



www.figo.org

Contents lists available at ScienceDirect

International Journal of Gynecology and Obstetrics

journal homepage: www.elsevier.com/locate/ijgo



SPECIAL COMMUNICATION

FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age

Malcolm G. Munro^{a,b,*}, Hilary O.D. Critchley^c, Michael S. Broder^d, Ian S. Fraser^e; for the FIGO Working Group on Menstrual Disorders^a Department of Obstetrics and Gynecology, University of California, Los Angeles, USA^b Kaiser Permanente, Los Angeles Medical Center, Los Angeles, USA^c Centre for Reproductive Biology, University of Edinburgh, Queen's Medical Research Institute, Edinburgh, UK^d Partnership for Health Analytic Research, Beverly Hills, USA^e University of Sydney, Queen Elizabeth II Research Institute for Mothers and Infants, Sydney, Australia

ARTICLE INFO

Article history:

Received 27 November 2010

Accepted 7 January 2011

Keywords:

Abnormal uterine bleeding

Causes

Classification

Investigations

Terminologies

ABSTRACT

There is general inconsistency in the nomenclature used to describe abnormal uterine bleeding (AUB), in addition to a plethora of potential causes—several of which may coexist in a given individual. It seems clear that the development of consistent and universally accepted nomenclature is a step toward rectifying this unsatisfactory circumstance. Another requirement is the development of a classification system, on several levels, for the causes of AUB, which can be used by clinicians, investigators, and even patients to facilitate communication, clinical care, and research. This manuscript describes an ongoing process designed to achieve these goals, and presents for consideration the PALM-COEIN (**p**oly; **a**denomyosis; **l**eiomyoma; **m**alignancy and hyperplasia; **c**oagulopathy; **o**vulatory dysfunction; **e**ndometrial; **i**atrogenic; and **n**ot yet classified) classification system for AUB, which has been approved by the International Federation of Gynecology and Obstetrics (FIGO) Executive Board as a FIGO classification system.

© 2011 Published by Elsevier Ireland Ltd. on behalf of International Federation of Gynecology and Obstetrics.

1. Introduction

The investigation and management of abnormal uterine bleeding (AUB) among nongravid women of reproductive age has been hampered both by confusing and inconsistently applied nomenclature and by the lack of standardized methods for investigation and categorization of the various potential etiologies [1,2]. These deficiencies hamper the ability of investigators to study homogenous populations of patients experiencing AUB, and make it difficult to compare studies performed by different investigators or research groups. The investigative leverage provided by meta-analysis is undermined and, in some instances, made counterproductive because inaccurate conclusions may result. Consequently, a universally accepted system of nomenclature and classification seems a necessary step in the evolution of collaborative research and evidence-based application of results to clinical practice. The development of such a system is made somewhat more complex by the fact that a variety of potential causes may coexist in a given individual and because many definable entities that often contribute to, or cause, AUB are frequently asymptomatic. As a result, to be clinically reliable, the design of any AUB classification system must take this into consideration.

Experience with universal nomenclature and classification systems in the gynecologic specialty is mixed. For more than 85 years, cancer of the genital tract has been classified and staged according to what are now the International Federation of Gynecology and Obstetrics (FIGO) oncology staging systems. The systems are practical, universally accepted, and aid clinicians and investigators in the guidance of research, treatment, and prognostication [3]. Where necessary, they are modified by a standing committee that follows evidence-based principles and meets regularly. By contrast, the American Society for Reproductive Medicine (ASRM) staging system for endometriosis has been less successful [4]. This system, which uses laparoscopy-based visual assessment of disease extent, is hampered by complexity, the need for surgical assessment, and the lack of any consistent relationship among visual staging of disease and symptoms, appropriate treatment, and clinical outcome. Another system that has met with mixed review is the pelvic organ prolapse quantification system of pelvic floor defects, which seems to have clinical relevance but also a level of complexity that makes it difficult for most clinicians to use in practice [5]. As a result of these deliberations, it would seem important to develop a nomenclature and classification system that fits research/educational requirements and clinical needs, but is also practicable.

The present report, which includes contributions from an international group of clinician–investigators from 6 continents and over 17 countries, proposes a new system for the classification of AUB. A

* Corresponding author. Department of Obstetrics and Gynecology, Kaiser Permanente, Los Angeles Medical Center, 4900 Sunset Boulevard, Station 3-B, Los Angeles, CA 90027, USA. Tel.: +1 323 783 4211; fax: +1 818 474 7241.

E-mail address: mmunro@ucla.edu (M.G. Munro).

system for symptom nomenclature has been described in previous publications reporting the deliberations of this group [6,7].

2. Methods

This multistage development process was part of the methodology described for menstrual symptom nomenclature using a modification of the RAND/UCLA Delphi process, which is a nominal group process designed to elicit opinion about a clearly defined topic [8,9]. A group of panelists is presented with a series of items, which they rate anonymously and independently using a numerical scale. The aggregate ratings are then shared with the entire group and re-rated at an in-person meeting. After discussion, the panelists re-rate each item. The process has been used extensively to develop clinical guidelines, and guidelines developed in this way have been found to be both reliable and associated with improvements in clinical outcome [10].

The goal of our panel was to develop an agreed pragmatic classification system with a standardized nomenclature to be used worldwide by researchers and clinicians investigating and treating women of reproductive age with AUB. The panelists were selected to represent the international community of gynecologists, reproductive endocrinologists, and other clinicians and researchers—with a particular emphasis on including participants from low-income as well as high-income countries. Gynecologists in full-time clinical practice, together with those with both a primary clinical and a research orientation, were involved.

We began by developing a conceptual model of the elements necessary to diagnose AUB and then created a survey to elicit panelists' beliefs about classification. The survey also asked panelists to rate a variety of assessment tools and techniques for evaluating the cause of AUB. The panel was asked to complete the survey before the first face-to-face meeting. Results were tabulated as the proportion of respondents giving a particular answer and as to whether there was "agreement" among respondents. Most items were rated on a 4-point scale, and agreement was defined as at least 80% of respondents rating the item either 1 and 2, or 3 and 4. For example, if the rating scale was 1 = strongly disagree, 2 = disagree, 3 = agree, and 4 = strongly agree, at least 80% of respondents had to give either a "disagree" answer (1 or 2) or an "agree" answer (3 or 4) for there to be agreement on that item. Results were reported as the mean of the responses (e.g. 3.2).

The panelists met in person in Washington, USA, for 2.5 days from February 26 to 28, 2005, to discuss the survey results and work toward an internationally based agreement on the classification of diagnoses related to AUB. The aggregate survey responses were reviewed in a plenary session of all meeting participants, and again in small groups dedicated to particular aspects of classification and terminology.

After extensive discussion, the small groups identified areas of agreement and disagreement, which were used to create new survey questions. These modified surveys were then administered—using electronic voting—to all participants during a plenary session. In this second round of ratings, 2 levels of agreement were identified. Panelists were considered to have agreed on an item if ratings met the original criteria ($\geq 80\%$ of answers were either 1 and 2, or 3 and 4). Panelists were considered to have unanimously agreed if all rated an item either 1 and 2, or 3 and 4 (e.g. 100% of respondents selected either 4 [strongly agree] or 3 [agree]). Following the in-person meeting, the Scientific Committee of the group merged and refined the components into a unified system, then distributed the draft to the members of the entire group for comment and approval. Contentious issues were further addressed via another short Delphi-type questionnaire. A draft system was developed and revised, distributed for comments, then discussed at a face-to-face meeting held in association with the 2009 FIGO World Congress in Cape Town, South Africa. Following minor modifications, the system was presented to a group of over 700 FIGO attendees, 250 of whom had

anonymous keypad response systems with which to provide feedback. A preliminary version of the system was included in the book *Abnormal Uterine Bleeding* [11].

Throughout the process, the concept was the creation of a "living" document, together with a system of periodic analysis and appropriate modification/revision.

3. Results

3.1. Results of the rating process

The results of the nomenclature development process have been published elsewhere [6,7]. The group agreed that AUB was not restricted to just menstrual bleeding that was abnormally heavy, but also included bleeding that was abnormal in timing (27/28 [96.4% agreement])—a feature that was felt to be necessary for inclusion in the classification system.

There was near unanimity among participants in agreeing that the term "dysfunctional uterine bleeding (DUB)" should be discarded (29/31 [93.5%]). There was general agreement that abnormalities of bleeding associated with pathology of the lower reproductive tract that could be defined as "abnormal reproductive tract bleeding" but which were not within the domain of AUB would not be included in the classification system (26/30 [86.7%]).

In Cape Town, 215/237 (90.7%) respondents agreed that "AUB" was a suitable overarching term for the symptom of disturbed menstrual bleeding, and 96/141 (68.1%) and 171/223 (76.7%), respectively, supported proposals that the terms "menorrhagia" and "DUB" be discarded. Finally, 198/237 (83.5%) agreed that the term "heavy menstrual bleeding (HMB)" should replace the term "menorrhagia" for the symptom of excess menstrual bleeding.

Members of the group determined that the following general sources of bleeding should be considered in the classification system: (1) primary disorders of the endometrium that most often manifest as disturbances of local endometrial hemostasis, but which may also include other entities such as altered vasculogenesis or abnormalities in the local inflammatory response; (2) endometrial polyps; (3) leiomyomas (fibroids); (4) adenomyosis; (5) disorders of ovulatory function; (6) systemic disorders of hemostasis that could be called coagulopathies; (7) malignant and premalignant conditions; (8) iatrogenic causes such as gonadal steroid administration; and (9) other local lesions or systemic conditions that may be rare causes of AUB (e.g. arteriovenous malformations and myometrial hypertrophy) or those which may sometimes cause abnormal bleeding (e.g. endometriosis). Detailed stratification of malignant and premalignant diseases and disorders—including endometrial hyperplasia and carcinoma, in addition to sarcomas of the endometrium and myometrium—were felt to be outside the scope of the system, in part because there are existent classification systems for these entities [12,13]. Consequently, they would be referenced in the relevant category, but detail would be left to the appropriate disease-specific classification, grading, or staging system.

The Cape Town audience was polled [14], with 96/141 (68.1%) supporting the proposal that "coagulopathy," "endometrial dysfunction," and "ovulatory disorders" replace the collection of disorders previously encompassed by the discarded term "DUB" [15].

In Washington, USA, there was general agreement to include the following investigations for determining the presence or cause of AUB (mean scores [1–4]): duration of flow (3.32); measurement of hemoglobin and/or hematocrit (3.26); evaluation of the uterus for myomas by ultrasound (3.28); assessment of the endometrial cavity by any method (3.44); and assessment for coagulopathies (3.14). A separate agreement process, co-chaired by members of the current agreement process, convened in 2004 and determined that systemic disorders of hemostasis (coagulopathies) should be screened for using a structured history [16].

Because it was felt to be important to ensure that the system would be both applicable and practicable in the spectrum of healthcare environments worldwide, the group was polled as a way to estimate the ease or difficulty in undertaking a number of evaluations. More than 80% determined that the following were “not at all” or only “somewhat” difficult to assess (provided that one had access to basics of modern diagnostic technologies): predictability, duration, and volume of flow; presence of moderate or severe adenomyosis, determined via transvaginal ultrasound (TVUS); presence of leiomyomas, determined by hysteroscopy or ultrasound (including saline infusion sonography [SIS]); systemic disorders of hemostasis, identified by any of a number of means; ovulation; and hemoglobin and/or hematocrit measurement.

3.2. Acute, chronic, and intermenstrual AUB

It is recognized that the available literature has not formally distinguished between acute and chronic AUB in non-pregnant women. The group attending the Cape Town meeting in 2009 recommended that chronic AUB be defined as bleeding from the uterine corpus that is abnormal in volume, regularity, and/or timing, and has been present for the majority of the past 6 months. Chronic AUB would not, in the opinion of the clinician, require immediate intervention.

By contrast, acute AUB was defined as an episode of heavy bleeding that, in the opinion of the clinician, is of sufficient quantity to require immediate intervention to prevent further blood loss [17,18]. Acute AUB may present in the context of existing chronic AUB or might occur without such a history. Although women of reproductive age with acute AUB require immediate intervention, their follow-up may be largely dependent upon whether they require investigation and ongoing care for an underlying chronic condition.

Intermenstrual bleeding (IMB) occurs between clearly defined cyclic and predictable menses. Such bleeding may occur at random times or may manifest in a predictable fashion at the same day in each cycle. This designation is designed to replace the word “metrorrhagia,” which was one of the terms that the group recommended should be abandoned.

4. Proposed classification system

The basic/core classification system is presented in Fig. 1. The categories were developed based on the group recommendations

described earlier; each was designed to facilitate the development of subclassification systems, as necessary. It was envisioned that the most straightforward parts of the system would be used at a primary care level and that the subclassifications would be most relevant at specialist and research levels. The system has been approved by the FIGO Executive Board as a FIGO classification system.

There are 9 main categories, which are arranged according to the acronym PALM-COEIN (pronounced “pahm-koin”): **p**olyp; **a**denomyosis; **l**eiomyoma; **m**alignancy and hyperplasia; **c**oagulopathy; **o**vulatory dysfunction; **e**ndometrial; **i**atrogenic; and **n**ot yet classified. In general, the components of the PALM group are discrete (structural) entities that can be measured visually with imaging techniques and/or histopathology, whereas the COEIN group is related to entities that are not defined by imaging or histopathology (non-structural).

The term “DUB,” which was previously used as a diagnosis when there was no systemic or locally definable structural cause for AUB, is not included in the system and should be abandoned, per the agreement process [6,7]. Women who fit this description generally have 1 or a combination of coagulopathy, disorder of ovulation, or primary endometrial disorder—the last of which is most often a primary or secondary disturbance in local endometrial hemostasis.

Abnormal uterine bleeding associated with the use of exogenous gonadal steroids, intrauterine systems or devices, or other systemic or local agents is classified as “iatrogenic.” A category of “not yet classified” was created to accommodate entities that are rarely encountered or are ill-defined. For the “malignancy and hyperplasia” group, it is proposed that malignant or premalignant lesions (e.g. atypical endometrial hyperplasia, endometrial carcinoma, and leiomyosarcoma) be categorized as such within the major category, but further dealt with using existent WHO and FIGO classification and staging systems [12,13].

The system was constructed recognizing that any patient could have 1 or several entities that could cause or contribute to AUB and that definable entities such as adenomyosis, leiomyomas, and endocervical/endometrial polyps may frequently be asymptomatic and, therefore, not contribute to the presenting symptoms.

4.1. Polyp (AUB-P)

There seems to be little controversy regarding the inclusion of endometrial and endocervical polyps. These epithelial proliferations comprise a variable vascular, glandular, and fibromuscular and connective tissue

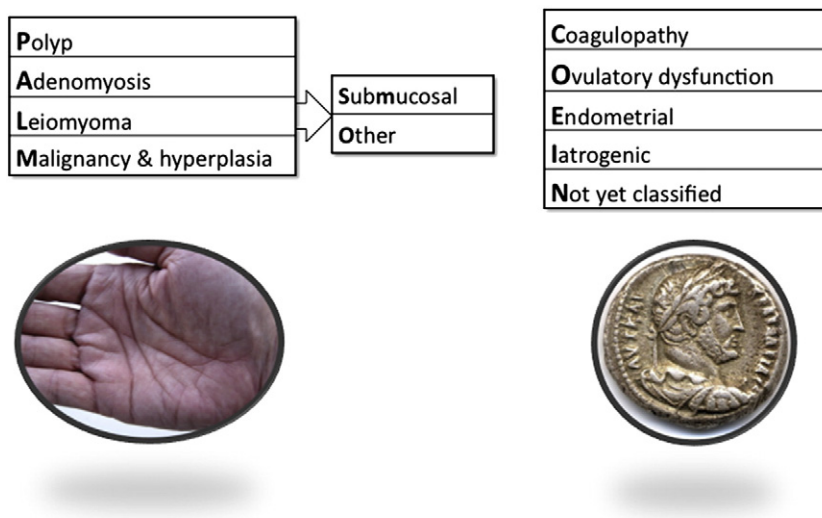


Fig. 1. Basic classification system. The basic system comprises 4 categories that are defined by visually objective structural criteria (PALM: **p**olyp; **a**denomyosis; **l**eiomyoma; and **m**alignancy and hyperplasia), 4 that are unrelated to structural anomalies (COEI: **c**oagulopathy; **o**vulatory dysfunction; **e**ndometrial; **i**atrogenic), and 1 reserved for entities that are not yet classified (N). The leiomyoma category (L) is subdivided into patients with at least 1 submucosal myoma (L_{SM}) and those with myomas that do not impact the endometrial cavity (L_0).

component and are often asymptomatic, but it is generally accepted that at least some contribute to the genesis of AUB [19]. The lesions are usually benign but a small minority may have atypical or malignant features [20,21].

For the basic classification system, polyps are categorized as being either present or absent, as defined by 1 or a combination of ultrasound and hysteroscopic imaging with or without histopathology. Although there is no distinction regarding the size or number of polyps, it is probably important to exclude polypoid-appearing endometrium from this category because such an appearance may well be a variant of normal.

The P category enables the development of a subclassification for clinical or investigative use that may include a combination of variables, including polyp dimension, location, number, morphology, and histology. Until that time, individual clinicians or investigators could include such information, if appropriate, in their own data collection systems.

4.2. Adenomyosis (AUB-A)

The relationship between adenomyosis and the genesis of AUB is unclear, lending strength to the notion that extensive additional research is required [22]. Estimates of the prevalence of adenomyosis vary widely, ranging from 5% to 70% [23]—an observation that, at least in part, is probably related to inconsistencies in the histopathologic criteria for diagnosis. Generally, these criteria have been based on histopathologic evaluation of the depth of “endometrial” tissue beneath the endometrial–myometrial interface, as determined via hysterectomy. The histopathologic criteria vary substantially [23] and the requirement to diagnose adenomyosis solely from specimens obtained at hysterectomy is an approach that has limited value in a clinical classification system. Consequently, and because there exist both sonographic [24] and magnetic resonance imaging (MRI)-based [25,26] diagnostic criteria, adenomyosis has been included in the classification system.

Recognizing women's limited access to MRI worldwide, it is proposed that sonographic criteria for adenomyosis comprise the minimum requirements for assigning an individual the diagnosis of adenomyosis in the PALM-COEIN classification system [27]. The sonographic appearance of adenomyosis is partly related to the absolute presence of heterotopic endometrial tissue in the myometrium and partly due to the related myometrial hypertrophy. Issues that must be addressed in such an imaging-based system include the minimum sonographic criteria for diagnosis, the distinctions between diffuse and focal (or multifocal) disease, and whether a metric indicating volume or extent of the disease should or can be included at this time.

As is the case with polyps and leiomyomas, adenomyosis is a disorder that should have its own subclassification system [28], and it is clear that there should be an initiative to standardize methods of both imaging and histopathologic diagnosis.

4.3. Leiomyoma (AUB-L)

Benign fibromuscular tumors of the myometrium are known by several names, including “leiomyoma,” “myoma,” and the frequently used “fibroid.” “Leiomyoma” is generally accepted as the more accurate term and was selected for use in the present system. The prevalence of these lesions (up to 70% in Caucasians and up to 80% in women of African ancestry [29]), their spectrum of size and location (subendometrial, intramural, subserosal, and combinations of these), and the variable number of lesions in a given uterus require that they be afforded a separate categorization in the system. Like polyps and adenomyosis, many leiomyomas are asymptomatic, and frequently their presence is not the cause of AUB. Furthermore, leiomyomas have widely varying rates of growth, even in a single individual [30].

Consequently, several issues were considered when constructing the classification system, including: the relationship of the leiomyoma to the endometrium and the serosa; the uterine location of the leiomyoma (upper segment, lower segment; cervix, anterior, posterior, lateral); the size of the lesions; the number of lesions; and existing leiomyoma classification systems [31].

In addition to the primary classification system, both secondary and tertiary classification systems for leiomyomas are submitted; these latter systems have potential clinical applications but should also be useful for clinical investigation (Fig. 2).

The primary classification system reflects only the presence or absence of 1 or more leiomyomas, regardless of the location, number, and size. It is proposed that the criteria for determining the presence of leiomyomas would require only sonographic examination confirming that 1 or more such lesions are present.

In the secondary system, the clinician is required to distinguish leiomyomas involving the endometrial cavity (submucosal [SM]) from others (O) because it is generally considered that submucosal lesions are the most likely to contribute to the genesis of AUB.

The root of the tertiary classification system is a design for subendometrial or submucosal leiomyomas that was originally submitted by Wamsteker et al. [31] and subsequently adopted by the European Society for Human Reproduction and Embryology (ESHRE). This system has been in use worldwide for more than 15 years and was considered important when designing the present system. As a result, the PALM-COEIN system includes the categorization of intramural and subserosal leiomyomas, in addition to a category that includes types such as the parasitic lesions that become detached from the uterus after establishing blood supply from another source. When a leiomyoma abuts or distorts both the endometrium and the serosa, it is categorized initially via the submucosal classification, then by the subserosal location—with the 2 values separated by a hyphen. It is thought that this tertiary classification would be most useful for clinical investigators but it is possible that clinicians, particularly those who perform resectoscopic myomectomy, would find immediate clinical use.

Considered but not yet included are the size of the uterus (weeks of gestation) and/or the single longest measurement, the location (e.g. fundus, lower segment, or cervix), and the estimated number of leiomyomas. Clinicians and investigators would be free to include such data in their recording systems and forms. For example, an investigator could choose to categorize by a single leiomyoma or they could provide detailed classification, including documentation of size by mean diameter or volume, for each leiomyoma identified in the uterus.

4.4. Malignancy and hyperplasia (AUB-M)

Although relatively uncommon, atypical hyperplasia and malignancy are important potential causes of, or findings associated with, AUB and must be considered in nearly all women of reproductive age. The present classification system is not designed to replace those of WHO and FIGO for categorizing endometrial hyperplasia and neoplasia [12,13]. Consequently, when a premalignant hyperplastic or malignant process is identified during investigation of women of reproductive age with AUB, it would be classified as AUB-M and then subclassified using the appropriate WHO or FIGO system.

4.5. Coagulopathy (AUB-C)

The term “coagulopathy” encompasses the spectrum of systemic disorders of hemostasis that may be associated with AUB. High-quality evidence demonstrates that approximately 13% of women with HMB have biochemically detectable systemic disorders of hemostasis, most often von Willebrand disease [32]. However, it is not clear how often these abnormalities cause or contribute to the genesis of AUB and how often they are asymptomatic or minimally

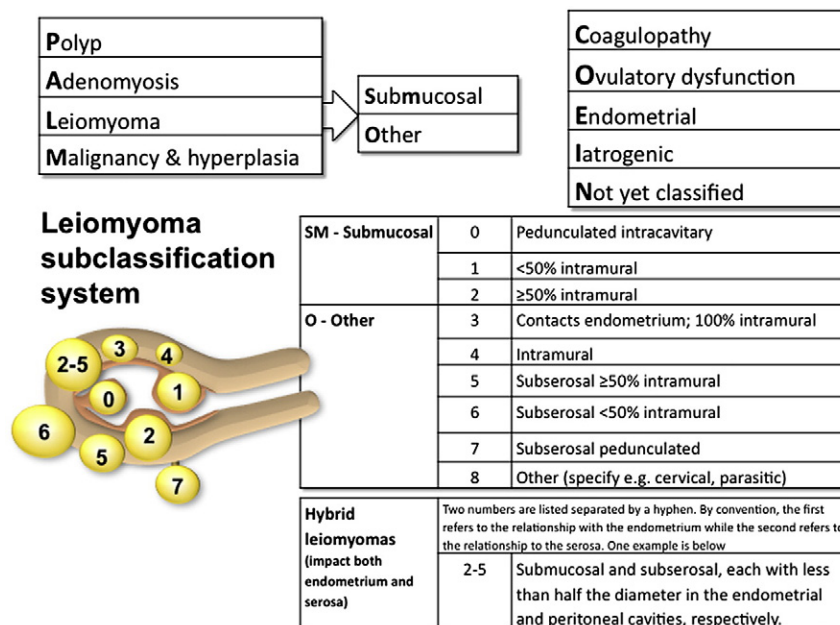


Fig. 2. Classification system including leiomyoma subclassification system. The system that includes the tertiary classification of leiomyomas categorizes the submucosal (SM) group according to the Wamsteker et al. system [31] and adds categorizations for intramural, subserosal, and transmural lesions. Intracavitary lesions are attached to the endometrium by a narrow stalk and are classified as type 0, whereas types 1 and 2 require a portion of the lesion to be intramural—with type 1 being less than 50% and type 2 at least 50%. The type 3 lesions are totally extracavitary but abut the endometrium. Type 4 lesions are intramural leiomyomas that are entirely within the myometrium, with no extension to the endometrial surface or to the serosa. Subserosal (types 5–7) leiomyomas represent the mirror image of the submucosal leiomyomas—with type 5 being at least 50% intramural, type 6 being less than 50% intramural, and Type 7 being attached to the serosa by a stalk. Classification of lesions that are transmural would be categorized by their relationship to both the endometrial and the serosal surfaces. The endometrial relationship would be noted first, with the serosal relationship second (e.g. 2-3). An additional category, Type 8, is reserved for leiomyomas that do not relate to the myometrium at all, and would include cervical lesions, those that exist in the round or broad ligaments without direct attachment to the uterus, and other so-called “parasitic” lesions. Adapted, with permission, from Ref. [11].

symptomatic biochemical abnormalities. Nevertheless, it seems important to consider such disorders, partly because they probably do contribute to some cases of AUB and partly because evidence indicates that relatively few clinicians consider systemic disorders of hemostasis in the differential diagnosis of women with HMB [33].

For some reproductive-aged women, chronic anticoagulation is a necessary and life-preserving intervention, but one that may result in the undesirable adverse effect of AUB, most often HMB. Although such AUB could justifiably be considered iatrogenic and classified accordingly, the group determined that it would be more appropriate to classify affected women as having a coagulopathy (AUB/HMB-C).

4.6. Ovulatory dysfunction (AUB-O)

Ovulatory dysfunction can contribute to the genesis of AUB, generally manifesting as a combination of unpredictable timing of bleeding and variable amount of flow (AUB), which in some cases results in HMB [34]. In many regions, particularly (but not limited to) the USA, ovulatory disorders comprised the vast majority of cases encompassed by the now-discarded term “DUB.” Disorders of ovulation may present as a spectrum of menstrual abnormalities—ranging from amenorrhea, through extremely light and infrequent bleeding, to episodes of unpredictable and extreme HMB requiring medical or surgical intervention. Some of these manifestations relate to the absence of predictable cyclic progesterone production from the corpus luteum every 22–35 days, but in later reproductive years many relate to unusual “disturbed” ovulations, which have been labeled as “luteal out-of-phase” events [34,35].

Although most ovulatory disorders elude a defined etiology, many can be traced to endocrinopathies (e.g. polycystic ovary syndrome, hypothyroidism, hyperprolactinemia, mental stress, obesity, anorexia, weight loss, or extreme exercise such as that associated with elite athletic training). In some instances, the disorder may be iatrogenic,

caused by gonadal steroids or drugs that impact dopamine metabolism, such as phenothiazines and tricyclic antidepressants. It is also well recognized that otherwise-unexplained ovulatory disorders frequently occur at the extremes of reproductive age: adolescence and the menopause transition.

4.7. Endometrial (AUB-E)

When AUB occurs in the context of predictable and cyclic menstrual bleeding, typical of ovulatory cycles, and particularly when no other definable causes are identified, the mechanism is probably a primary disorder of the endometrium. If the symptom is HMB, there may exist a primary disorder of mechanisms regulating local endometrial “hemostasis” itself. Indeed, high-quality evidence has demonstrated deficiencies in local production of vasoconstrictors such as endothelin-1 and prostaglandin F_{2α}, and/or accelerated lysis of endometrial clot because of excessive production of plasminogen activator [36], in addition to increased local production of substances that promote vasodilation, such as prostaglandin E₂ and prostacyclin (I₂) [37,38]. Despite this evidence, some of which has been available for more than 2 decades, tests measuring such abnormalities are not currently available to clinicians.

There may be other primary endometrial disorders that do not present as HMB per se, but instead may cause IMB or prolonged bleeding, the latter of which may be a manifestation of deficiencies in the molecular mechanisms of endometrial repair. Such disorders may be secondary to: endometrial inflammation or infection; abnormalities in the local inflammatory response; or aberrations in endometrial vasculogenesis. However, the role of infection and other local inflammatory disorders in the genesis of AUB is not well defined and is sometimes confounded by the normal presence of inflammatory cells in the endometrium. Retrospective evaluation of women with chronic endometritis has failed to demonstrate a consistent relationship

between histopathologic diagnosis and presence of AUB [39,40] but there are data indicating a relationship between otherwise subclinical infection with *Chlamydia trachomatis* and AUB [41].

As a result of these issues, and for the present version of the classification system, the diagnosis of endometrial disorders should probably be determined by exclusion of other identifiable abnormalities in women of reproductive age who seem to have normal ovulatory function.

4.8. Iatrogenic (AUB-I)

There are several mechanisms by which medical interventions or devices can cause or contribute to AUB (AUB-I). These include medicated or inert intrauterine systems and pharmacologic agents that directly impact the endometrium, interfere with blood coagulation mechanisms, or influence the systemic control of ovulation.

Unscheduled endometrial bleeding that occurs during the use of gonadal steroid therapy is termed “breakthrough bleeding (BTB)” and is the major component of the AUB-I classification. For the clinician faced with patients experiencing unscheduled vaginal bleeding while using gonadal steroid therapy, it is important to ensure that the bleeding is coming from the endometrium (and not serious pathology), then be properly equipped to counsel and, if necessary, treat the patient appropriately.

Systemically administered single-agent or combination gonadal steroids—including estrogens, progestins, and androgens—impact the control of ovarian steroidogenesis via effects on the hypothalamus, pituitary, and/or ovary itself, and also exert a direct effect on the endometrium. These features of gonadal steroids are exploited in the form of hormonal contraceptive agents such as oral, transdermal/vaginal, and injectable progestin or estrogen–progestin compounds. When estrogen–progestin agents are administered cyclically, scheduled uterine bleeding generally occurs in conjunction with the periodic withdrawal of the steroidal agents. However, when unscheduled bleeding occurs in the context of cyclic administration, the woman may be considered to have BTB and be categorized as AUB-I. Combined estrogen–progestin preparations may be administered continuously (in the case of progestin-only agents such as depomedroxyprogesterone acetate, continuous administration is the norm) with the goal of achieving amenorrhea. In such instances, any bleeding may be considered to be unscheduled and, therefore, classified as AUB-I.

It is likely that many episodes of unscheduled bleeding/BTB are related to reduced circulating gonadal steroid levels secondary to compliance issues such as missed, delayed, or erratic use of pills, transdermal patches, or vaginal rings. With the resulting reduced suppression of follicle-stimulating hormone production and subsequent development of follicles that produce endogenous estradiol, additional and irregular stimulation of the endometrium may result in BTB. In a pooled study of 7 trials, 35% of women with large follicles had BTB [42]. Other potential causes of reduced levels of circulating estrogens and progestins include the use of agents such as anticonvulsants and antibiotics (e.g. rifampin and griseofulvin) [43]. Cigarette smoking can reduce levels of contraceptive steroids because of enhanced hepatic metabolism, which may explain the relatively high incidence of BTB in smokers [44].

Many women experience unscheduled vaginal spotting/bleeding in the first 3–6 months of use of the levonorgestrel-releasing intrauterine system (LNG-IUS) [45,46]. In a UK study [46], 10% of new users of the LNG-IUS ceased use by the end of the first year because of bleeding complaints. This contributed to a reported total 5-year cumulative discontinuation rate for bleeding problems of 16.7% [46]. In a Brazilian study [47], 25% of women complained of vaginal spotting in the first 6 months of LNG-IUS use, and removals because of menstrual bleeding problems were concentrated in this time period.

Systemic agents that interfere with dopamine metabolism have the potential to cause AUB secondary to disorders of ovulation. Tricyclic antidepressants (e.g. amitriptyline and nortriptyline) and phenothiazines belong to a group of drugs that impact dopamine metabolism by reducing serotonin uptake. It is thought that the resulting reduced inhibition of prolactin release causes prolactin-related disruption in the hypothalamic–pituitary–ovarian axis and consequent disorders of ovulation, including anovulation. Consequently, any agent that impacts serotonin uptake is a candidate for causing ovulatory dysfunction and resulting amenorrhea or irregular uterine bleeding.

Finally, HMB is a relatively common consequence of the use of anticoagulant drugs such as warfarin, heparin, and low molecular weight heparin. The mechanism seems to be straightforward because, in such instances, there is impairment of the formation of an adequate “plug” or clot within the vascular lumen. Women using such agents essentially have a systemic disorder of hemostasis that is similar in manifestation and management to inherited disorders of hemostasis. Consequently, by convention, the group determined that this type of iatrogenic AUB should be placed in the AUB-C category.

4.9. Not yet classified (AUB-N)

Several uterine entities might contribute to, or cause, AUB in a given individual; however, this has not been demonstrated conclusively because these entities—such as chronic endometritis, arteriovenous malformations, and myometrial hypertrophy—have been poorly defined, inadequately examined, or both. In addition, there may be other disorders, not yet identified, that would be defined only by biochemical or molecular biology assays. Collectively, these entities (or future entities) have been placed in a category termed “not yet classified.” As further evidence becomes available, they may be allocated a separate category or be placed into an existing category in the system.

5. Notation

Following appropriate investigation, discussed below, an individual may be found to have 1 or more potential causes of, or contributors to, their AUB symptoms. Consequently, the system has been designed to enable categorization and notation in a fashion that allows for this circumstance. It is recognized that this increased level of complexity will be of most value to specialists and researchers.

The formal approach follows the example of the WHO TNM staging of malignant tumors, with each component addressed for all patients (Fig. 3). For example, if it were determined that an individual had a disorder of ovulation, a type 2 leiomyoma, and no other abnormalities, they would be categorized as follows in the context of a complete evaluation: AUB P₀ A₀ L_{1(SM)} M₀ - C₀ O₁ E₀ I₀ N₀. Recognizing that, in clinical practice, the full notation might be considered to be cumbersome, an abbreviation option has been developed. The patient previously described would be categorized AUB-L_{SM}; O.

6. Guidelines for investigation

Women with AUB may have 0, 1, or multiple identifiable factors that may contribute to the genesis of the abnormal bleeding. There may also be pathology (e.g. subserosal leiomyoma) that is present but thought not to be a contributor to AUB. Consequently, the investigation of women with AUB must be undertaken in as diligent and comprehensive a fashion as is practicable given the clinical situation and the available resources. This suggested approach is demonstrated in Figs. 4 and 5, and described below.

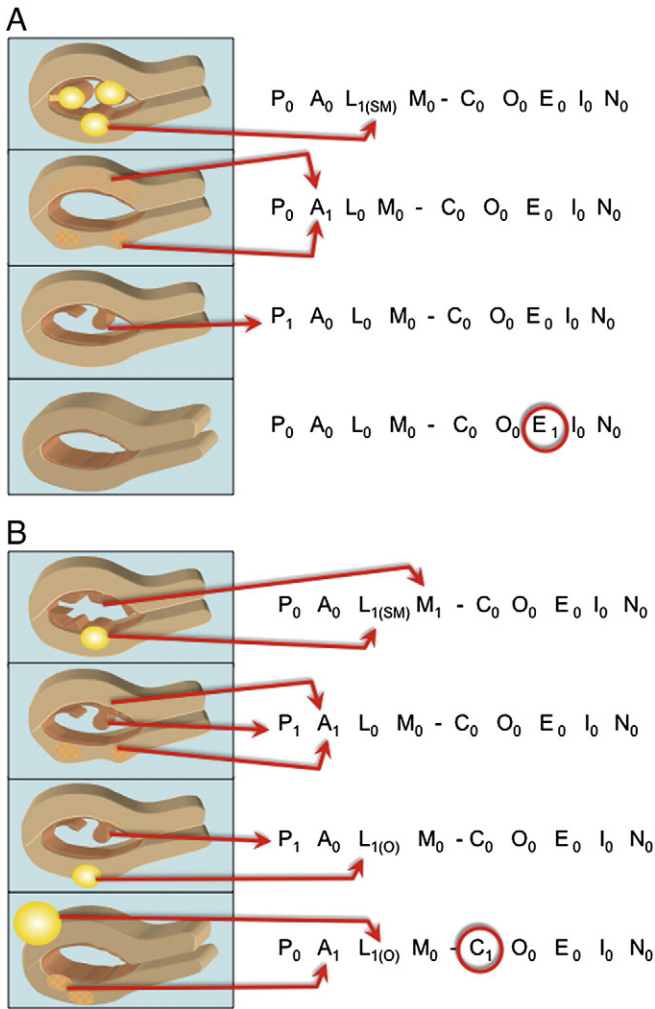


Fig. 3. Notation. A. In all cases, the presence or absence of each criterion is noted using “0” if absent, “1” if present, and “?” if not yet assessed. Each of the cases shown has 1 abnormality identified. From the top: at least one submucosal leiomyoma (L_{SM}); adenomyosis (A)—focal and/or diffuse; endometrial polyps (P); and an absence of any abnormality, leaving endometrial causes (E) as a diagnosis of exclusion. B. Each of the cases shown has more than 1 positive category. From the top: submucosal leiomyoma and atypical endometrial hyperplasia (M), as diagnosed by endometrial sampling; endometrial polyps and adenomyosis; endometrial polyps and subserosal leiomyoma (L_O); and adenomyosis, subserosal leiomyoma and coagulopathy (C), as determined by positive screening test and subsequent biochemical confirmation of von Willebrand disease.

6.1. General assessment

Presented with a woman of reproductive age with either acute or chronic vaginal bleeding thought to be AUB, the clinician would perform a careful evaluation to ensure that the bleeding was not related to an undiagnosed pregnancy and was emanating from the cervical canal, rather than another location. The presence of a pregnancy may be reliably determined with a combination of directed history and urine/serum assay for the presence of the β -subunit of human chorionic gonadotropin. (Determination of the location or viability of a pregnancy is not considered to be within the domain of the classification system.) Women with both acute and chronic AUB should be evaluated for anemia with an assay of hemoglobin and/or hematocrit (preferably a full blood count, including platelets). Once the bleeding has been confirmed or, in the absence of any other identifiable source, suspected to be of uterine origin, the clinician would proceed in a systematic fashion, designing the assessment to address each of the components of the classification system.

6.2. Determination of ovulatory status

Predictable cyclic menses every 22–35 days are usually associated with ovulation [48,49], whereas bleeding associated with AUB-O is typically irregular in timing and flow, and often interspersed with episodes of amenorrhea. If there is uncertainty regarding ovulatory status, measurement of serum progesterone, timed to the best estimate of mid-luteal phase or, alternatively, a similarly timed endometrial biopsy may provide evidence supporting or refuting the presence of ovulation in a given cycle. If a woman were deemed to have a disorder of ovulation, she would be categorized as AUB-O.

6.3. Screening for systemic disorders of hemostasis

A structured history can be used as a screening tool with 90% sensitivity for the detection of these relatively common disorders [50] (Table 1). For women with a positive screen, and for selected others such as those about to undergo surgery, further testing is necessary, often following consultation under the direction of a hematologist. Such tests may include assays for von Willebrand factor, ristocetin cofactor, and other measures [51]; if positive, such results would lead to women being categorized as C_1 . By convention, individuals with AUB associated with the use of anticoagulant therapy are also categorized as C_1 .

6.4. Evaluation of the endometrium

Endometrial sampling is not required for all patients with AUB, making it necessary to identify those women for whom such an evaluation would be appropriate. Patients are selected for endometrial sampling based on a combination of factors that reflect the risk for the presence of atypical hyperplasia or carcinoma. Several reports and guidelines use some combination of age, personal and genetic risk factors, and TVUS screening for endometrial echo-complex thickness to determine which patients should undergo endometrial sampling [52–56]. Although some studies indicate that age is not important as an independent variable [53], most suggest that endometrial sampling be considered for all women over a certain age, usually 45 years [54]. Women from families with hereditary nonpolyposis colorectal cancer syndrome have a lifetime risk of endometrial cancer of up to 60%, with a mean age at diagnosis of 48–50 years [57,58]. Regardless of guideline structure, persistent AUB that is unexplained or not adequately treated requires endometrial sampling—if possible, in association with hysteroscopic evaluation of the uterine cavity.

Several techniques can be used to perform endometrial sampling, but it is important that an adequate sample be obtained before the patient can be considered at low risk for a malignant neoplasm [59]. Finally, given the apparent relationship between chlamydial infection of the endometrium and AUB, it may be prudent to consider evaluating for the organism in symptomatic patients [60]. Although cervical sampling seems reasonable, the relationship between cervical specimens and endometrial infection is not clear.

6.5. Evaluation of the structure of the endometrial cavity

Structural evaluation of the endometrial cavity is performed to identify abnormalities—including endometrial/encervical polyps (AUB-P) and submucosal leiomyomas (AUB- L_{SM})—that could contribute to AUB. Transvaginal ultrasound is an appropriate screening tool and, in most instances, should be performed first or early in the course of the investigation. For ideal imaging, the ultrasound equipment must be of adequate quality to display myometrial and endometrial features clearly, and the examiner must have the ability to operate the scanning device and interpret the images displayed. Even in ideal circumstances, TVUS is not 100% sensitive because polyps and other small lesions may elude detection, even in the context of a normal study [61,62].

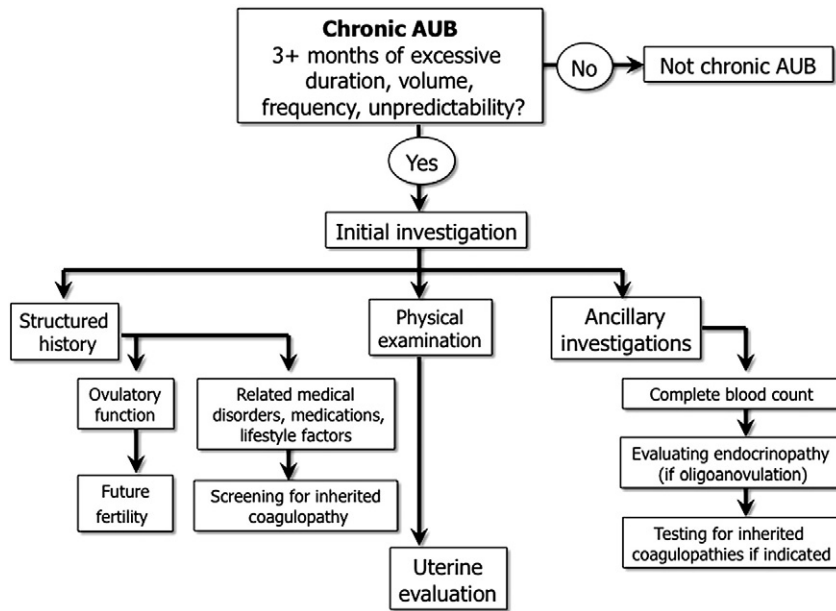


Fig. 4. Initial evaluation. For a diagnosis of chronic abnormal uterine bleeding (AUB), the initial assessment requires the patient to have experienced 1 or a combination of unpredictability, excessive duration, abnormal volume, or abnormal frequency of menses for at least the previous 3 months. Patients should undergo a structured history designed to determine ovulatory function, potential related medical disorders, medications, and lifestyle factors that might contribute to AUB. For those with heavy menstrual bleeding, the structured history should include the questions from Table 1. Understanding the future fertility desires of the patient will help to frame the discussion of therapy following appropriate investigation. Ancillary investigations should include a hemoglobin and/or a hematocrit assessment, appropriate tests for features that could contribute to an ovulatory disorder (thyroid function, prolactin, and serum androgens), and if the Table 1-based structured history is positive for coagulopathy either referral to a hematologist or appropriate tests for von Willebrand disease. Reproduced, with permission, from Ref. [11].

If good ultrasonic images are obtained and there is an absence of findings indicative of endometrial polyps or submucosal myomas, the endometrial cavity may presumptively be considered normal from the perspective of lesions causing or contributing to AUB. However, if there

are imaging features indicative of endometrial polyp(s), if there are myomas that may be encroaching on the endometrial cavity, or if the exam is suboptimal, imaging with other, more sensitive techniques is recommended—generally SIS (also called sonohysteroscopy

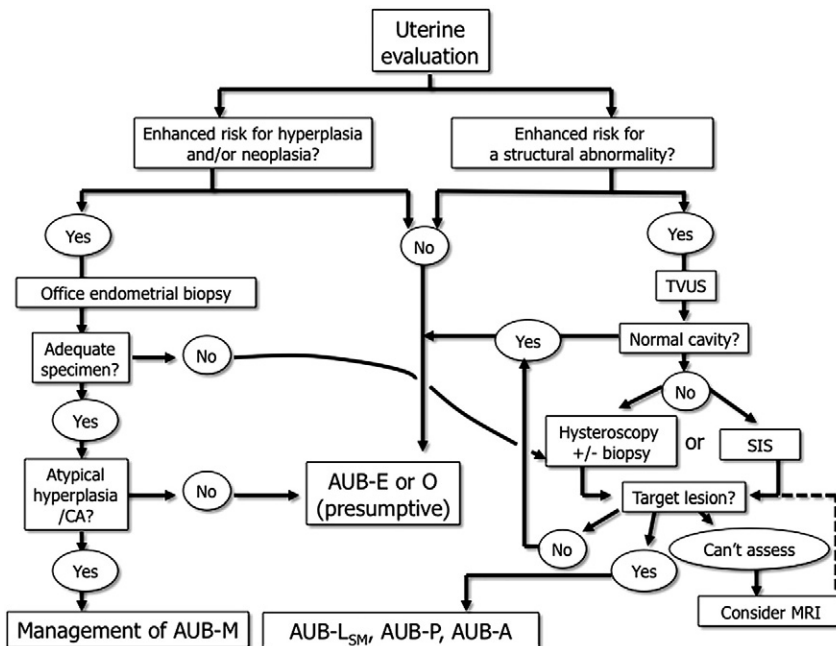


Fig. 5. Uterine evaluation. The uterine evaluation is, in part, guided by the history and other elements of the clinical situation, such as patient age, presence of an apparent chronic ovulatory disorder, or presence of other risk factors for endometrial hyperplasia or malignancy. For those at increased risk, endometrial biopsy is probably warranted. If there is a risk of structural anomaly, particularly if previous medical therapy has been unsuccessful, evaluation of the uterus should include imaging, at least with a “screening” transvaginal ultrasound (TVUS) examination. Unless the ultrasound image indicates a normal endometrial cavity, it will be necessary to use either or both hysteroscopy and saline infusion sonography (SIS) to determine whether target lesions are present. Such an approach is also desirable if endometrial sampling has not provided an adequate specimen. Uncommonly, these measures are inconclusive or, in the instance of virginal girls and women, not feasible outside of an anesthetized environment. In these instances, magnetic resonance imaging (MRI) may be of value, if available. Abbreviations: AUB, abnormal uterine bleeding; CA, carcinoma. Reproduced, with permission, from Ref. [11].

Table 1

Clinical screening for an underlying disorder of hemostasis in the patient with excessive menstrual bleeding.^a

Initial screening for an underlying disorder of hemostasis in patients with excessive menstrual bleeding should be by a structured history (positive screen comprises any of the following): ^b
Heavy menstrual bleeding since menarche
One of the following:
Postpartum hemorrhage
Surgical-related bleeding
Bleeding associated with dental work
Two or more of the following symptoms:
Bruising 1–2 times per month
Epistaxis 1–2 times per month
Frequent gum bleeding
Family history of bleeding symptoms

^a Table reproduced, with permission, from Ref. [51].

^b Patients with a positive screen should be considered for further evaluation, including consultation with a hematologist and/or testing of von Willebrand factor and Ristocetin cofactor.

and hysterosonography) or hysteroscopy, depending on the resources available to the clinician. In most instances, SIS will be more readily available, particularly when the only resources for hysteroscopy are in an operating room. However, if office hysteroscopy is available, there may be additional value should polyps be identified because they could be removed in the same setting.

When vaginal access is difficult, as may be the case with adolescents and virginal women, TVUS, SIS, and office hysteroscopy may not be feasible. In such cases, there may be a role for MRI. Alternatively, hysteroscopic examination under anesthesia may be the best approach.

With the PALM-COEIN classification, P (for endometrial and endocervical polyps) is confirmed only with documentation of 1 or more clearly defined polyps, generally with either SIS or hysteroscopy. Usually, a patient may be categorized with 1 or more submucosal leiomyomas (AUB- L_{SM}) with either SIS or hysteroscopy, but care must be taken not to infuse the distending medium with such pressure that the natural relationships of the leiomyoma with the endometrium and myometrium are distorted.

6.6. Myometrial assessment

The myometrium is assessed primarily with a combination of TVUS and transabdominal ultrasound to identify leiomyomas, with any such lesion leading to an L_1 assignment. Should the combination of TVUS with or without abdominal ultrasound plus either hysteroscopy or SIS fail to identify leiomyomas, the patient would be classified as L_0 . For the secondary subclassification, it is necessary to perform some combination of TVUS, SIS, hysteroscopy, and MRI.

The tertiary subclassification of leiomyoma type requires the clinician to determine the relationship of the leiomyomas with the endometrium, myometrium, and serosa. Clinically, at least for non-submucosal myomas, this would probably require the use of MRI (Fig. 2).

The myometrium should also be evaluated for the presence of adenomyosis or to distinguish between leiomyomas and adenomyomas [26]. The sonographic criteria are described elsewhere in this document. An assignment of A_1 requires 3 of the criteria to be met; otherwise, the patient is classified as A_0 .

If available, MRI may be used to evaluate the myometrium to distinguish between leiomyomas and adenomyosis [25]. It may also be superior to TVUS, SIS, and hysteroscopy for measuring the myometrial extent of submucosal leiomyomas [61]. However, it was determined that reliance on MRI would not be practical at the present time because of the relative or absolute lack of access in many healthcare systems.

7. Discussion

Abnormal uterine bleeding in women of reproductive age is a manifestation of any of a number of disorders or pathologic entities. To date, the absence of a universally accepted method for classifying such patients has impeded basic science and clinical investigation, as well as the practical, rational, and consistent application of medical and surgical therapy. In the past, at least some staging and classification systems have proven to be useful as a way to compare research on clinically similar populations, and for the guidance of the clinician in the investigation and treatment of affected patients. The current agreement process was designed to create a practical system that could be used by clinicians in most countries worldwide to classify patients with AUB readily and consistently, based on the results of a systematic evaluation. Another recognized impediment to communication between and among clinicians and patients was the absence of standardized nomenclature for the description of symptoms of AUB. The results of the present agreement process are published elsewhere [1,6,7] and the proposed classification system presented in preliminary form [11].

The participation of clinicians from 6 continents was, in part, designed to provide input into the practicality of performing the investigations described for classifying patients according to the proposed system. Clearly, at this time, the characterization of structural lesions of the uterus using MRI is not feasible and, consequently, use of the modality is not included as a mandatory tool for classification of patients with chronic AUB. This does not mean that clinicians cannot or should not use MRI if it is deemed necessary and is available, with the results of MRI assessments used to determine the presence or absence of adenomyosis when classifying a patient according to the present system.

8. Conclusion

A multinational group of clinician–investigators with broad experience in the investigation of AUB has agreed on a system of classification to facilitate multi-institutional investigation into the epidemiology, etiology, and treatment of women with acute and chronic AUB. The system should also foster meta-analysis of clinical trials that are appropriately designed and reported. It is recognized that the system will require periodic modification and occasional substantial revision depending on advances in knowledge and technology, and increasing availability of investigative options across geographic regions. Consequently, we recommend a scheduled systematic review of the system on a regular basis by a permanent committee of an international organization such as FIGO, which has already endorsed the establishment of a suitable ongoing Working Group on Menstrual Disorders.

Journal editors and editorial boards are encouraged to request that materials, methods, and reporting sections of manuscripts dealing with AUB be designed accordingly.

Conflict of interest

MGM, HODC, and ISF have acted as consultants for, given lectures for, and received honoraria from Bayer Schering Pharma, which has partly funded this initiative (as outlined in the relevant publications). Many other organizations and companies have contributed in direct or indirect ways to the development of this process. These contributions are clearly outlined in the relevant publications. The process has been approved by FIGO and the FIGO Working Group on Menstrual Disorders.

Appendix A

The participants in this process have contributed substantially to the evolving debate around several aspects of the common symptoms of AUB at workshops in Washington and/or Cape Town, and in private

debate. They have all approved the listing of their names in the present manuscript. The names are listed alphabetically and none of the individuals represented the views of their organizations.

Ahmad Abdel-Wahed, MD, Jordan
 Luis Bahamondes, MD, Brasil
 Vivian Brache, PhD, Dominican Republic
 Andrew Brill, MD, USA (AAGL)
 Michael Broder, MD, USA
 Ivo Brosens, MD, Belgium
 Kris Chwalisz, PhD, USA
 Hilary Critchley, MD, UK
 Catherine d'Arcangues, MD, Switzerland (WHO)
 Margit Dueholm, MD, Sweden
 Cynthia Farquhar, MD, New Zealand
 Mario Festin, MD, Switzerland (WHO)
 Ian Fraser, MD, Australia
 Marc Fritz, MD, USA
 Rohana Hathtootuwa, MD, Sri Lanka
 William Hurd, MD, USA, (Fertil Steril)
 Lee Learman, MD, USA
 Charles Lockwood, MD, USA
 Andrea Lukes, MD, USA
 Kristen Matteson, MD, USA
 Ian Milsom, MD, Sweden
 Andrew Mok, MD, Canada
 Malcolm Munro, MD, USA
 Anita Nelson, MD, USA
 Shaughn O'Brien, MD, UK (RCOG)
 David Olive, MD, USA
 Rachel Pope, Medical Student (USA–Israel)
 Oskari Heikinheimo, MD, Finland
 Elisabeth Persson, MD, Sweden
 Robert Rebar, MD, USA (ASRM)
 Dorothy Shaw, MD, Canada (FIGO)
 Shirish Sheth, MD, India (FIGO)
 Robert Schenken, MD, USA
 James Spies, MD, USA
 Elizabeth Stewart, MD, USA
 Zephne van der Spuy, MD, South Africa
 Paolo Vercellini, MD, Italy (ESHRE)
 Kirsten Vogelsong, PhD, Switzerland (WHO)
 Pamela Warner, PhD, UK

References

- Woolcock JG, Critchley HO, Munro MG, Broder MS, Fraser IS. Review of the confusion in current and historical terminology and definitions for disturbances of menstrual bleeding. *Fertil Steril* 2008;90(6):2269–80.
- Fraser IS, Critchley HO, Munro MG. Abnormal uterine bleeding: getting our terminology straight. *Curr Opin Obstet Gynecol* 2007;19(6):591–5.
- Benedet JL, Odicino F, Maisonneuve P, Beller U, Creasman WT, Heintz AP, et al. Carcinoma of the cervix uteri. *Int J Gynecol Obstet* 2003;83(Suppl 1):41–78.
- Revised American Society for Reproductive Medicine classification of endometriosis: 1996. *Fertil Steril* 1997;67(5):817–21.
- Bump RC, Mattiasson A, Bo K, Brubaker LP, DeLancey JO, Klarskov P, et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. *Am J Obstet Gynecol* 1996;175(1):10–7.
- Fraser IS, Critchley HO, Munro MG, Broder M. A process designed to lead to international agreement on terminologies and definitions used to describe abnormalities of menstrual bleeding. *Fertil Steril* 2007;87(3):466–76.
- Fraser IS, Critchley HO, Munro MG, Broder M. Can we achieve international agreement on terminologies and definitions used to describe abnormalities of menstrual bleeding? *Hum Reprod* 2007 Mar;22(3):635–43.
- Brook RH, Chassin MR, Fink A, Solomon DH, Koseoff J, Park RE. A method for the detailed assessment of the appropriateness of medical technologies. *Int J Technol Assess Health Care* 1986;2(1):53–63.
- Shekelle PG, Park RE, Kahan JP, Leape LL, Kamberg CJ, Bernstein SJ. Sensitivity and specificity of the RAND/UCLA Appropriateness Method to identify the overuse and underuse of coronary revascularization and hysterectomy. *J Clin Epidemiol* 2001;54(10):1004–10.
- Park RE, Fink A, Brook RH, Chassin MR, Kahn KL, Merrick NJ, et al. Physician ratings of appropriate indications for six medical and surgical procedures. *Am J Public Health* 1986;76(7):766–72.
- Munro MG. *Abnormal Uterine Bleeding*. Cambridge: Cambridge University Press; 2010.
- Tavassoli FA, Devilee P. *World Health Organization Classification of Tumors: Pathology and Genetics of Tumours of the Breast and Female Genital Organs*. Lyon: IARC Press; 2003.
- Creasman WT, Odicino F, Maisonneuve P, Quinn MA, Beller U, Benedet JL, et al. Carcinoma of the corpus uteri. FIGO 6th Annual Report on the Results of Treatment in Gynecological Cancer. *Int J Gynecol Obstet* 2006;95(Suppl 1):S105–43.
- Fraser IS, Critchley HO, Munro MG. A five year international review process concerning terminologies, definitions and related issues around abnormal uterine bleeding. *Semin Reprod Med* (in press).
- Munro MG, Broder M, Critchley HO, Matteson K, Hathtootuwa R. An international response to questions about terminologies, investigation and management of abnormal uterine bleeding: use of an electronic audience response system. *Semin Reprod Med* (in press).
- Munro MG, Lukes AS. Abnormal uterine bleeding and underlying hemostatic disorders: report of a consensus process. *Fertil Steril* 2005;84(5):1335–7.
- DeVore GR, Owens O, Kase N. Use of intravenous Premarin in the treatment of dysfunctional uterine bleeding—a double-blind randomized control study. *Obstet Gynecol* 1982;59(3):285–91.
- 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):924–9.
- Lieng M, Istre O, Sandvik L, Qvistad E. Prevalence, 1-year regression rate, and clinical significance of asymptomatic endometrial polyps: cross-sectional study. *J Minim Invasive Gynecol* 2009;16(4):465–71.
- Anastasiadis PG, Koutlaki NG, Skaphida PG, Galazios GC, Tsikouras PN, Liberis VA. Endometrial polyps: prevalence, detection, and malignant potential in women with abnormal uterine bleeding. *Eur J Gynaecol Oncol* 2000;21(2):180–3.
- Shushan A, Revel A, Rojansky N. How often are endometrial polyps malignant? *Gynecol Obstet Invest* 2004;58(4):212–5.
- Weiss G, Maseelall P, Schott LL, Brockwell SE, Schocken M, Johnston JM. Adenomyosis a variant, not a disease? Evidence from hysterectomized menopausal women in the Study of Women's Health Across the Nation (SWAN). *Fertil Steril* 2009;91(1):201–6.
- Dueholm M. Transvaginal ultrasound for diagnosis of adenomyosis: a review. *Best Pract Res Clin Obstet Gynaecol* 2006;20(4):569–82.
- Brosens JJ, de Souza NM, Barker FG, Paraschos T, Winston RM. Endovaginal ultrasonography in the diagnosis of adenomyosis uteri: identifying the predictive characteristics. *Br J Obstet Gynaecol* 1995;102(6):471–4.
- Mark AS, Hricak H, Heinrichs LW, Hendrickson MR, Winkler ML, Bachica JA, et al. Adenomyosis and leiomyoma: differential diagnosis with MR imaging. *Radiology* 1987;163(2):527–9.
- Togashi K, Nishimura K, Itoh K, Fujisawa I, Noma S, Kanaoka M, et al. Adenomyosis: diagnosis with MR imaging. *Radiology* 1988;166(1 Pt 1):111–4.
- Dueholm M, Lundorf E, Hansen ES, Sorensen JS, Ledertoug S, Olesen F. Magnetic resonance imaging and transvaginal ultrasonography for the diagnosis of adenomyosis. *Fertil Steril* 2001;76(3):588–94.
- Gordts S, Brosens JJ, Fusi L, Benagiano G, Brosens I. Uterine adenomyosis: a need for uniform terminology and consensus classification. *Reprod Biomed Online* 2008;17(2):244–8.
- Day Baird D, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. *Am J Obstet Gynecol* 2003;188(1):100–7.
- Davis BJ, Haneke KE, Miner K, Kowalik A, Barrett JC, Peddada S, et al. The fibroid growth study: determinants of therapeutic intervention. *J Womens Health (Larchmt)* 2009;18(5):725–32.
- Wamsteker K, Emanuel MH, de Kruijff JH. Transcervical hysteroscopic resection of submucous fibroids for abnormal uterine bleeding: results regarding the degree of intramural extension. *Obstet Gynecol* 1993;82(5):736–40.
- Shankar M, Lee CA, Sabin CA, Economides DL, Kadir RA. von Willebrand disease in women with menorrhagia: a systematic review. *BJOG* 2004;111(7):734–40.
- Dilley A, Drews C, Lally C, Austin H, Barnhart E, Evatt B. A survey of gynecologists concerning menorrhagia: perceptions of bleeding disorders as a possible cause. *J Womens Health Gend Based Med* 2002;11(1):39–44.
- Hale GE, Hughes CL, Burger HG, Robertson DM, Fraser IS. 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(1):50–9.
- Hale GE, Manconi F, Luscombe G, Fraser IS. Quantitative measurements of menstrual blood loss in ovulatory and anovulatory cycles in middle- and late-reproductive age and the menopausal transition. *Obstet Gynecol* 2010;115(2 Pt 1):249–56.
- Gleeson NC. Cyclic changes in endometrial tissue plasminogen activator and plasminogen activator inhibitor type 1 in women with normal menstruation and essential menorrhagia. *Am J Obstet Gynecol* 1994;171(1):178–83.
- Smith SK, Abel MH, Kelly RW, Baird DT. A role for prostacyclin (PGI₂) in excessive menstrual bleeding. *Lancet* 1981;1(8219):522–4.
- Smith SK, Abel MH, Kelly RW, Baird DT. Prostaglandin synthesis in the endometrium of women with ovular dysfunctional uterine bleeding. *Br J Obstet Gynaecol* 1981;88(4):434–42.
- Pitsos M, Skurnick J, Heller D. Association of pathologic diagnoses with clinical findings in chronic endometritis. *J Reprod Med* 2009;54(6):373–7.
- Heatley MK. The association between clinical and pathological features in histologically identified chronic endometritis. *J Obstet Gynaecol* 2004;24(7):801–3.

- [41] Toth M, Patton DL, Esquenazi B, Shevchuk M, Thaler H, Divon M. Association between Chlamydia trachomatis and abnormal uterine bleeding. *Am J Reprod Immunol* 2007;57(5):361–6.
- [42] Endrikat J, Gerlinger C, Plettig K, Wessel J, Schmidt W, Grubb G, et al. A meta-analysis on the correlation between ovarian activity and the incidence of intermenstrual bleeding during low-dose oral contraceptive use. *Gynecol Endocrinol* 2003;17(2):107–14.
- [43] Murphy PA, Kern SE, Stanczyk FZ, Westhoff CL. Interaction of St. John's Wort with oral contraceptives: effects on the pharmacokinetics of norethindrone and ethinyl estradiol, ovarian activity and breakthrough bleeding. *Contraception* 2005;71(6):402–8.
- [44] Rosenberg MJ, Waugh MS, Stevens CM. Smoking and cycle control among oral contraceptive users. *Am J Obstet Gynecol* 1996;174(2):628–32.
- [45] Backman T, Huhtala S, Blom T, Luoto R, Rauramo I, Koskenvuo M. Length of use and symptoms associated with premature removal of the levonorgestrel intrauterine system: a nation-wide study of 17,360 users. *BJOG* 2000;107(3):335–9.
- [46] Cox M, Tripp J, Blacksell S. Clinical performance of the levonorgestrel intrauterine system in routine use by the UK Family Planning and Reproductive Health Research Network: 5-year report. *J Fam Plann Reprod Health Care* 2002;28(2):73–7.
- [47] Hidalgo M, Bahamondes L, Perrotti M, Diaz J, Dantas-Monteiro C, Petta C. Bleeding patterns and clinical performance of the levonorgestrel-releasing intrauterine system (Mirena) up to two years. *Contraception* 2002;65(2):129–32.
- [48] Metcalf MG. Incidence of ovulation from the menarche to the menopause: observations of 622 New Zealand women. *N Z Med J* 1983;96(738):645–8.
- [49] Malcolm CE, Cumming DC. Does anovulation exist in eumenorrheic women? *Obstet Gynecol* 2003;102(2):317–8.
- [50] Kadir RA, Economides DL, Sabin CA, Owens D, Lee CA. Frequency of inherited bleeding disorders in women with menorrhagia. *Lancet* 1998;351(9101):485–9.
- [51] 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. *Fertil Steril* 2005;84(5):1345–51.
- [52] Farquhar CM, Lethaby A, Sowter M, Verry J, Baranyai J. An evaluation of risk factors for endometrial hyperplasia in premenopausal women with abnormal menstrual bleeding. *Am J Obstet Gynecol* 1999;181(3):525–9.
- [53] Ash SJ, Farrell SA, Flowerdew G. Endometrial biopsy in DUB. *J Reprod Med* 1996;41(12):892–6.
- [54] 44 NCG. Heavy menstrual bleeding. United Kingdom: National Institute for Health and Clinical Excellence; 2007.
- [55] An evidence-based guideline for the management of heavy menstrual bleeding. Working Party for Guidelines for the Management of Heavy Menstrual Bleeding. *N Z Med J* 1999;112(1088):174–7.
- [56] Guidelines for the management of abnormal uterine bleeding. *J Obstet Gynaecol Can* 2001;104:1–6.
- [57] Lu KH, Broaddus RR. Gynecological tumors in hereditary nonpolyposis colorectal cancer: We know they are common—now what? *Gynecol Oncol* 2001;82(2):221–2.
- [58] Lu KH, Dinh M, Kohlmann W, Watson P, Green J, Syngal S, et al. Gynecologic cancer as a "sentinel cancer" for women with hereditary nonpolyposis colorectal cancer syndrome. *Obstet Gynecol* 2005;105(3):569–74.
- [59] Critchley HO, Warner P, Lee AJ, Brechin S, Guise J, Graham B. Evaluation of abnormal uterine bleeding: comparison of three outpatient procedures within cohorts defined by age and menopausal status. *Health Technol Assess* 2004;8(34):iii–iv, 1–139.
- [60] Srivastava A, Mansel RE, Arvind N, Prasad K, Dhar A, Chabra A. Evidence-based management of Mastalgia: a meta-analysis of randomised trials. *Breast* 2007;16(5):503–12.
- [61] Dueholm M, Lundorf E, Hansen ES, Ledertoug S, Olesen F. Evaluation of the uterine cavity with magnetic resonance imaging, transvaginal sonography, hysterosonographic examination, and diagnostic hysteroscopy. *Fertil Steril* 2001;76(2):350–7.
- [62] Breitkopf DM, Frederickson RA, Snyder RR. Detection of benign endometrial masses by endometrial stripe measurement in premenopausal women. *Obstet Gynecol* 2004;104(1):120–5.