Diagnosing Abnormal Uterine Bleeding: The Standard of Care Has Changed

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9.1 Introduction

Abnormal uterine bleeding (AUB) is a common gynecologic complaint which accounts for one-third of the outpatient visits to gynecologists and represents more than 70% of all gynecological consults in the perimenopausal and postmenopausal years [1]. A US population-based survey of women ages 18–50 years reported an annual prevalence rate of AUB as 53 per 1000 women [2]. The estimated annual direct cost of AUB in 2007 was approximately $1 billion, with indirect economic costs of $12 billion [3]. The overwhelming problem of AUB is due to its tremendous impact on women's quality of life, productivity, and utilization of healthcare services, and thus diagnosis and treatment of this condition needs to be undertaken judiciously. Therefore, it should be clear that evaluation of patients with AUB aims (1) to exclude serious underlying pathology such as carcinoma or complex atypical endometrial hyperplasia and (2) to diagnose the cause of bleeding so an appropriate management can be implemented.

9.2 Etiology

The definition of AUB is "flow outside of normal volume, duration, regularity, or frequency" [1]. AUB can be caused by uterine structural abnormalities or nonstructural causes. In 2011 the International Federation of Gynecology and Obstetrics (FIGO) introduced a new classification system for abnormal uterine bleeding that was endorsed by the American Congress of Obstetrics and Gynecology in 2012, as

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an effort to standardize the terminology used to describe AUB, and eventually this system has now become widely accepted [4]. This system, known by the acronym PALM-COEIN, distinguishes abnormal uterine bleeding based upon the suspected etiology: *p*olyp, *a*denomyosis, *l*eiomyoma, *m*alignancy and *h*yperplasia, *c*oagulopathy, *o*vulatory dysfunction, *e*ndometrial, *i*atrogenic, and *n*ot yet classified [4]. The PALM portion of the PALM-COEIN covers the structural causes of abnormal uterine bleeding. In contrast, the COEIN acronym represents the nonstructural, hormonal, or systemic causes of abnormal uterine bleeding.

Descriptive terms are paired with AUB to indicate the bleeding patterns. Heavy menstrual bleeding (AUB/HMB) is now used instead of the term menorrhagia, and intermenstrual bleeding (AUB/IMB) has replaced the term metrorrhagia [1]. AUB is further denoted by the qualified letter or letters to indicate the underlying etiology such as AUB-P for AUB-polyp, AUB-L for AUB-leiomyoma, etc. Leiomyomas may be subclassified as either submucosal (AUB-L_{SM}) or those that do not affect the uterine cavity (AUB-L_O). Abnormal bleeding associated with the use of exogenous steroids (i.e., hormonal treatments), intrauterine systems (IUSs) or devices, or other systemic or local agents is classified as iatrogenic, whereas the remainder of rare or ill-defined causes is categorized as not yet classified. Ovulatory dysfunction (AUB-O) is usually related to exposure to unopposed estrogen by different mechanisms such as PCOS or oligo-ovulation which is common in the perimenopausal years.

The term dysfunctional uterine bleeding is usually used to indicate AUB which is caused by nonstructural abnormalities, and it is not a part of the PALM-COEIN, so the American Congress of Obstetrics and Gynecology recommended to discontinue using this term [1].

9.3 Premenopausal and Perimenopausal Women

AUB most frequently occurs in women aged 19–39 as a result of pregnancy, structural abnormalities such as leiomyoma and polyps, anovulatory cycles (e.g., PCOS (polycystic ovarian syndrome)), hormonal contraceptive, and endometrial hyperplasia [1]. Endometrial carcinoma is less common at this age group, but it may occur [5]. In women aged 40 years to menopause, AUB is most likely due to anovulatory bleeding, as a result of the exhaustion of the functioning ovarian follicles. It also may be due to endometrial hyperplasia or carcinoma, endometrial atrophy, and leiomyomas [1].

9.4 Postmenopausal Bleeding

Postmenopausal bleeding (PMB) is defined by any uterine bleeding in a menopausal woman who is not taking cycling postmenopausal hormone therapy. It represents 5% of office gynecology visits [6]. Even though, the most common cause of PMB is atrophy of the vaginal mucosa or endometrium [7], and in clinical practice, only 3–7% of women presenting with PMB will ultimately be found to have cancer; all women with PMB should be evaluated for endometrial cancer. Endometrial cancer is

the most common type of gynecological cancer in the United States. In 2017, the incidence of uterine cancer was estimated as 61,380 cases, with a mortality of 10,920 cases [8]. Most cases of uterine cancer occur in the endometrium and have been reported to represent 92% of cases [8]. Additionally, vaginal bleeding is the presenting sign in more than 90% of postmenopausal women with endometrial cancer [9].

9.5 Diagnosis in Women Presenting with Abnormal Uterine Bleeding

The evaluation of women with AUB includes a through medical history and physical exam and appropriate laboratory and imaging tests as indicated. A medical history should be guided by the PALM-COEIN system and include inquiries about the menstrual bleeding pattern, the amount, the presence of pain, any family history of AUB or underlying bleeding disorders, medication or herbal preparations that might affect bleeding in general such as ginseng, ginkgo, motherwort, contraceptives, nonsteroidal anti-inflammatory drugs (NSAIDs), and warfarin or heparin derivatives [10, 11]. One of the most important aspects of the medical history will be careful assessment of the bleeding pattern, although, admittedly, many women will not be aware of exactly how often or how long they bleed. However, when possible, for instance, very cyclic heavy menstrual bleeding without any intermenstrual bleeding would be unlikely to be carcinoma or even hyperplasia. Most often, an irregular bleeding pattern is not associated with any structural abnormality as mentioned above but clearly one must be excluded.

The physical examination may also reveal findings that contribute to AUB. Physical signs suggestive of an underlying cause include excessive weight, hyperprolactinemia (galactorrhea), signs of polycystic ovaries syndrome PCOS (e.g., acne, hirsutism), signs of thyroid disease (e.g., thyroid nodule or goiter), and signs of bleeding disorders (e.g., ecchymosis and petechiae). Additionally, a pelvic exam using a speculum should be performed to exclude lower genital tract causes as cervical or vaginal etiologies of bleeding, and bimanual assessment of size and contour of the uterus should be performed as well.

Laboratory testing should be ordered depending on the patient's history and physical examination. In general, the initial laboratory assessment of AUB should include complete blood count (CBC) to ascertain whether anemia is present, in attempt to assess the severity of bleeding, pregnancy testing, as well as assessment of underlying bleeding disorders if concerning or suspected. Thyroid-stimulating hormone (TSH) level assessment and cervical cancer screening may also be appropriate. In some cases, testing for *Chlamydia trachomatis* may also be necessary to rule out AUB associated with infection.

Uterine evaluation for AUB may also include endometrial biopsy and imaging studies when indicated. The best initial imaging test of the uterus to assess AUB is transvaginal ultrasound (TVU). If transvaginal ultrasound images are not adequate or further evaluation is required, then sonohysterography which is also called saline infusion sonography SIS (the installation of fluid or gel into the endometrial cavity

to further delineate endometrial anatomy) or hysteroscopy is recommended. Hysteroscopy is more expensive, requires more anesthesia, and, if performed, is preferably done in an office setting [1]. Newer disposable hysteroscopy, recently developed, makes this recommendation easier to follow.

One study of 443 women [9] used transvaginal ultrasound and saline infusion sonohysterography as the first step in triage reported 79% of women between 35 years old and menopause with AUB had no anatomic pathology, presumably secondary to anovulatory bleeding. Some, whose AUB is heavy menstrual bleeding, may have an enlarged cavity with increased surface area due to increasing parity, uterine hypertrophy secondary to leiomyoma with no submucous component, or adenomyosis without endometrial abnormality. In that study, endometrial abnormalities included hyperplasia, polyps, and submucous myomas.

9.6 Endometrial Sampling

As stated in ACOG 2012, the current recommendation is that endometrial sampling should be the first-line test for tissue sampling in patients presenting with AUB who are older than 45 years. Additionally, it should be also done in patients who are younger than 45 years, in the case there is a history of unopposed estrogen exposure commonly seen in obesity and PCOS patients, or failed medical management, or persistent AUB or those who have any irregularity in the appearance of endometrium on TVU, and in women at high risk of endometrial cancer (e.g., tamoxifen therapy, Lynch or Cowden syndrome) [1].

Choosing 45 years of age as the cutoff point for increased concern regarding endometrial neoplasia is supported by evidence that the risk of endometrial hyperplasia and carcinoma is quite low prior to age 45 years and increases with advancing age, as the incidence rate of 16.3% was reported in women aged 45–54 years compared with an incidence rate of 5.4% in those aged 35–44 years [12, 13].

In postmenopausal women, the endometrial evaluation is essential in triaging patients to no anatomic pathology or anatomic pathology and then, furthermore, whether such pathology is focal in nature and needs to be distinguished from more global processes. Historically, this is used to utilize dilatation and curettage as the primary diagnostic test. In fact, it was the most common surgical procedure in women during much of the twentieth century. More recently, endometrial biopsy in an outpatient setting has gained great regularity. The aim of such endometrial sampling was expected to diagnose the presence of carcinoma or premalignant lesion.

After a single study by Stovall and colleagues [14], blind endometrial sampling with disposable suction piston devices became the standard approach to patients with AUB. Stovall performed such an outpatient biopsy on 40 patients with known carcinoma in the week prior to their hysterectomy and obtained endometrial carcinoma in 39 of the 40 samples, thus reporting a 97.5% accuracy. This was widely publicized, marketed, and promoted and was rapidly accepted as "standard of care." In a similar study, Guido and colleagues performed such blind endometrial sampling in 65 patients with known carcinoma in the operating room just prior to their

hysterectomy [15]. They missed 11/65 cancers (sensitivity only 83%) but, upon opening all those uteri, they reported that, when the cancers occupied 50% or more of the endometrial surface, the biopsy was 100% accurate. Others did similar studies to those of Stovall and Guido.

In women with known carcinomas, the sensitivity of blind sampling was only 84% [16] and 68% [17] in those studies, yielding a false-negative rate of 16% and 32%, respectively! And again, these were blind biopsies done on women with known carcinoma. In trying to understand why such biopsies failed in non-global pathology, one needs to look no further than the pre-hysterectomy study by Rodriguez and colleagues [18] in which the Pipelle brand sampled an average of 4% of the endometrial surface area (range 0–12%). All the previous data were as a red flag of using blind sampling as the standard care.

Finally, in 2012, the American College of Obstetricians and Gynecologists (ACOG), in their Practice Bulletin [1], acknowledged "the primary role of endometrial sampling in patients with AUB is to determine if carcinoma or premalignant lesions are present." The Bulletin goes on to state that endometrial biopsy has "high overall accuracy in diagnosing endometrial cancer when an adequate specimen is obtained and when the endometrial process is global. If the cancer occupies less than 50% of the surface area of the endometrial cavity, the cancer can be missed by blind endometrial biopsy. Therefore, these tests are only an endpoint when they reveal cancer or atypical complex hyperplasia." This has tremendous ramifications for clinical practice. Certainly, healthcare providers, especially in low-resource areas, can begin the evaluation with a blind biopsy, but if the results do not indicate cancer or atypical hyperplasia, the evaluation is not adequate and cannot be accepted as an endpoint, especially if bleeding persists, so further testing becomes necessary [8]. Thus, the concept of distinguishing "global" from "focal" pathologies by using SIS is becoming increasingly utilized.

To conclude, the biopsy shortcomings and ACOG acknowledgment of this non-trivial problem represent a major shift in how blind endometrial sampling should be reviewed and has led to a fundamental change in the standard care of AUB patients.

9.7 Imaging Techniques

The decision to proceed with imaging technique should be based on the medical history, physical exam, patient's age, and the clinician's assessment.

9.7.1 Transvaginal Ultrasonography (TVU)

TVU is the best initial imaging study in women presenting with AUB, as it is a safe and cost-effective method of diagnosing structural causes of abnormal uterine bleeding by exploring the uterine cavity, so it is a substantial diagnostic tool to exclude the PALM portion of the PALM-COEIN system. The vaginal probe provides a degree of image magnification as if we were doing ultrasound through a

low-power microscope and can be considered a form of "sonomicroscopy" [19]. The use of TVU in the assessment of endometrial thickness is not an optimal tool to assess abnormalities in premenopausal woman as compared to its use in exclusion of malignancy in postmenopausal [20–22]. Endometrial thickness varies during the menstrual cycle as a result of the dynamic hormonal changes, leading to a limited application of endometrial thickness as a diagnostic tool in *premenopausal* women.

There are insufficient data collected on *perimenopause* women with AUB. Perimenopause is defined as "the period around the onset of menopause that is often marked by various physical signs such as hot flushes and menstrual irregularities" [23]. One potential pitfall in perimenopause women is that their cycling of the endometrium is dependent on erratic estrogen production of perimenopausal ovaries. Thus, the use of TVU in such patients must be timed to the end of bleeding episode when the endometrial echo will be as thin as one would expect throughout the whole month. Additionally, this prevents misinterpretation of endometrial "moguls," which can occur because of the heterogeneity of the topography of the endometrium's functionalis as it proliferates.

In a study of 433 perimenopausal patients [24] aged 37–54, 10.2% required sonohysterography because the unenhanced transvaginal ultrasound done at the end of a bleeding cycle was inadequate effectively to characterize and measure the endometrium.

In postmenopausal women, the earliest reports comparing transvaginal ultrasound (TVU) with endometrial sampling in women with PMB consistently showed an endometrial thickness 4–5 mm or less reliably excluded endometrial cancer [25]. Since that time, a number of confirmatory multicenter studies have been performed. Accordingly, ACOG in 2009 stated that when TVU reveals a thin, distinct endometrial echo 4 mm or less, the risk of malignancy is 1 in 917, and therefore, endometrial sampling is not required [26]. When the endometrial thickness is less than 4 mm there was a greater than 99% negative predictive value for endometrial cancer [8]. Thus, the initial evaluation of women with PMB may begin with a TVU, and if sufficiently distinct and thin, no further workup is necessary. In fact, if one does attempt endometrial sampling in such women, often no tissue is present, and if present, it is often insufficient for histologic evaluation [26]. Since rarely cases of endometrial carcinoma, particularly type II cancers, can present with an endometrial thickness of less than 4 mm, in cases of persistent or recurrent uterine bleeding, furthermore extensive evaluation irrespective of the endometrial thickness is indicated [8].

Additionally, an endometrial thickness greater than 4 mm that is incidentally diagnosed in postmenopausal women without bleeding should not prompt automatic further evaluation, unless the clinician's assessment is concerning for other cancer risk factors [8].

9.7.1.1 Limitation of TVU

Unfortunately, the main drawbacks of using TVU are the low sensitivity and specificity for assessing the intracavity lesions as they were reported as only 56% and 73%, respectively [27]. In addition, transvaginal ultrasound does not adequately

image the endometrial cavity in all women with PMB. An axial uterus, obesity, coexisting myomas, adenomyosis, or previous uterine surgery can preclude satisfactory endometrial evaluation. Failure to adequately identify a thin, distinct endometrial echo in a postmenopausal woman with bleeding should trigger an alternative method of evaluation.

9.7.2 Sonohysterography (Saline Infusion Sonography (SIS))

Saline infusion sonography (SIS) is a very useful adjunct to the traditional TVU. As stated in ACOG 2012, when TVU is insufficient in cases of endometrial echo not sufficiently thin to exclude pathology or the endometrial thickness is inadequately visualized (as previously mentioned in cases of axial uterus, marked obesity, coexisting myomas, previous surgery, or adenomyosis), then SIS or hysteroscopy, preferably in an office setting, can be employed [1]. Many studies [27, 28] have concluded that SIS is a more valuable tool than TVU to assess the intracavity lesions such as polyps and submucosal leiomyoma.

Saline infusion sonohysterography involves instillation of a small amount of saline through a special catheter under ultrasound guidance. By distending the endometrial cavity, SIS highlights the endometrial contents, revealing causes of AUB/PMB, including endometrial polyps, intracavitary (submucosal) fibroids, and focal endometrial abnormalities more concerning for hyperplasias or carcinoma. A sonohysterogram demonstrating uniformly smooth endometrial surfaces without intracavitary masses provides reassurance that organic pathology is not present.

Only SIS can differentiate between focal and global thickening of the endometrium. A localized thickening of the endometrium is considered an obstacle to obtain an adequate endometrial sampling with blind biopsy. Therefore, using SIS can be a turning point in the decision of performing an endometrial biopsy under direct vision of hysteroscopy in cases of focal endometrial thickening or obtaining a blind endometrial biopsy which is ultimately appropriate for the cases of global endometrial thickening.

One study [27] compared the accuracy of several diagnostic modalities in the evaluation of AUB case showed that the effectiveness of using SIS is not inferior than performing hysteroscopy in detecting structural abnormalities. “Some data suggested that three-dimensional SIS is more accurate than two-dimensional SIS in determining the size and depth of myometrium invasion of submucosal leiomyoma, which may help predict the success of hysteroscopic resection” [1].

SIS should not be done during active bleeding which may produce false-positive results, as shedding endometrial lining and small clots clinging to the wall may appear similar to other intrauterine pathology such as endometrial polyps. If the patient is bleeding so heavily or so often that it is difficult to achieve the correct timing, it may be beneficial to perform a “medical curettage” with progestin inducing a withdrawal bleed and then timing the ultrasound evaluation to that bleeding episode. An alternative to SIS involves using new disposable office hysteroscopes that facilitate direct endometrial visualization in the office setting.

9.7.3 Hysteroscopy

Hysteroscopy is a technique that allows direct visualization of the uterine cavity and taking directed biopsies by placing a thin endoscopic instrument through the cervix into the uterus [29]. It shows high accuracy in detecting endometrial cancer, but it has a limited use in diagnosing endometrial hyperplasia [30].

9.7.4 Magnetic Resonance Imaging (MRI)

There is no indication for routine use of MRI in evaluation of AUB cases. It can be used as a tool to guide the treatment of cases of multiple myomas, especially when the uterus is diffusely enlarged. However, the benefit-cost ratio has to be weighed when considering its use.

9.8 Summary

Abnormal uterine bleeding (AUB) is a common gynecologic problem. A prompt diagnosis and evaluation of patients presenting with AUB aims to exclude serious underlying pathology such as carcinoma and to diagnose the cause of bleeding, so an appropriate management can be implemented. The standard of care of patients with AUB has changed due to the results of many studies that showed that blind uterine biopsy can often have a high false-negative rate which can be explained by the presence of focal versus global endometrial findings. Endometrial cancer can be misdiagnosed by the blind uterine sampling if it does not occupy more than 50% of the endometrial thickness. In 2012, ACOG acknowledged this nontrivial problem and recommended that blind endometrial biopsy cannot be an endpoint unless it shows cancer or endometrial complex atypical hyperplasia, especially if bleeding persists, so a further testing such as saline infusion sonohysterography or hysteroscopy, preferably in an office setting, is an appropriate choice. Blind endometrial sampling still remains the first-line test for endometrial in patients presenting with AUB who are older than 45 years of age or those patients who are younger with concerning risk factors for endometrial hyperplasia or cancer, keeping in mind the limitations of such blind sampling when negative, especially in cases of persistent bleeding.

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