

# Abnormal uterine bleeding: Terminology, FIGO classification and management

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## ABSTRACT

Throughout the history of medicine, a wide range of terms has attempted to define normal menstruation and abnormal uterine bleeding in relation to its various etiologies. Over time, terminological variations have hampered the documentation of symptoms, the establishment of consensus on the use of various diagnostic techniques and medical or surgical methods of treatment, and the results of multicenter or multinational clinical trials. Abnormal uterine bleeding (AUB) in women of reproductive age is a common gynecological symptom outside of pregnancy, which includes any symptomatic variation starting from the criteria defining normal menstruation, respectively variations in frequency, regularity, duration, or volume, including intermenstrual bleeding, formerly known as spotting. Abnormal intermenstrual bleeding is typically associated with benign lesions such as chronic cervicitis or cervical or endometrial polyps, although it can rarely be caused by cervical or endometrial cancers. Abnormal uterine bleeding in postmenopause requires endometrial biopsy.

**Keywords:** abnormal uterine bleeding, FIGO classification, reproductive age, menstruation, menopause, postmenopause

## INTRODUCTION

Throughout the history of medicine, a wide range of terms has attempted to define normal menstruation and abnormal uterine bleeding in relation to its various etiologies. Society's perception of menstruation is wide and substantially variable, mainly due to cultural and religious differences. Understanding the historical context that determines the taboos and mysticism related to a woman's uterine bleeding is an important part of the

medical education of the clinician in any field, who must treat a woman of reproductive age, but especially in adolescence or postmenopause (1).

Considering menstruation as a disease of women has remained unchanged since the first century AD, for 1500 years. The contempt and pejoration that followed brought us back to the 17th century, when menstruation was first described as "a menstrual cycle" (2,3).

As for the causes of abnormal uterine bleeding, until the early 1800s, when the list of risk factors

started to include physical effort, multiple pregnancies, obesity and “being passionate”, Aristotle was the only one who attributed the abnormal bleeding to vein rupture, overheating of blood or trauma (1). In the late 19th century, Beckwith Whitehouse academically described menstruation as “one of the sacrifices that women must make on the altar of evolution and civilization” (1,4). The start of the attempts to standardize terminology date back to the 1700’s, when William Cullen, Professor of Medicine at the University of Edinburgh, Scotland, began writing his research results in English and not Latin. Thus, the Latin term “menorrhagia” was included in English terminology to describe the excessive bleeding that many patients experience, Cullen implementing different terms to refer to abnormal bleeding outside pregnancy (menorrhagia rubra) or during pregnancy (menorrhagia abortus) (5,6). In 1935, Graves introduced the term dysfunctional uterine bleeding, but it was never clearly defined (7,8).

Over time, terminological variations have hampered the documentation of symptoms, the establishment of consensus on the use of various diagnostic techniques and medical or surgical methods of treatment, and the results of multicenter or multinational clinical trials.

In FIGO, this terminological heterogeneity initiated the formation of the Menstrual Disorders Working Group in 2005, which later became a stable structure, the Menstrual Disorders Committee (2012), which developed international recommendations on definitions and terminology (FIGO AUB SYSTEM 1) and classification of the causes of abnormal uterine bleeding during the reproductive period (FIGO AUB SYSTEM 2) (6,9-12). In 2018, the same structure revised the criteria for normal and abnormal uterine bleeding for women of reproductive age (13). Together, these terminological and classification systems are ways to improve the accuracy of communication on the etiology, symptoms, diagnosis, and treatment of abnormal uterine bleeding at reproductive age. The process of developing the new system of terms and definitions included the identification of old descriptive terms for abnormal uterine bleeding, terms that should no longer be used due to their weak defining characters and the high degree of confusion they induce. Among the most used classic terms are menorrhagia and metrorrhagia. Menorrhagia has never been explicitly defined, being used in various ways to describe the symptoms of heavy, severe uterine bleeding, regardless of context, predictable or not, and metrorrhagia has had the significance of irregular uterine bleeding for a long time. The FIGO Expert Group also recommends abandoning the term dysfunctional uterine bleeding. Dysfunctional metrorrhagia is

the term often used with great variability, both as a vague symptom and as a poorly argued diagnosis. Most often used as a diagnosis to rule out bleeding whose structural pathogenic substrate cannot be identified, it is no longer useful now that scientific, technological, diagnostic, and therapeutic progress has led to a better understanding of the mechanisms of abnormal uterine bleeding, which currently has well-defined causes (1,12-16).

Many other well-established terms have been removed from modern terminology set forth by the FIGO Committee: functional uterine bleeding, hypermenorrhea, hypomenorrhea, menometrorrhagia, hemorrhagic metropathy, polymenorrhagia, polymenorrhea, uterine hemorrhage, oligomenorrhea.

Another element that was the basis of the development of the new terminology was the need to extend the updating process to develop a new system for classifying the causes of abnormal uterine bleeding, which should be a flexible and easy-to-apply concept, clearly indicating the abilities of modern medicine to etiologically define abnormal uterine bleeding (12).

The consensus on terms and definitions was achieved following numerous international meetings with the participation of both clinicians and researchers, based on many proposals analyzed and voted plenary (12,13).

## TERMINOLOGY AND DEFINITIONS

Premenopausal abnormal uterine bleeding is any intermenstrual bleeding, or menstrual bleeding at less than 24 days or more than 38 days, and/ or with a loss of blood volume greater than 80 ml, and/ or lasting longer than 8 days, and/ or which has variability between the duration of the cycles greater than, or equal to 8-10 days; any postmenopausal woman’s uterine bleeding, except for cyclic bleeding caused by postmenopausal sequential hormone replacement therapy, is considered abnormal.

The definition of abnormal uterine bleeding begins with the establishment of the standardized definition of normal menstruation, which was based on population studies, using medians and confidence intervals (6,10). Normal menstruation is defined by the following characteristics, which are located between the 5th and 95th percentiles:

- Frequency: between 24 and 38 days; menstruation is considered rare if it occurs at > 38 days and frequent if it occurs at intervals < 24 days.
- Regularity: variations ≤ 7-9 days. The duration of the menstrual cycle is represented by the number of days from the first day of a menstrual cycle to the first day of the next cy-

cle; between the shortest and longest menstrual cycle, the difference should not be more than 7-9 days. Variations > 9 days define irregular menstrual cycles. These regulations exclude extremes of reproductive age and can be practically expressed as variations of +/- 4 days.

- Duration: ≤ 8 days; the duration of normal menstruation is the number of bleeding days of a single menstrual period; there are no specific clinical features associated with the reduction in duration < 4 days, except for amenorrhea. Thus, the duration of menstruation can be normal or prolonged.
- Volume: 5-80 ml of blood lost during a period, objectively appreciated. The clinical definition is developed by the UK National Institute for Health and Care Excellence and consists of a volume of lost blood that does not affect a woman's quality of life physically, socially, emotionally and/ or materially. The loss of a volume of blood < 5 ml per cycle defines light menstruation, while the loss of a volume > 80 ml, or a volume that affects a woman's quality of life, define heavy menstrual bleeding (6,10,17).

Abnormal uterine bleeding (AUB) in women of reproductive age is a common gynecological symptom outside of pregnancy, which includes any symptomatic variation starting from the criteria defining normal menstruation, respectively variations in frequency, regularity, duration, or volume, including intermenstrual bleeding, formerly known as spotting. The 2018 FIGO update defines intermenstrual bleeding as always being abnormal, random, or predictable, cyclical (early cycle, mid cycle, late cycle) (13).

Acute AUB is defined by FIGO and accepted by the American College of Obstetricians and Gynecologists (ACOG) as an episode of uterine bleeding that occurs in a woman of reproductive age who is not pregnant and who loses a large enough amount of blood to require an immediate intervention for prevention of further bleeding (1,13,18,19).

Chronic AUB is defined as abnormal uterine bleeding regarding frequency, regularity, duration and/ or volume, which is present for at least most of the last 6 months (12,17) (Figure 1).

Adolescents or women who have previously had regular menstrual cycles and who currently have no bleeding for at least 6 months are diagnosed using the term secondary amenorrhea (17). It is worth noting that some experts suggest the use of the term secondary amenorrhea in the absence of menstruation for more than 3 months in adolescents or women who have previously had regular menstrual cycles, and for 6 months respectively for young women or women who have previously had irregular menstrual cycles. Primary amenorrhea is defined as the absence of menses until the age of 15.

Based on numerous studies, it can be argued that menstruation should occur at regular and reasonably predictable intervals. The duration of the menstrual cycle between the 5th and 95th percentiles, representing the difference between the longest and shortest menstrual cycle over a period of one year, should not exceed 20 days. This cut-off is established based on studies conducted on the general population of women, which includes those with very short (under 18 days) and very long (over 43 days) occasional menstrual cycles. Excluding these extremes leads to a variability in the duration of the menstrual cycle of 7-9 days, depending on age, typically the cycles being longer in younger

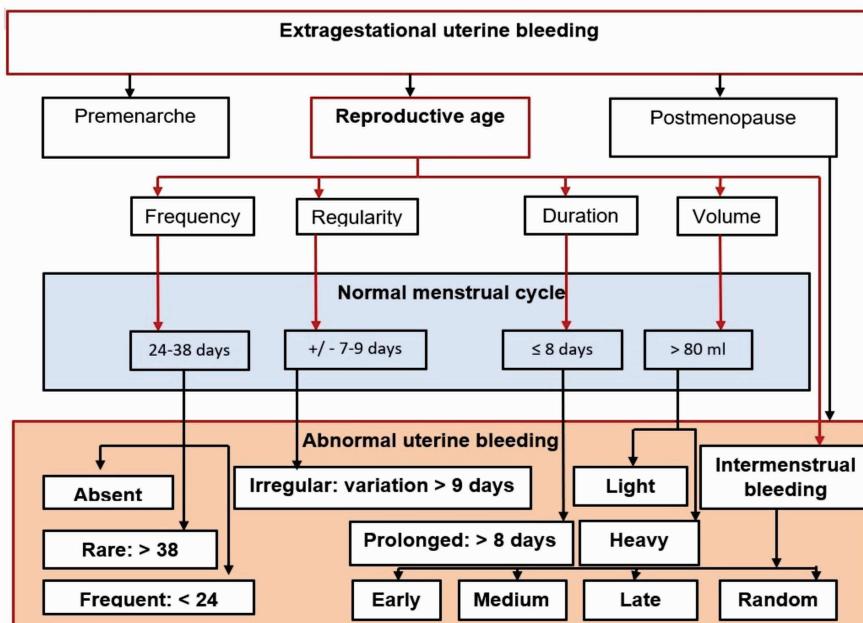


FIGURE 1. Defining characteristics of normal menstruation and abnormal types of uterine bleeding (1,16)

women (18-25 years) and in women approaching the transition period to menopause (43-45 years).

The duration of normal menstruation in population studies was up to 8 days (17-22). Consequently, the prolongation of the menstrual period beyond 8 days will be recorded using the term prolonged menstrual bleeding. Until now, it is considered that there is no clinical relevance to justify the definition of a short bleeding time.

The term heavy menstrual bleeding was first introduced in the medical literature by the New Zealand Guideline Group in 1999 and then taken up in the guide of the National Institute for Health and Clinical Excellence (NICE) of Great Britain (23,24). Typically, heavy menstrual bleeding is part of a symptomatic complex that includes varying degrees of dysmenorrhea and fatigue, along with other symptoms. Mild menstrual bleeding is an occasional report of patients, and may be based on cervical stenosis or uterine synechia. Heavy menstrual bleeding is defined by the loss of more than 80 ml of blood/ cycle (25,26). However, it is necessary to remember that over 50% of the total blood loss is an endometrial transudate, the blood component varying between 30-50%.

Abnormal uterine bleeding that occurs between well-defined menstrual cycles is called intermenstrual bleeding, a pattern that cannot be established in the case of irregular and/ or very frequent menstrual cycles. Intermenstrual uterine bleeding can be cyclical, with predictable recurrence either in the middle of the cycle, or in the early follicular period, or in the late luteal phase. Alternatively, intermenstrual bleeding may be acyclic, with a random occurrence between menstrual cycles. Repeated intermenstrual bleeding in the middle of the menstrual cycle is a common physiological phenomenon. Clear bleeding in small amounts or bloody leukorrhea released at about the time of ovulation can be recognized on a regular basis in almost 9% of healthy women of reproductive age (27). It usually occurs shortly after ovulation and is associated with a mediocyclic decrease in circulating estradiol levels (28). Occult intermenstrual bleeding revealed only by testing the vaginal secretion is a much more common phenomenon, present in about 90% of women, occurring shortly after ovulation (29). Early or late cyclic intermenstrual bleeding typically presents as very mild bleeding lasting one or more days, indicating either a luteal phase defect (in the case of premenstrual cyclic bleeding) or the existence of other conditions such as endometriosis, endometrial polyps, or other structural lesions of the genital tract.

Abnormal intermenstrual bleeding is typically associated with benign lesions such as chronic cervicitis or cervical or endometrial polyps, although it

can rarely be caused by cervical or endometrial cancers.

All the above definitions apply to women who are not receiving systemic or topical treatment with steroid hormones or other pharmacological agents that may directly affect gonadal steroid hormones production or endometrial function. These agents include progesterone-based contraceptives with or without estrogen, GnRH agonists, aromatase inhibitors, and selective estrogen or progesterone receptor modulators. Defining the terminology applicable to this patient population, a reference period of 90 days is used, which complies with the WHO recommendations (16,30-32).

### CLASSIFICATION SYSTEM FOR THE CAUSES OF ABNORMAL UTERINE BLEEDING

The basic but comprehensive system for classifying the causes of abnormal uterine bleeding, FIGO, from 2011, updated in 2018, is divided into nine categories in the order of acronym PALM-COEIN, the causes being structural (polyps, adenomyosis, leiomyomas, malignancy, and hyperplasia) and independent of structural abnormalities, respectively coagulopathies, ovulatory dysfunction, endometrial dysfunction, and iatrogenic causes. A separate class comprises unclassified entities.

The category of leiomyomas is subdivided in the presence of at least one submucosal leiomyoma and the presence of leiomyomas that do not affect the endometrial cavity (Table 1) (1). During the evaluation, the possibility of coexistence of multiple pathological aspects potentially generating abnormal bleeding should be considered. In such cases, failure to treat the most likely cause of bleeding should be followed by further investigation of the other etiologies found (1).

Structural causes are visible, measurable, and evident imagistically and histopathologically; the causes of the COEIN system are imagistically unapproachable, organized to form a matrix for the exploration of abnormal uterine bleeding (16).

**TABLE 1.** PALM-COEIN adapted classification of the etiology of abnormal uterine bleeding (FIGO 2011/ 2018) (1,12,13)

Structural causes of AUB	Non-structural causes of AUB
Polyp	Coagulopathies
Adenomyosis	Dysfunctional ovulations
Leiomyoma	Endometrial
<ul style="list-style-type: none"> <li>• At least one submucosal myoma (SMM)</li> <li>• Myomas that do not affect the endometrial cavity (EC)</li> </ul>	Iatrogenic Includes the use of pharmacological agents for anticoagulation and those that interfere with ovulation
Malignancy and hyperplasia	Unclassified

The diagnosis of dysfunctional uterine bleeding should be reclassified into one of the following: coagulopathy or systemic hemostasis (AUB-C), ovulatory dysfunction (AUB-O) generally reflecting hypothalamic-pituitary-ovarian axis dysfunction, or primary endometrial disorder (AUB-E) due to dysfunction of the cellular and molecular mechanisms responsible for regulating the volume of menstrual bleeding or endometritis such as Chlamydia (16).

Endometrial or endocervical polyps (AUB-P) may be present in hysterosonographic evaluation (such as saline instillation ultrasonography) and/ or hysteroscopy, with or without histopathological confirmation. The classification does not include the polypoid endometrium.

Adenomyosis (AUB-A) traditionally requires histopathological diagnosis. Currently, transvaginal ultrasound or nuclear magnetic resonance imaging can accurately diagnose adenomyosis. The role that this pathology plays in the genesis of AUB continues to be misunderstood, but some studies attribute a low degree of involvement, while other studies define a population with severe and concomitant symptoms of menorrhagia and dysmenorrhea. Like polyps and leiomyomas, adenomyosis is a condition to which its own subclassification system will be dedicated, including the standardization of diagnostic, ultrasound, and histopathological methods (12,33-37).

Leiomyomas (AUB-L) can be sensed by clinical examination, but pelvic ultrasound is necessary for an accurate diagnosis. FIGO has hierarchically created 3 classification systems for uterine leiomyomas: the first classification performed by ultrasound examination exclusively reflects the presence or absence of one or more benign tumors of the smooth muscle; the secondary classification requires the radiologist to differentiate the myomas that imprint the endometrium or distort the endometrial cavity from those with other locations, submucosal myomas being those that most likely contribute to AUB, although some studies support the effect of intramural myomas on the amount of menstrual blood lost; the differentiation within the secondary classification is based on hysterosonography or hysteroscopy. The third classification system is a characterization of all types of leiomyomas in relation to the endometrium or uterine serosa, the category of lesions located in the cervix being also present along with the fibroids detached from the uterus, called “parasite” due to blood supply from extrauterine sources. The system valuable to the surgeon specializing in the treatment of infertility, who will determine the most appropriate method of removal of leiomyomas based on the classification: hysteroscopic or abdominal approach, laparoscopic or laparotomy. The location of a tumor at both the

endometrial and serosa border will be mainly included in the category of submucosal leiomyomas and secondary in the category of subserosal localization, the clinician benefiting from the description of the size, number, and locations of uterine leiomyomas (Table 2).

**TABLE 2.** Adapted subclassification system for leiomyoma localization within the PALM-COEIN classification of the etiology of abnormal uterine bleeding (FIGO 2011/ 2019) (12,13)

	Primary subclassification system		Tertiary subclassification system
Polyp Adenomyosis Leiomyoma Malignancy & hyperplasia	Submucosae	0	Pedunculated intracavitary
		1	> 50% intracavitary
		2	≤ 50% intracavitary
	Other	3	It reaches the endometrium 100% intramural
		4	Intramural
		5	Subserosal ≥ 50% intramural
		6	Subserosal < 50% intramural
		7	Pediculate subserosal
		8	Other
		Hybrid leiomyomas	2-5

Malignancy and hyperplasia (AUB-M) include atypical endometrial hyperplasia, carcinomas, stromal endometrial sarcomas diagnosed by endometrial biopsy, and some cases of leiomyosarcoma, accidentally detected by the same method (36,37).

Congenital or acquired coagulopathy (AUB-C) contributes 24% to the causes of abnormal uterine bleeding, the most common systemic condition affecting hemostasis, being von Willebrand’s disease.

Screening for coagulation disorders is based on a medical history that may include the following issues: heavy menstruation after menarche, postpartum hemorrhage, bleeding during surgery or dental treatment, minor symptoms whose tandem is required by positive screening including bruises with a frequency of 1-2/ month, or epistaxis with the same temporal pattern, frequent gingival bleeding, or a positive family history of hemorrhagic diathesis. Patients with positive screening require further evaluation including hematologic consultation, von Willebrand factor testing, and ristocetin cofactor assay (38-40).

Ovulatory dysfunction (AUB-O) manifested as anovulation or sporadic late ovulation characteriz-

es the late reproductive period in which luteal phase events occur, characterized by follicular recruitment in the early luteal phase followed by premature maturation that causes high circulating levels of estradiol and associates increased menstrual cycle volume. Females with AUB-O typically show a combination of menstrual cycle irregularity and volume variability that can be included in the category of menorrhagia. The classification of ovulatory dysfunction is based on population studies according to which patients must have variations of more than 7 days between menstrual cycles in the last 12 months. Although there is often no identifiable cause, ovulatory dysfunction may be associated with psychological stress, weight loss or gain, excessive physical exercise, medication that affects dopamine metabolism, endocrine disorders that affect the hypothalamic-pituitary-ovarian axis, such as hyperprolactinemia, thyroid disease, and polycystic ovary syndrome. Ovulatory disorders caused by treatments such as the above-mentioned ones should be classified as AUB-I (iatrogenic causes).

It is interesting that the incidence of anovulation is increased at all ages, sometimes even in the presence of menstrual cycles considered regular, manifesting exclusively by infertility (41).

Endometrial causes (AUB-E) determine menorrhagia with or without intermenstrual bleeding, in the absence of other obvious causes. Many of these patients have primary endometrial impairment. In the case of menorrhagia, the main cause is affecting the mechanisms of regulation of local endometrial hemostasis. Given that there are no specific tests, the diagnosis is of exclusion (42,43).

AUB-I iatrogenic causes include the use of medical devices and mainly intrauterine contraceptive systems or pharmacological agents.

AUB-N includes several additional entities that may contribute to the cause of abnormal uterine bleeding in certain individuals. This category includes arterio-venous malformations and abnormal uterine bleeding in the context of the existence of an isthmocele developed secondary to the incision of the segment during cesarean section (44,45).

## **ABNORMAL UTERINE BLEEDING CLINICAL MANIFESTATIONS**

Acute abnormal uterine bleeding, which can go as far as hypovolemic shock, requires emergency medical or surgical intervention; a number of oral or systemic drugs have been shown to be effective in stopping at least temporary the bleeding, before resorting to invasive interventions such as intrauterine tamponade, selective uterine artery embolization, endometrial ablation or hysterectomy, transvaginal clamping of uterine arteries under Doppler

guidance being the latest innovative suggestion in the attempt of a conservative approach of these cases. Assessment of AUB causes can usually be done only after hemodynamic recovery, exclusion of pregnancy and the possibility of applying the methods of investigation in conditions of acceptable hemostasis (1).

Bleeding between the first week of life and menarche is considered abnormal, as is metrorrhagia; before the age of 10, determined according to the chronological age and stage of puberty established by examination, bleeding may be due to trauma or sexual abuse, malignancy, exogenous estrogen intake, early puberty and hypothyroidism, urethral prolapse, genital warts, lichen sclerosus, infectious vaginitis or foreign bodies, platelet dysfunction or deficiency of coagulation factors usually manifesting after menarche (1).

Abnormal uterine bleeding occurs in 64-88% of women with endometrial polyps, which is an indication for polypectomy. Typically, polyps cause intermenstrual bleeding by superficial necrosis, but the patient's medical history includes metrorrhagia and dysmenorrhea relatively frequent (1).

Abnormal uterine bleeding is the most common manifestation of endometrial hyperplasia: abundant, prolonged, and/ or irregular. In premenopause, these bleedings occur in most cases due to the background of a hyperplasia that occurred a long time ago, evolving asymptotically. Infertility may or may not be associated with menstrual disorders. The pattern of transition to menopause is characterized by an increase in the interval between menstrual cycles that become progressively smaller in quantity; evaluation becomes necessary whenever the intermenstrual period is less than 24 days or burdened with spotting, bleeding or bloody leukorrhea, menstrual cycle lasts more than 8 days and has an ascending quantitative evolution from one cycle to another, or total blood volume lost exceeds 80 ml (1).

Abnormal uterine bleeding is the most common manifestation of endometrial cancer and its early onset contributes significantly to the early diagnosis of the disease. It is variable, from quantitatively reduced red or pink blood loss in elderly women, to pre- and perimenopausal menometrorrhagia. A classic sign described is pink hydrodischarge with the appearance of "meat juice". Elderly patients with cervical stenosis may present purulent leukorrhea, with or without hemato-pyometra, signs frequently associated with advanced stages of the disease. The pain may manifest as a feeling of pressure or pelvic discomfort, sometimes colicative, generated by the prolapse of some tumor parts into the cervix (1).

Approximately 15% of diagnosed endometrial cancers are asymptomatic, their detection being

due to suggestive images obtained by ultrasound or computed tomography indicated in other conditions, or the evidence of atypical endometrial cells at the Pap smear cytological examination, a situation that also correlates with an advanced stage. The presence of normal endometrial cells on cervical cytology after the age of 40, although incompletely elucidated, also seems to show the presence of an endometrial disease, the risk of endometrial cancer being 2 times lower than in the case of atypical cell detection. Abnormal uterine bleeding does not correlate in terms of volume with cancer risk, but the following bleeding patterns are suggestive of endometrial cancer:

- postmenopausal women with any type of bleeding, including spotting; of postmenopausal women with bleeding, 3-20% have endometrial cancer and another 5-15% have endometrial hyperplasia (46-48).
- women between 45 and menopause, with any abnormal uterine bleeding including intermenstrual bleeding, frequent bleeding at intervals less than 24 days between bleeding, menorrhagia with loss of more than 80 ml of blood or prolonged bleeding over 8 days. In addition, endometrial neoplasia should be suspected in women with amenorrhea greater than or equal to 6 months by anovulation.
- women under 45 with persistent abnormal uterine bleeding due to unantagonized estrogenic exposure (obesity, chronic anovulation) or failure of drug therapy, as well as patients at high risk of endometrial cancer (Lynch syndrome) (1).

The use of the 45-year threshold adopted by ACOG is supported by studies proving the low risk of cancer and endometrial hyperplasia under this age. The risk of endometrial hyperplasia and cancer increases with age from 6% cases occurring between 35 and 44 years and 19% cases occurring between 45 and 54 years, to cases occurring between 13 and 18 years, representing 0.05% (49).

The volume of bleeding is suggestive, with heavy bleeding most often coming from the uterus. Blood color has limited etiological value. Systematic post-coital bleeding is suggestive of cervical pathology, but can occur in any friable/inflamed area of the lower genital tract.

Metrorrhagia is most often due to uterine leiomyomas, especially but not exclusively submucosal adenomyosis, accompanied by dysmenorrhea, or segmental-transverse scar defects post-cesarean section, knowing that more than 2/3 of patients with one or more scars develop endomyometrium defects, of which about 30% show postmenstrual cyclic bleeding (50). Other common etiologies include endometrial hyperplasia, carcinoma, and rarely

uterine sarcoma, use of Tcu-380A intrauterine devices, endometrial polyps, endometritis, and pelvic inflammatory disease, which usually manifests by intermenstrual bleeding and less frequently by regular heavy menstruation.

Congenital or acquired arteriovenous malformations after exploratory procedures, as well as disorders of endometrial hemostasis involving alterations in the biosynthesis of progesterone-dependent prostaglandins (PGF<sub>2α</sub> and endothelin-1) due to ovulatory dysfunction, can also cause menorrhagia. Arteriovenous malformations are localized conglomerations of arteries and veins with thin, abnormally connected walls, capable of causing acute, foudroyant, menstrual or intermenstrual AUB. Congenital forms are rare, derived by the embryological development of primitive vascular structures, but the acquired forms are more frequent, uterine curettage for residual ovular fragments being one of the main etiological factors that determine the formation of multiple arteriovenous fistulas between intramural arteries and uterine venous plexuses, belonging par excellence to the color Doppler ultrasound examination, and the optimal treatment being performed by interventional radiology (51,52).

Intermenstrual bleeding has multiple causes, the most common of which are endometrial polyps and endometrial hyperplasia (53), the use of contraceptives, carcinoma or very rarely uterine sarcoma, endometritis or pelvic inflammatory disease, post-traumatic endometrial abnormalities such as post-myectomy uterine scar defects. As mentioned before, many women with regular menstrual cycles have ovulatory spotting. Frequent intermenstrual bleeding is due to cervical pathology that includes cervical cancer, endocervical polyps, cervicitis, or ectropion.

Irregular menstrual cycle due to ovulatory dysfunction such as anovulation/ oligoovulation is characterized by alternating periods of amenorrhea lasting 2-3 months with periods of marked spotting or metrorrhagia. Irregular pattern of cycles occurs particularly at the extremes of reproductive age. Among the most common causes of ovulatory dysfunction are polycystic ovary syndrome, thyroid disease, and hyperprolactinemia. Although thyroid disease has long been considered to cause hypermenorrhea, recent studies disprove this association (54).

Low menstrual cycle volume occurs during contraception, with other causes including partial cervical stenosis or Asherman's syndrome. Regular menstrual cycles with a high frequency, but not less than 24 days, occur during the transition to menopause.

According to Women's Health Initiative (55), 7% of postmenopausal women present bleeding. Ana-

lyzing Hofmeister's data (56) and those from the National Surveillance Epidemiology and End Results (SEER) program (57), the U.S. National Cancer Registry, Smith-Bindman et al. (58) state that, however, 15% of endometrial cancers are diagnosed in the absence of bleeding, and the 23% of women over 50 years of age diagnosed based on symptomatology with stage II or more advanced endometrial cancer, assume the existence of a period of subclinical evolution of the disease.

Any postmenopausal woman with spontaneous uterine bleeding should be evaluated for endometrial cancer, as this potentially fatal condition is the cause of bleeding in about 10% of cases (variable depending on the risk factors present, 1-25%) (59). The most common cause of postmenopausal bleeding is atrophy of the vaginal or endometrial mucosa (60). Endometrial hyperplasia, polyps and submucosal leiomyomas are the most common etiologies of the first postmenopausal years. The incidence of bleeding seems to be correlated with the time elapsed since the onset of menopause, decreasing in proportion to the moving away from this moment. Etiologically, the abnormal bleeding is usually attributed to an intrauterine source, but it can also come from the cervix, vagina, vulva, fallopian tubes, or it can be related to a form of ovarian pathology. The origin of the bleeding may also be non-gynecological, affecting the urethra, bladder, rectum, or intestine. Cervical stenosis can prevent the externalization of blood from the uterine cavity resulting in hematometry.

A large study involving 1,138 women between the ages of 41 and 91 years reported bleeding from atrophy in 59% of cases, polyps in 12% of cases, endometrial cancer in 10% of cases, and endometrial hyperplasia in 9.8% of cases, hormonal effect in 7% of cases, cervical cancer in less than 1% of cases, the remaining 2% being due to hydrometry, pyometra or hematometry (59). By comparison, two studies determining the prevalence of endometrial pathology in asymptomatic women in postmenopause report a basal risk of endometrial abnormalities of 17-18%, represented mainly by atrophy and polyps (61,62). Hypoestrogenism causes endometrial and vaginal atrophy. Atrophic endometrial surfaces in contact in the absence of intracavitary fluid to prevent friction produce microerosions of the surface epithelium and a consecutive chronic inflammatory reaction that is a factor in spotting or mild bleeding (63). Endometrial cancer is the leading cause of postmenopausal bleeding, its incidence increasing with advancing age (59).

Investigating any bleeding in menopausal women, less than 8 weeks after onset, has been shown to have similar efficacy to screening for the early diagnosis of endometrial cancer and survival rate, in

other words, there is no prognostic advantage of menopausal screening of asymptomatic women compared to those under 8 weeks of bleeding (64).

The clinical profile is very important in the development of this condition, nulliparous women, over the age of 70, with diabetes, having an 87% risk of developing endometrial cancer or complex hyperplasia, compared to the 3% risk of women without these characteristics (65).

Uterine sarcoma represents 3-5% of all uterine tumors, also manifested by bleeding in menopause. This form of neoplasia arises from the endometrial stroma or myometrium, a situation in which the tumors look like benign leiomyomas, the endometrial histology being normal, the diagnosis requiring hysterectomy. Choriocarcinoma is a very rare cause of bleeding in menopause.

Endometrial polyps with an unexplained etiology, but with growth stimulated by estrogen therapy or tamoxifen are the second leading cause of bleeding in menopause. Estrogen replacement therapy causes vaginal bleeding, the frequency of which depends on the regimen.

Endometrial hyperplasia clinically manifested by uterine bleeding, due to normal estrogenic deficiency in postmenopause, is an abnormality that requires additional biopsy to transvaginal ultrasonography that caused increased endometrial thickness due to abnormal uterine bleeding in menopause. In these situations, endogenous estrogen production is increased, coming from estrogen-secreting ovarian or adrenal tumors or from processes that take place in the peripheral adipose tissue.

Leiomyomas, the most common pelvic tumors in women, with a postmenopausal prevalence of 1/10 compared to premenopausal prevalence, are a potential but extremely rare cause of bleeding in menopause. The diagnosis of uterine sarcoma should be considered a more likely cause of symptoms in postmenopausal women with intramyometrial tumors, although the overall incidence of sarcoma is low. Adenomyosis does not cause postmenopausal symptoms in the absence of hormone replacement therapy. Pelvic irradiation may cause late vaginal bleeding.

Anticoagulant therapy, including heparin, low molecular weight heparin, or coumarins, is another common cause of uterine bleeding in menopause.

Endometritis is an unusual cause of bleeding in the elderly, with endometrial tuberculosis still occurring in developing countries (66).

The medical history determines the menstrual cycle history, the characteristics of the physiological menstrual cycle being the interval of 24-38 days between cycles, regularity, global volume of blood lost less than 80 ml and duration of maximum 8 days (49,67), pattern of abnormal uterine bleeding, asso-



upper genital tract bleeding is ectopic pregnancy, which is ruled out by a negative pregnancy test. From the point of view of frequency, exceptional extrauterine etiology of upper genital tract bleeding is ovarian and fallopian tube cancer.

The methods of paraclinical evaluation of endometrial pathology are shown in figure 2.

The etiological diagnosis of structural causes is based on transvaginal ultrasound with Doppler ultrasound and saline instillation in sonohysterography and endometrial biopsy by aspiration/ endometrial biopsy by dilation and curettage/ targeted hysteroscopic endometrial biopsy +/- endometrial biopsy by post hysteroscopy uterine curettage (Figure 2) (1).

USTV differentiates the etiological structural classes of bleeding and guides the optimal way of endometrial biopsy: by hysteroscopic visualization and targeted biopsy, followed by uterine curettage of the entire endometrial cavity in focal pathology, or by aspiration or dilation and uterine curettage in global endometrial pathology.

## CONCLUSIONS

In postmenopause, abnormal uterine bleeding occurs in 4-11% of women, 10% of whom are due to endometrial cancer. Abnormal uterine bleeding

with endometrial thickness  $\leq 4$  mm ultrasound evaluated does not require further investigation (endometrial cancer risk 1/ 917 cases, method sensitivity 96%, false negative rate 0.25-0.5%), USTV application as a first-line investigation reducing more than 40% of unnecessary biopsies (ACOG and HRS). Recurrence/ persistence of bleeding requires endometrial biopsy. In the case of USTV determination of intracavitary fluid in menopause, endometrial cancer with an added endometrial thickness  $\geq 4.5$  mm or a focal lesion and cervical cancer as a potential cause of cervical stenosis that led to fluid accumulation, should be excluded. Prioritization on ultrasound criteria of patients at high risk of endometrial cancer for urgent histopathological confirmation includes in the predictive risk score for endometrial cancer, BMI along with Doppler score, endometrial thickness, interruption of exploration junction mode B and irregularity surface to sonohysterography. Using these parameters, a score  $\geq 4$  identifies endometrial cancer with a sensitivity of 91% and a specificity of 94%.

Abnormal uterine bleeding in postmenopause requires endometrial biopsy in the following situations: endometrial thickness (USTV)  $\geq 4.5$  mm, the endometrium cannot be adequately viewed via USTV +/- SHG, endometrial thickness (USTV) is  $\leq 4$  mm but with persistent/ recurrent bleeding.

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