



Classification and the diagnostics of abnormal uterine bleeding in nongravid women of reproductive age: the PALM-COEIN classification system adopted by the International Federation of Gynecology and Obstetrics

Patološko krvarenje iz uterusa kod žena u reproduktivnom dobu: PALM-COEIN klasifikacija Internacionalne federacije ginekologa i opstetričara

Svetlana Spremović Radjenović*†, Aleksandar Stefanović*†, Saša Kadija*†, Katarina Jeremić*†, Radmila Sparić*†; Working Group for Abnormal Uterine Bleeding, Association of Gynecologists and Obstetricians of Serbia, Montenegro and Republic of Srpska

*Faculty of Medicine, University of Belgrade, Belgrade, Serbia; †Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Belgrade, Serbia

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Introduction

A nomenclature applied invariably and non-standardized investigation methods for abnormal uterine bleeding (AUB) complicate comparison of studies by different researchers. To design a universally accepted system for describing bleeding problems in reproductive-aged women, a new classification system was created named for the acronym PALM-COEIN (polyp, adenomyosis, leiomyoma, malignancy and hyperplasia; coagulopathy, ovulatory dysfunction, endometrial, iatrogenic and not yet classified). The International Federation of Gynecology and Obstetrics (FIGO) adopted and published this classification in 2011¹, and the American College of Obstetricians and Gynecologists adopted it in 2012². Subsequently, all publications, recommendations and guidelines have used the PALM-COEIN classification in their methodology³⁻⁵. Journal editors and editorial boards are advised to request that the materials, methods and reporting sections of the manuscripts dealing with AUB be designed in accordance with the PALM-COEIN classification¹. The Association of Gynecologists and Obstetricians of Serbia, Montenegro and the Republic of Srpska presented the information about this new classification at the Congress in Belgrade in 2015⁶.

The aim of this paper was to present the PALM-COEIN classification and the recommendations referring to non-

pregnant women in their reproductive age suffering from abnormal uterine bleeding in relation to the currently used classification in Serbia.

Investigations used to determine the patient's condition and the cause of AUB

The following investigations are used to assess the causes of AUB in the affected woman: duration and quantity of flow, measurement of hemoglobin and hematocrit, assessment of coagulopathies, evaluation of the uterus for leiomyomas by ultrasound, assessment of endometrial cavity by any method, assessment of ovulation. These data are clinical, ultrasound and laboratory measures used in the clinical practice for AUB evaluation, and they have also been retained in the PALM-COEIN classification.

Acute, chronic, intermenstrual and heavy menstrual bleeding – new terminology, first-time adopted in the PALM-COEIN classification

Available classifications used before the PALM-COEIN did not make a distinction between acute and chronic AUB in non-pregnant women. In everyday practice, most clinicians record if a patient requires immediate volume re-

placement as the first step in clinical examination. However, they formally described the patient's condition as hemodynamically unstable, shocked, or seriously anemic.

The PALM-COEIN defines acute AUB as an episode of heavy bleeding, which demands immediate intervention in order to prevent copious blood loss. After the immediate intervention, a following examination will reveal the underlying cause of the acute episode of AUB.

By contrast, chronic AUB is characterized by bleeding that lasted for the bulk of the past six months. Bleeding is also unexpected and abnormal in volume and frequency. Chronic AUB, in a clinician's opinion, does not require immediate intervention.

The intermenstrual bleeding (IMB) by the PALM-COEIN, occurs between two regular menses. This term is to replace the word metrorrhagia, which should be abandoned¹.

Terms from the previous classifications that should be abandoned according to the PALM-COEIN classification

The term metrorrhagia has been replaced by the term intermenstrual bleeding and the term menorrhagia by the term heavy menstrual bleeding (HMB). It is recommended that the previously used term dysfunctional uterine bleeding should also be abandoned. This term was previously used in the diagnosis when there were no systemic or locally definable structural causes of AUB; therefore, it is not used in the PALM-COEIN classification. Women diagnosed according to the previous classification of dysfunctional uterine bleeding have a disorder of ovulation, or primary endometrial disorder or coagulopathy. What is common for all these states is that there are no systemic or locally definable structural causes for uterine bleeding. Thus, the abandoned terms dysfunctional uterine bleeding, metrorrhagia and menorrhagia are not part of the PALM-COEIN system¹.

Definition and nomenclature in the PALM-COEIN classification

The PALM-COEIN classification has 9 main categories and the first letter of each category makes the acronym PALM-COEIN. The main categories are the following: polyp, adenomyosis, leiomyoma, malignancy and hyperplasia; coagulopathy, ovulatory dysfunction, endometrial, iatrogenic and not yet classified. The PALM comprises groups where the etiology of bleeding is a structural disorder that can be determined by imaging techniques and/or histopathology, whereas the COEIN comprises groups which have dysfunctional disorders in the etiology of bleeding and they cannot be defined by imaging techniques (Table 1)¹.

P – polyp

Polyps are not a frequent cause of AUB, however, some can be included in its etiology. Polyps are endometrial proliferations and they are composed of a variable quantity of glandular, connective and vascular tissue components. They are diagnosed by ultrasound, or by ultrasound combined with

Table 1

PALM-COEIN: Basic Classification System¹

P	Polyp
A	Adenomyosis
L	Leiomyoma submucosal other
M	Malignancy and hyperplasia
C	Coagulopathy
O	Ovulatory dysfunction
E	Endometrial
I	Iatrogenic
N	Not yet classified

hysteroscopic imaging, which is also crucial for excluding polypoid – appearing endometrium (considered to be a variant of normal) from this category. Histopathology may or may not be part of the diagnostics that will determine the presence of a polyp.

For the basic classification system, polyps are categorized as being either present or absent¹.

A – adenomyosis

The PALM-COEIN accepted the sonographic criteria as the minimum requirements for the diagnosis of adenomyosis. Transvaginal ultrasonography (TVUS) has proven to be useful for detecting adenomyosis, but the technique depends highly on the operator. The magnetic resonance imaging (MRI) is the most accurate, non-invasive diagnostics procedure for determining adenomyosis; however, it is not widely available, so that is why it is not mandatory.

In compliance with the PALM-COEIN publication document, adenomyosis, similar to leiomyomas, is a disorder that should have its own subclassification system¹. To our knowledge, there is no new data related to the adenomyosis subclassification, which is still being researched.

The project dealing with adenomyosis subclassification suggests that any subclassification of adenomyosis must begin with an evaluation of the myometrium underlying the endometrium, the so-called junctional zone (JZ). The imaging of the homogeneous thickening of the JZ has become the standard criterion for non-invasive diagnosis. The MRI is currently the most precise technique for detecting a whole spectrum of lesions, which is also the basis for subclassification, ranging from increased thickness of the JZ to overt adenomyosis and adenomyomas⁷.

The absolute presence of heterotopic endometrial tissue in the myometrium and the myometrial hypertrophy are the two main components of the sonographic appearance of adenomyosis.

The 3-dimensional reconstruction of the uterus in the coronal plane has recently provided a different view of the JZ. In relation to the standard 2-dimensional imaging, the 3-dimensional TVUS coronal and multiplanar views of the uterus provide an improved view of the lateral and fundal aspects of the uterine cavity and JZ. It can be concluded that 3-dimensional TVUS evaluation of the JZ is more accurate in detecting adenomyosis than the conventional 2-dimensional evaluation⁸.

L – leiomyoma

The term leiomyoma has been selected out of several terms that are in use as the most adequate for defining benign fibromuscular tumors in the PALM-COEIN system. Leiomyomas are frequently present in women of reproductive age, however, as with polyps they are rarely the cause of AUB.

Several issues are taken into consideration when making the classification system: the relation of the leiomyoma to the endometrium and serosa; the uterine location of the leiomyoma (upper segment, lower segment, cervix, anterior, posterior and lateral); the size of the lesions; the number of the lesions and the existing leiomyoma classification system⁹.

In addition to the primary classification system, which reflects only the presence or absence of one or more leiomyomas, there are also secondary and tertiary classification systems. In the secondary system, leiomyomas involving the endometrial cavity (submucosal, marked as SM) must be distinguished from the others (marked as O), because submucosal lesions are generally considered to be the most common contributors 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.¹⁰ and subsequently adopted by the European Society for Human Reproduction and Embryology (ESHRE). The system has been in use worldwide for more than 15 years and is considered important in the design of the PALM-COEIN system. As a result, the PALM-COEIN system involves the categorization of intramural and subserosal leiomyomas; when the leiomyoma abuts or distorts the endometrium and the serosa, it is categorized initially by the submucosal classification, followed by the subserosal classification – within the two values separated by a hyphen. This tertiary classification (Table 2) is believed to be the most useful to clinical investigators, but clinicians, particularly those who perform resectoscopic or hysteroscopic myomectomy may find immediate clinical use¹ for it.

The relationship between AUB and leiomyomas has not been completely understood¹¹. Previous postulated theories included an increased endometrial surface area and the pres-

ence of fragile and engorged vasculature in the perimyoma environment. The increase in vascular flow observed along with these enlarged vessels can overcome platelet action. The increasing knowledge reveals very complex cellular and molecular changes associated with leiomyomas, with an impact on angiogenesis, an alteration in vasoactive substrates and growth factors, as well as an alteration in coagulation¹². The effect of leiomyomas on endometrial function is now thought to represent a field change within the uterine cavity rather than just being limited to regions overlying the leiomyoma(s). Some of these changes may have an impact on endometrial receptivity and implantation as well as on AUB¹³.

M – malignancy and hyperplasia

In reproductive-aged women, atypical hyperplasia and malignancy are a relatively uncommon, but very significant potential cause of AUB. These etiologies classified as AUB-M are further subclassified using the appropriate World Health Organization (WHO) and FIGO classification system. Thus, the PALM-COEIN classification system is not created to replace the present FIGO and WHO categorization of malignant diseases^{1, 14, 15}. It should be noted that malignancy, as an etiology of AUB, must be considered in all women of reproductive age.

C – coagulopathy

High quality evidence demonstrates that approximately 13% of women with HMB have biochemically detectable systemic disorders of hemostasis, most often Von Willebrand disease¹⁶. It is important that considering systemic hemostasis becomes a part of everyday practice, particularly in the differential diagnosis of HMB, partly because such disorders do contribute to some cases of AUB, and partly because evidence shows that few clinicians consider systemic hemostasis disorders as an etiology of AUB.

Although chronic anticoagulation therapy could be considered iatrogenic, and classified accordingly, the PALM-COEIN designers determined that it would be more appropriate to classify the affected women as having coagulopathy (AUB-HMB-C).

Table 2

Leiomyoma subclassification system ¹		
SM – Submucosal	0	Pedunculated intracavitary
	1	< 50% intramural
	2	≥ 50% intramural
O – Other	3	Contacts endometrium, 100% intramural
	4	Intramural
	5	Subserosal ≥ 50% intramural
	6	Subserosal < 50% intramural
	7	Subserosal pedunculated
Hybrid leiomyomas (impact both endometrium and serosa)	8	Other (specify e.g. cervical, parasitic)
	Two numbers are listed separated by a hyphen. By convention, the first refers to the relationship with the endometrium while the second refers to the relationship to the serosa. One example is below: 2–5	Submucosal and subserosal, each with less than half the diameter in the endometrial and peritoneal cavities, respectively.

O – ovulatory dysfunction

Ovulatory dysfunction can contribute to the genesis of AUB and is usually manifested as a combination of unpredictable timing of bleeding and variable amount of flow, which can result in HMB in some cases. Ovulation disorders may be 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 and surgical intervention¹⁷. Ovulatory dysfunction comprised a vast majority of cases encompassed by the now discarded term dysfunctional uterine bleeding.

Endocrinopathies should be considered in the etiology of most ovulatory disorders (e.g., polycystic ovary syndrome, thyroid diseases, hyperprolactinemia, adrenal gland diseases, weight related disturbances such as obesity, anorexia, weight loss, and mental and physical stress experienced during extreme exercise associated with elite athletic training)¹⁸. In transitional periods, such as adolescence and perimenopause, ovulatory disorders are frequent and expected. The etiology of some disorders cannot be adequately determined^{19,20}.

E – endometrial

When the menstrual periods are predictable but heavy, and no other causes are identified, this can indicate to a case of primary disorder of endometrium. In such cases the mechanisms regulating local endometrial hemostasis are changed, which can result in HMB. In fact, high quality evidence has demonstrated deficiencies in the local production of vasoconstrictors, such as endothelin1 and prostaglandin F2 α , or accelerated lysis of endometrial clot, because of the excessive production of plasminogen activator in addition to the increased local production of substances that promote vasodilatation, such as prostaglandin E2 and prostacyclin²¹.

HMB can be a manifestation of the primarily changed molecular mechanisms of endometrial repair. Such disorders of endometrial repair may be primary or secondary, caused by endometrial inflammation or infection. The consistent relationship between the histological diagnosis of endometritis and the presence of AUB has not been demonstrated, but the studies that published these data are retrospective and included a small cohort of women. There is a well-defined relationship between AUB and subclinical infection with *Chlamydia trachomatis*.

Endometrial disorders in reproductive-aged women should be diagnosed after a normal ovulatory function and excluding other identifiable abnormalities.

I – iatrogenic

The major component of AUB-I classification is abnormal endometrial bleeding that occurs during gonadal steroid therapy. Such type of bleeding is termed as breakthrough bleeding. In a pooled study, 35% of women with large follicles that produce endogenous estradiol had breakthrough bleeding. Other potential causes of reduced levels of circulating estrogens include agents, such as anticonvulsants and antibiotics^{22,23}.

Systemic agents that interfere with dopamine metabolism have the potential to cause ovulation disorders, and

AUB secondary to ovulation disorders can be the result of medication use that impacts dopamine metabolism. Within this group of medicaments, the tricyclic antidepressants are often present and they impact the dopamine metabolism indirectly by reducing the serotonin uptake, which further reduces the inhibition of prolactin release.

Anticoagulant drugs (warfarin, heparin and low molecular weight heparin) often induce HMB. The manifestations are similar to those in inherited hemostasis disorders. By convention, it was determined that this type of iatrogenic AUB should be placed in the AUB-C category¹.

N – not yet classified

Various other uterine conditions and disorders may play a role in the AUB occurrence, but specific diagnostic assays are needed to determine this. These entities include chronic endometritis, arteriovenous malformations, as well as myometrial hypertrophy. Such conditions have not been adequately identified and examined yet.

Notation

The formal approach follows the WHO tumor, nodus, metastasis (TNM) staging of malignant tumors, with each component addressed for all patients. The presence or absence of pathology in each category is noted using 0- if absent, 1- if present, or ? - if not yet assessed. For example, if submucosal leiomyoma is present, the notation will be: Po Ao L1SM Mo- Co OoEo Io No. Since the full notation might be considered cumbersome in clinical practice, an abbreviation option has been developed, which will record only positive findings¹. Therefore, the abbreviation option for our example will be L1SM.

Guidelines for investigation

Women with AUB may have zero, one, or multiple identifiable factors contributing to the genesis of abnormal bleeding. There may also be a pathology present, but one that is believed not to contribute to AUB¹.

Firstly, a clinician faced with AUB has to ensure that bleeding is not related to an undiagnosed pregnancy and that emanates from the cervical canal, rather than from another location. A pregnancy may be reliably determined by a beta-subunit of human chorionic gonadotropin (HCG) assay. For the first distinguishing, the cervix is visualized by gynecological examination. Women with both acute and chronic AUB should be tested for anemia; preferably full blood count should be taken.

Once the bleeding is confirmed to be of uterine origin, the clinician will follow the schedule designed for dealing with each of the components of the classification system¹.

Endometrial and uterine cavity assessment

If good ultrasonic images are obtained and there are no findings indicative of endometrial polyps and submucosal leiomyomas, the endometrial cavity may be considered normal in relation to lesions causing AUB. However, if the exam is suboptimal, if there are imaging features indicative of

endometrial polyps, and if there are leiomyomas that may be encroaching on the endometrial cavity, imaging with other, more sensitive techniques is recommended – usually saline infusion sonohysterography (SIS) (also called sonohysteroscopy or hysterosonography) or hysteroscopy, whichever is available to the clinician. If office hysteroscopy is available, there may be an additional benefit should polyps be identified as they could be removed in the same setting.

When vaginal access is difficult (adolescents and virginal women), the MRI or alternatively hysteroscopic examination under anesthesia may be the best approach.

With the PALM-COEIN classification, P-polyp is confirmed only with the documentation of 1 or more clearly defined polyps, generally either with SIS or hysteroscopy. A patient may be categorized as AUB L1SM with either SIS or hysteroscopy, but with care as not to infuse the distending medium with such pressure that the natural relationships of the leiomyoma with the endometrium and myometrium are distorted.

Myometrial assessment

Myometrium is assessed primarily with the combination of TVUS and transabdominal ultrasonography to identify the presence of leiomyomas (primary subclassification), if there is a lesion leading to L1 assignment. A combination of imaging tools (TVUS, SIS, hysteroscopy or MRI) is necessary for the secondary subclassification. The relationship of leiomyoma with the endometrium, myometrium and serosa is required for the tertiary subclassification of the leiomyoma type. In clinical terms, this would require the use of an MRI.

It is important to distinguish between leiomyomas and adenomyomas. An assignment of A1 requires three of the criteria to be met; otherwise the patient is classified as Ao. If available, an MRI may be used to distinguish between leiomyomas and adenomyosis and to measure the myometrial extent of submucosal leiomyomas. MRI use is not obligatory according to the PALM-COEIN classification, because it is not part of everyday clinical practice in many healthcare systems.

The diagnostic procedure in chronic AUB patients in clinical settings

Initial evaluation – the patient has experienced one or a combination of unpredictability, excessive duration, abnormal volume or abnormal frequency of bleeding for at least 3 months. Structured history will determine ovulatory function, potentially related medical disorders, medications and lifestyle factors that may contribute to AUB. For those with HMB, the structured history should include specific questions. Patients with a positive screen are those with HMB associated with one of these symptoms: *post partum* hemorrhage, surgical – related bleeding or bleeding after dental work; or patients with HMB associated with two of these symptoms: bruising 1–2 times per month, epistaxis 1–2 times per month, frequent gum bleeding and a family history of bleeding. Physical examination will explore the appearance of the visible part of the cervix.

The proposed ancillary investigations are: determination of the beta- subunit of HCG as a reliable diagnostic tool

for pregnancy exclusion, complete blood count, testing for endocrinopathies – thyroid function, serum prolactin and serum androgens, if there is oligoanovulation. Measurement of the serum progesterone has to be timed to the best estimate of the mid-luteal phase and may provide evidence of ovulation presence in the given cycle. The frame of the therapy depends on the future fertility desires, which have to be discussed beforehand.

Examination is guided by the patient's history and clinical situation, such as age, chronic ovulatory disorder, risk factors for endometrial hyperplasia and malignancy. Uterine examination begins with TVUS.

Selection of patients for endometrial sampling is based on the combination of factors that indicate to the risk for atypical hyperplasia or carcinoma. Several guidelines use the same combination of age, personal and genetic risk factors and TVUS screening for endometrial echo-complex thickness. According to some studies, age is not important as the independent factor. However, most of them suggest that endometrial sampling should be considered after a certain age, usually after the age of 45. Endometrial biopsy is advised for those at increased risk. Evaluation of the uterus should include imaging, if there is the risk of: structural disease, previous endometrial sampling has not provided an adequate specimen or previous medical therapy has been unsuccessful. Endometrial sampling is necessary for persistent, unexplained AUB or AUB which does not react adequately to treatment. If it is possible, hysteroscopic evaluation of the uterine cavity should accompany the sampling procedure in these situations¹. Similarly, hysteroscopic evaluation of the uterine cavity is useful for endometrial evaluation in cases of virginal girls or women, and it is more convenient in an anesthetized environment. Finally, given the apparent relationship between a chlamydial infection of the endometrium and AUB, it is advisable to consider testing for *Chlamydia trachomatis* in cervical smears¹.

Worldwide implementation of the PALM-COEIN classification

After the adoption of the PALM-COEIN classification system, some publications compared the classic with the new terminology. One of the publications found that in a total of 471 women included, the term "hypermenorrhea" covered 15 different pathology combinations, "menorrhagia" nine, "metrorrhagia" 14, and "menometrorrhagia" 18, according to the old classification²⁴.

The suggested diagnostic methodology and protocols in PALM-COEIN do not differ from those used so far in Serbia. According to the classification, the minimal necessary diagnostic tools are standardized for each PALM-COEIN group and defined to be widely applicable worldwide.

Conclusion

A multinational group of clinicians and researchers have created a classification system to facilitate a multi-institutional investigation of the epidemiology, etiology and

treatment of women with acute and chronic AUB. The classification system is based on group formation done according to the etiology and clinical valuation of the amount of blood loss. The PALM-COEIN classification immediately points to the etiology of bleeding, and accordingly, it has very precise, non-descriptive terminology. Descriptive terms widely used in the old terminology are not used in the PALM-COEIN classification, which can make difficulties for some clinicians when they encounter them for the first time. The agreement

process created a practical system, which contains recommendations for the minimal necessary diagnostic procedures that could be used to classify patients with AUB by clinicians in most countries worldwide. The task of national professional associations is to present and enable the adoption of the PALM-COEIN classification at national level, with the aim of allowing clinicians to compare diagnostics strategies and therapies in patients with AUB with gynecologists worldwide.

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