



## Research and clinical management for women with abnormal uterine bleeding in the reproductive years: More than PALM-COEIN

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In the developed world, abnormal uterine bleeding (AUB) that occurs during the reproductive years, although rarely life threatening, is frequently life altering. It interferes with quality of life, and those afflicted spend substantial personal resources on menstrual products and pharmaceuticals. Furthermore, there is evidence that chronic AUB is associated with a reduction in work productivity by about 30%, a circumstance that results in a similar impact on income.<sup>1,2</sup> In the developing world, the high prevalence of iron deficiency in women has been linked to a number of factors, including poor nutrition, limited or lack of access to simple iron replacement, and the symptom of heavy menstrual bleeding (HMB). Pregnant women who are anaemic become especially susceptible to the sequelae of peripartum haemorrhage, which include mortality. The estimated prevalence of nongestational chronic AUB is high, affecting about 30% of women at some time in their reproductive years. This translates into a substantial impact on the resources of healthcare systems: about 5% of reproductive-aged women seek AUB-related care each year. Although about a third of all visits to gynaecologists are related to one or more AUB symptoms, only half of the affected women actually seek care, and, when they do, the level of satisfaction is frequently low.<sup>3</sup> Regardless, chronic AUB places a burden on the economy, employers, and on the women affected and their families. In 2007, it was estimated that the total annual direct and indirect costs of AUB exceeded \$37 billion in the USA.<sup>4</sup>

### Rationale for the International Federation of Gynecology and Obstetrics (FIGO) systems

The massive worldwide impact of AUB underscores the importance of the development and implementation of effective clinical care strategies. Although the treatment of iron deficiency anaemia with iron is logical, it is frequently unavailable in low-resource environments, and is often underused even in developed countries. Regardless, such an approach deals only with the result of the symptom of HMB, and does not address the cause of the problem in a given patient.

It is increasingly apparent that nongestational AUB in the reproductive years is the result of one or more of a group of disorders that include disruption of endocrine, endometrial, and haemostatic function, as well as a spectrum of structural anomalies of the uterus, including polyps, adenomyosis, and leiomyomas. A confounding issue is the fact that identified polyps, adenomyosis, or leiomyomas may or may not actually contribute to the patient's symptoms—the cause or causes may lie elsewhere. So finding the cause—from the bench to the 'bedside'—remains a major challenge for investigators, clinicians, and educators.

Over the past decade, it became apparent that there were two barriers to resolving these challenges. One was the quagmire of ill-defined and inconsistently used terms and definitions that impaired communication among clinicians, trainees, and both bench and clinical investigators.<sup>5</sup> The

other was the absence of a well-designed and accepted system for categorising the potential cause, or contributors, to the genesis of AUB. These circumstances have led to considerable confusion and confounding in the design and interpretation of bench and clinical research, as both laboratory specimens and enrolled patients with a host of potential confounding factors could be included. Consequently, to standardise education and facilitate the design and interpretation of more informative basic science research, as well as translational and clinical investigation, a consensus-based approach to nomenclature and classification became necessary.

It was in this context—poorly defined terms and definitions, and the lack of a structured approach to a frequently multifactorial clinical problem—that the FIGO Menstrual Disorders Committee (MDC) was ultimately created. In 2005, a group of experts was assembled comprising representatives from the US Food and Drug Administration (FDA), relevant professional societies and medical journals, and members of the basic, translational, and clinical sciences communities interested in the problem of AUB in the reproductive years. The goal was to first confirm the existence of the problems, and then to tackle the issues in a systematic fashion.<sup>6,7</sup>

### The FIGO systems for nomenclature of terms and classification of causes of AUB in the reproductive years

The collective recognition of the disparity and inconsistency in definitions and terminology was a surprise to many, and the result was a near unanimous decision to create a new set of unambiguous terms. This became what could be considered the first FIGO system: one of nomenclature and definitions of normal and abnormal uterine bleeding based on the fifth to 95th percentiles according to the large-scale epidemiological studies available (Figure 1).<sup>6,7</sup> Included was the adoption of the term HMB, as a symptom (not a diagnosis), described by the National Institute for Health and Clinical Excellence as ‘excessive menstrual blood loss, which interferes with a woman’s physical, social, emotional and/or material quality of life’.<sup>8</sup> First published in 2007, FIGO’s system of nomenclature and definitions has undergone very modest modifications that will continue to be clarified, modified, and revised as appropriate.<sup>6,7</sup>

The classification system of potential causes of AUB, summarised by the acronym ‘PALM-COEIN’, was first presented in a textbook,<sup>9</sup> and with slight modification was

Category	Days (past 6 months)	Normal or Abnormal	<input checked="" type="checkbox"/>
Frequency	every <input type="text"/> <input type="text"/> <input type="text"/> days	Absent (no periods or bleeding) = amenorrhea	<input type="checkbox"/>
		Frequent (<24 days)	<input type="checkbox"/>
		Normal (24 to 38 days)	<input type="checkbox"/>
		Infrequent (>38 days)	<input type="checkbox"/>
Duration	shortest: <input type="text"/> <input type="text"/> days longest: <input type="text"/> <input type="text"/> days	Prolonged (>8 days)	<input type="checkbox"/>
		Normal (up to 8 days)	<input type="checkbox"/>
Regularity	shortest: <input type="text"/> <input type="text"/> <input type="text"/> days longest: <input type="text"/> <input type="text"/> <input type="text"/> days	Regular variation (shortest to longest ≤ 9 days)	<input type="checkbox"/>
		Irregular (shortest to longest 10+ days)	<input type="checkbox"/>
Flow volume	As determined by the patient - based on her assessment of the impact on her quality of life	Heavy	<input type="checkbox"/>
		Normal	<input type="checkbox"/>
		Light	<input type="checkbox"/>
Intermenstrual Bleeding (IMB) Bleeding between cyclically regular onset of menses	None		<input type="checkbox"/>
	Random		<input type="checkbox"/>
	Cyclic (Predictable)	Early Cycle	<input type="checkbox"/>
		Mid Cycle	<input type="checkbox"/>
Unscheduled Bleeding on Hormone Medication (eg Birth Control Pills, Rings or Patches)	Not Applicable (not on hormone medication)		<input type="checkbox"/>
	None (on hormone medication)		<input type="checkbox"/>
	Present		<input type="checkbox"/>

**Figure 1.** FIGO system 1. Nomenclature and definitions. Gone are the terms ‘menorrhagia’, ‘menometrorrhagia’, and ‘oligomenorrhea’, and other poorly defined and inconsistently used terms. There are four basic criteria to define menses: frequency, duration, regularity, and volume, all as reported by the patient. Intermenstrual bleeding is reported only when one can clearly define normal ovulatory menses. Unscheduled bleeding when using hormonal medications is reported separately.

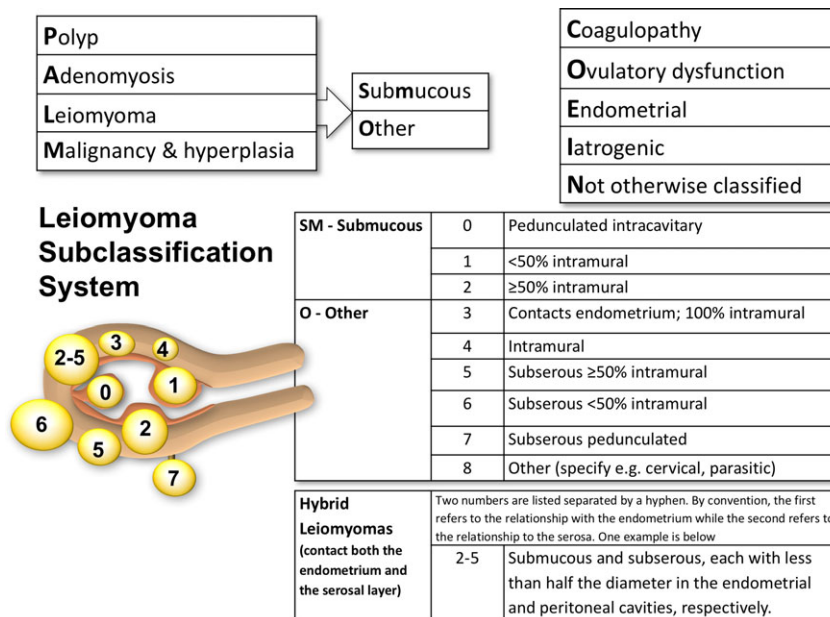
ultimately accepted by FIGO in 2010, and then published together with the definition and nomenclature system in 2011.<sup>10</sup> Each of the letters stands for a category of abnormality or disorder potentially found or presumed existent in an individual with one or more AUB symptoms (Figure 2). The four ‘PALM’ categories comprise abnormal findings that are defined by imaging and/or histopathological evaluation; the ‘COEI’ classifications cannot be defined structurally. The systemic disorders of haemostasis, called coagulopathies, require confirmation by laboratory testing, whereas ovulatory disorders are suggested by a structured history of irregular menses, potentially supported by a number of laboratory and histopathological assessments. This system introduced the concept of a primary endometrial disorder (AUB-E) present in women with normal ovulatory cycles. Based on a relatively extensive body of evidence, the most common manifestation of AUB-E is the symptom of HMB, although some instances of intermenstrual bleeding may also be related.<sup>11</sup> The AUB-I category refers to AUB that is iatrogenic: associated with intrauterine devices or pharmaceutical agents that disrupt ovulatory function, directly affect the endometrium, or (with a recent modification) interfere with systemic haemostasis. The ‘N’ category, originally called ‘Not yet classified’ is now referred to as ‘Not otherwise classified’, and is reserved for entities that are rare or that have undetermined relationship to AUB symptoms. Examples include arteriovenous malformations and the so-called ‘isthmocele’ related to the uterine scar from a previous caesarean section.

The FIGO Menstrual Disorders Committee (FMDC) recognised the need for subclassification of at least some of the nine categories to provide further granularity for research and/or clinical purposes. The first of these ‘subclassification systems’ for leiomyomas is based on a widely used existing classification system for submucous fibroids (Figure 2).<sup>12</sup> The FIGO system adds additional categories for submucous myomas that do not distort the endometrial cavity (type 3), for intramural leiomyomas (type 4), various types of subserous myomas (types 5–7), and for leiomyomas not associated with the uterine corpus (type 8).

As well as a number of other papers from the FMDC, the groundbreaking 2011 publication provided explicit detail regarding the process of clinical investigation:<sup>10</sup> from the identification of the patient with one or more AUB symptoms (FIGO system 1) to the categorisation of the results of the investigation with FIGO system 2, the PALM-COEIN system.<sup>13</sup>

**The challenge of acceptance: more than ‘PALM-COEIN’**

The goals and aspirations that underlie the creation of the two FIGO systems will not be realised until there is broad-based implementation by the various stakeholders—investigators, educators, relevant societies, and regulatory bodies. Formal acknowledgement of the FIGO process has been made known by a number of national and international organisations, including the American College of Obstetricians and Gynecologists (ACOG), Society of Obstetricians



**Figure 2.** FIGO system 2. The PALM-COEIN system for categorising causes, or potential causes, of nongestational AUB in the reproductive years. Each of the PALM categories is definable with imaging or histopathology, whereas the COEI group is nonstructural. At this time, only leiomyomas are subclassified.

and Gynaecologists of Canada (SOGC), the Spanish Society of Gynecology and Obstetrics, and others. It is also recognised that bench and especially clinical research studies have a long gestation period, a factor that delays an evaluation of the 'uptake' of the systems in research. For comparative studies such as randomised controlled trials, the time from conception through design, to fundraising, approval, recruitment, performance, analysis, and publication is typically several years. As a result, it can be several years or more before the utility of these systems can truly be evaluated; however, based on continuing and as yet unpublished analyses by FMDC there is preliminary evidence that can provide insight into the use and utility of the systems to date.

The first, and perhaps, the major observation is that although the PALM-COEIN system has been recognised relatively widely, the system for definitions and nomenclature, a key starting point to diagnoses, has not. A number of textbooks, review articles, and guidelines have been published, describing the PALM-COEIN system, but persisting with the use and, by FIGO standards, misuse of terms and definitions that limit the value of the two systems. 'Menorrhagia', discarded by unanimous decision in FIGO deliberations, frequently persists as an ill-defined combination of symptom and diagnosis, and even the more evolved term, heavy menstrual bleeding, or HMB, is frequently used as a diagnosis rather than a symptom: a starting point in the search for a diagnosis. Furthermore, some authors seek to equate AUB with HMB, not recognising that abnormalities in frequency, regularity, or duration of menses, not associated with heavy bleeding, are also AUB symptoms. Clinical trials of pharmaceutical or procedural interventions persist in recruiting individuals with 'menorrhagia' or HMB as a diagnosis, a circumstance that virtually guarantees heterogeneity in classification and the inclusion of confounding factors that may confuse data analysis.

We also have not yet seen extensive use of the basic science literature. For example, if an investigator was to collect endometrial samples from patients with presumed AUB-E, it would be important to identify and probably exclude those with leiomyomas (AUB-L) and adenomyosis (AUB-A) because these entities, adjacent to the endometrium, could express confounding molecules.

### Next steps

Considerable additional work must be completed, and time must be spent fully evaluating the utility and adoption of the two FIGO systems, with appropriate related processes, for research, education, and clinical care. The members of the FMDC, past and present, have done much to facilitate this process, with publications, presentations, and workshops. This initial work must be built upon, however, adding to the educational and clinical resources, while

evaluating and responding with appropriate modifications and additions to the process. There must be a clear and persisting theme that the FIGO systems are not limited to PALM-COEIN: to do so would severely limit the utility and the uptake of the systems. Instead, the systems should be regarded as a total overhaul of how we approach the problem of AUB in the reproductive years, starting with symptoms, then proceeding with a prescribed investigative approach to reach a categorisation of potential causes for a given individual. In this way, more homogenous research populations can be defined, and defined groups of women may have a chance to be presented with similar and effective options for their clinical problem.

### Disclosure of interests

Full disclosure of interests available to view online as supporting information.

### Contribution to authorship

All have been involved with the development of the FIGO systems. MGM created the original draft of this commentary, with HODC and ISF providing manuscript review and editing.

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