Springer J.Adenomyosis: a sonographic diagnosis. Radiographics. 2018;38(5):1576-1589.

53. Pontis A, D'Alterio MN, Pirarba S, de Angelis C, Tinelli R, Angioni S. Adenomyosis: a systematic review of medical treatment. Gynecol Endocrinol. 2016;32(9):696-700.

54. Taran FA, Stewart EA, Bruker S. Adenomyosis: epidemiology, risk factors, clinical phenotype and surgical and interventional alternatives to hysterectomy. Geburtshilfe Frauenheilkd. 2013; 73(9):924-931.

55. Stewart EA. Clinical practice: uterine fibroids. N Engl J Med. 2015;372(17):1646-1655.

56. Munro MG. Practical aspects of the two FIGO systems for management of abnormal uterine bleeding in the reproductive years. Best Pract Res Clin Obstet Gynaecol. 2017;40:3-22.

57. Sinai Talaulikar V. Medical therapy for fibroids: an overview. Best Pract Res Clin Obstet Gynaecol. 2018;46:48-56.

58. Murji A, Whitaker L, Chow TL, Sobel ML. Selective progesterone modulators (SPRMs) for uterine fibroids. Cochrane Database Sys Rev. 2017;4:CD010770.

59. Practice Bulletin No. 149: endometrial cancer. Obstet Gynecol. 2015;125(4):1006-1026.

60. American Cancer Society. Key statistics for endometrial cancer. http://www.cancer.org/cancer/endometrial-cancer/about/keystatistics. html. Accessed January 5, 2019.

61. Committee on Practice BulletinseGynecology. Practice bulletin no. 128: diagnosis of abnormal uterine bleeding in reproductiveaged women. Obstet Gynecol. 2012;120(1):197-206.

62. Shankar M, Lee CA, Sabin CA, Economides DL, Kadir RA. Von Willebrand disease in women with menorrhagia: a systematic review. Br J Obstet Gynaecol. 2004;111(7):734-740.

63. Munro MG, Mainor N, Basu R, Brisinger M, Barreda L. Oral medroxyprogesterone acetate and combination oral contraceptives for acute uterine bleeding: a randomized controlled trial. Obstet Gynecol. 2006;108(4):924-929.

64. American College of Obstetricians and Gynecologists. ACOG committee opinion no. 557: management of acute abnormal bleeding in nonpregnant reproductive-aged women. Obstet Gynecol. 2013;121(4):891-896.

65. Curtis KM, Jatlaoui TC, Tepper NK, et al. U.S. selected practice recommendations for contraceptive use, 2016. MMWR Recomm Rep. 2016;65(4):1-66.