

DOI 10.29254/2077-4214-2022-3-166-12-17

UDC 618.14-005.1-036.1-048.445

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### FEATURES OF CLINICAL PRESENTATION OF ABNORMAL UTERINE BLEEDING IN WOMEN OF REPRODUCTIVE AGE

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*Abnormal uterine bleeding (AUB) is an urgent clinical problem that has not yet been fully studied. The purpose of the study is to outline and generalize principles of AUB diagnosis and presentation in reproductive age women based on literature analysis and international recommendations. A review of world citation databases (MEDLINE, EMBASE, Cochrane) over the last 10 years was conducted. The concept of a normal menstrual cycle and AUB, classification of the International Federation of Gynecology and Obstetrics are presented. Main disorders resulting in AUB have been determined. The choice of a rational strategy requires establishing the cause of AUB assigning it to one of PALM-COEIN categories. A morphologic cause (PALM) can be diagnosed by imaging and/or histology, while COEIN group is associated with non-visualized (non-morphologic) causes. Under international recommendations, laboratory studies in AUB include serum  $\beta$ -HCG level; examination for anemia; coagulography. Hormonal panel is required in irregular menstruation and hypothyroidism risk; tests on chlamydial infection (in infection risk); a Pap test to exclude cervical disorders. Hysteroscopy and endometrial biopsy are the "gold standard" in diagnosis of intrauterine abnormalities to rule out precancerous conditions and endometrial cancer.*

**Key words:** abnormal uterine bleeding, menstrual cycle, morphological and non-morphological causes, intrauterine disorders.

**Connection of the publication with planned research works.** This work is a fragment of the planned scientific work "Emergencies in obstetrics and gynecology in different age periods", state registration number 0119U002904.

**Introduction.** Abnormal uterine bleeding (AUB) is a clinical problem constantly observed in the practice of every gynecologist, while also being largely an understudied problem. Keeping up with the rapid development of medical science, AUB has also undergone important changes in its terminology and classification. Over the past few decades, the definition and clinical essence of AUB have been rethought, its elements have been reclassified, and approaches to diagnosis and treatment have become multifaceted. In this century of personalized medicine, every clinician must realize that one solution does not fit all the patients, and it is necessary to rely on modern protocols when determining diagnostic and treatment tactics, while taking into account the entire range of problems of a particular patient.

Menstrual disorders are the most common gynecological conditions in the general population. AUB can mean both heavy and irregular menstrual bleeding, and many women experience a combination of both. The significant impact of AUB lies not only in its prevalence, but also in its impact on quality of life, associated loss of productivity, and significant health care costs. AUB that occur during the reproductive period, not associated with pregnancy, are characterized by lengthening the duration of menstruation, volume of blood loss, or increased bleeding episodes. This is complicated by anemia, fatigue, pain, a decrease in the quality of life due to not only unpleasant symptoms, but also the limitation of social activity and/or an increase in material costs for the purchase of additional sanitary products, medicines,

as well as loss of remuneration due to temporary incapacity.

The importance of solving this problem is evidenced by numerous recommendations of leading societies of obstetricians and gynecologists of different countries, aimed at standardization and optimization of approaches to the diagnosis and treatment of AUB [1-3]. Gynecologists face several problems in providing care to such patients. The multifactorial etiology, numerous medical and surgical treatment options available, and the different clinical settings in which this abnormality is studied influence treatment outcomes, resulting in a large body of literature that is difficult to interpret and translate into clinical decision-making.

Considering the above, the **purpose of the review** is to outline and generalize the main principles of diagnosis and course of AUB in women of reproductive age based on literature analysis and international recommendations.

**Object and methods of research.** Based on the materials of the world's leading citation databases (MEDLINE, EMBASE, Cochrane), a review of literature data for the past 10 years, devoted to the issue of abnormal uterine bleeding in women of reproductive age, is presented. The possibilities of a complex of diagnostic studies and the course of this abnormality are considered. An analysis of the PALM-COEIN classification is given.

**Research results and their discussion.** AUB is a definition currently used to indicate changes in menstrual blood loss. Terms such as dysfunctional uterine bleeding or menorrhagia are recognized as outdated and canceled [1]. AUB is any deviation from normal menstrual cycle, in particular, changes in regularity and frequency of menstruation, duration of bleeding or the amount of blood loss [2].

In 2011, the International Federation of Gynecology and Obstetrics (FIGO) published a set of clinical guide-

lines to assist clinicians and researchers in the development and interpretation of diagnostic tests for AUB in the reproductive age and provided evidence-based clinical data [3]. FIGO introduced the concept of acute non-gestational AUB at a reproductive age, which distinguishes such bleeding from chronic AUB. This approach was approved by the American College of Obstetricians and Gynecologists [4]. Chronic non-gestational AUB in reproductive age is defined as bleeding from the uterine body, which is abnormal in duration, volume, frequency and/or regularity and is present over most of the previous 6 months. Acute AUB, on the other hand, is defined as an episode of severe bleeding, which the doctor considers sufficient for immediate intervention to minimize or prevent further blood loss. Acute severe menstrual bleeding can be detected during chronic AUB or may occur spontaneously [3, 4].

In practice, doctors confuse AUB and profuse menstrual bleeding (PMB). AUB is a deviation of menstrual bleeding from the norm by volume, duration or time of beginning. These include intermenstrual bleeding or bleeding secondary to irregular menstrual cycle. Thus, AUB is a generalized term. PMB is a type of AUB with a regular (ovulatory) cycle that occur, according to various sources, in 25-50% of women of reproductive age in one or another period of life [5, 6]. In our opinion, in clinical practice it is expedient to use PMB characteristics based on the definition of the National institute for health and care excellence (NICE), namely: "excessive menstrual blood loss that negatively affects physical, social, emotional, or material aspects of a woman's quality of life" [7].

When diagnosing AUB, the obstetrician-gynecologist always takes into account the parameters of the patient's menstrual cycle in parallel with the assessment of bleeding. This makes it possible to narrow down the diagnostic search very quickly and not to prescribe unnecessary tests. For example, PMB is a bleeding in a regular cycle without ovulatory dysfunction, so there is no need to check follicle-stimulating hormone, luteinizing hormone, or prolactin levels.

According to the FIGO definition, the duration of a normal menstrual cycle is 24–38 days. It stands to mention that in 2018, FIGO made some adjustments to the definition of a normal menstrual cycle, presented in **table 1** [4].

Thus, a period of 7–9 days or less is taken as normal variability of the menstrual cycle (from the shortest to the longest). Depending on age, fluctuations can be 9 days or less in 18-25 years; at the age of 26–41 years – 7 days or less; at 42–45 years old – 9 days or less. Going beyond these limits is the basis for the diagnosis of irregular menstruation. It is necessary to note that FIGO currently distinguishes only two categories of menstrual duration: normal (8 days or less) and long (more than 8 days). In 2019, the results of a large-scale British-Swedish study were published, which included 612,613 ovulatory cycles in 124,648 patients. The average cycle time in this review was slightly longer than the traditional 28 days at 29.3 days [8].

In practice, it is not uncommon when several causes of AUB are identified during the examination. For example, a woman with a uterine fibroid may have endometrial polyp or hyperplasia. That is why, in such a case, the doctor must always determine the leading cause of bleeding and, taking this into account, choose therapy. The classification of AUB causes, adopted by FIGO in 2011, is used to facilitate this process. Obstetricians and gynecologists all over the world actively employ this classification. Based on the results of its practical application, it can be concluded that it speeds up diagnosis and facilitates the choice of management tactics for patients with bleeding. The specified classification distinguishes 9 main categories, located according to the PALM-COEIN acronym (**fig.**).

According to the PALM-COEIN classification, two main groups of AUB are distinguished, related and not related to organic disorder of the uterus. A morphologic cause (PALM) can be diagnosed by imaging and/or histology, while the COEIN group is associated with causes that cannot be visualized (non-morphologic).

In 2020, the PALM-COEIN classification was revised and its main categories were clarified (**table 2**) [9].

Polyp (AUB-P) is a localized hyperplastic process of the endometrium, consisting of glands, stroma, blood vessels, and occasionally smooth muscle tissue. The exact cause of the development of polyps is still unknown; there is information about the role of abnormalities in chromosomes 6 and 12, which can regulate the proliferative process, resulting in endometrial hyperplasia and polyps, as well as changes in the content of matrix metalloproteinases and cytokines in the basal layer of the endometrium. Under such conditions, protein p 63, which is a marker of reserve cells of the basal layer of the endometrium, is of certain importance. Risk factors for the development of endometrial polyps include age over 40, hypertension, obesity, and tamoxifen intake. Polyps can be flat or on a thin leg, the size varies from a few millimeters to 3-4 centimeters. 64–88% of endometrial polyps have symptoms of heavy menstrual bleeding, intermenstrual or postcoital bleeding. At the same time, the severity of symptoms does not correlate with the number, size and location of polyps. Polyps are usually benign, but may be atypical or malignant (0–4.8%). Postmenopausal women with AUB have the highest risk of developing a malignant process. The main method of diagnosing endometrial polyps is ultrasound. Endometrial polyps are defined as intrauterine formations of

**Table 1 – Changes to the FIGO AUB system adopted in 2018 (normal and abnormal uterine bleeding) [4]**

Parameters	Changes
Frequency	Amenorrhea became part of the frequency category
Regularity	Revised definition of regularity Normal deviation (from the shortest to the longest) 7-9 days A small difference depends on age
Duration	There are currently only two duration categories Normal: ≤8 days Prolonged: >8 days
Volume	Definition of PMB symptoms NICE definition Bleeding volume sufficient to impair a woman's quality of life, intermenstrual bleeding Definition of symptoms of intermenstrual bleeding Spontaneous bleeding between menstruations Can be both cyclical and random

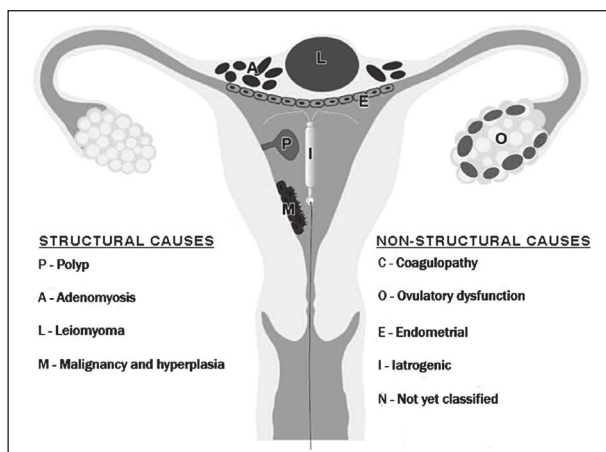


Figure – The PALM-COEIN classification.

high echogenicity, the minimum size of which is 2–4 mm during echoscopy, sometimes there are polyps spread over the entire uterine cavity. Visualization of the polyp improves in the proliferative phase of the cycle. However, it should be noted that transvaginal ultrasound does not have 100% sensitivity, as small polyps are not always visualized. If it is impossible to obtain a clear image of the endometrium, visualization with the involvement of more sensitive methods, such as hydrosalpingoscopy or hysteroscopy [10], is recommended.

Adenomyosis (internal endometriosis) (AUB-A) is determined by the presence of ectopy of endometrial glands and stroma in the myometrium, which induces a hypertrophic and hyperplastic reaction in the surrounding tissue of the myometrium. Adenomyosis is most often a diffuse disease that affects the entire myometrium. It can also be focal (adenomyoma).

Leiomyoma (AUB-L). The terms “fibromatous nodules”, “myoma”, “leiomyoma” are synonymous and denote a monoclonal tumor arising from the smooth muscle tissue of the uterus (myometrium). In the PALM-COEIN system, experts chose the term leiomyoma as the most accurate. Myomatous nodes can be single or multiple and differ in size, location, and blood supply. Myomas are usually classified into 3 subgroups depending on location: subserosal (on the outer wall of the uterus), intramural (in the myometrium), and submucosal or submucosal (on the inner wall of the uterus). FIGO pre-

sented a new, more detailed classification system [11]. The indicated classification is staged, contains three levels: the first is the presence of a leiomyoma, the second is the division of leiomyoma nodes into submucosal and other, the third is the division of nodes into types from 0 to 8. Leiomyoma is usually asymptomatic, but can be associated with a number of clinical problems. The most common symptom of uterine leiomyoma is AUB. The mechanism of AUB associated with leiomyoma is under investigation. An increase in the surface of the endometrium, a violation of vascular regulation and hemostasis in the endometrium are indicated as possible explanations [12].

Malignancy and hyperplasia (AUB-M). Hyperplastic processes of the endometrium are pathological diffuse or focal proliferation of the mucous membrane of the uterus with predominant damage to glandular structures and to a lesser extent to its stromal component [13]. Diagnosis of the type of hyperplasia involves the employment of generally accepted WHO classification (2014) [14]. According to this classification, endometrial hyperplasia is divided into hyperplasia without cellular atypia and hyperplasia with cellular atypia, distinguishing simple and complex forms in each group. Simple and complex atypical hyperplasia of the endometrium is interpreted as endometrial hyperplasia, simple and complex atypical forms of hyperplasia are interpreted as precancer.

AUB is considered as a risk factor for endometrial malignancy. Endometrial biopsy must be performed in the case of AUB in women over 40 years of age; as well as in the presence of additional risk factors for endometrial cancer, such as obesity, lack of childbirth in history, polycystic ovary syndrome, diabetes mellitus, heavy hereditary cancer history; in the absence of effect from conservative therapy; during intermenstrual bleeding or for functional evaluation of the endometrium [15]. The FIGO classification is used to diagnose the stage of endometrial cancer [16].

AUB associated with coagulopathy (AUB-C) includes a spectrum of systemic disorders of hemostasis. J. Marjoribanks et al. [17] reported that 33% of women with coagulation disorders had a history of AUB. Conversely, according to estimates, 13% of women with AUB were diagnosed with von Willebrand disease, which

is one of the most common disorders of hemostasis [18]. Specialized tests (Willibrand factor, ristocetin cofactor) should be performed in patients with a positive screening result for hemostasis disorders. Screening should be based on the patient’s medical history. It is considered positive if it contains any of the following items: profuse menarcheal bleeding, postpartum bleeding, bleeding associated with surgery. And also two or more of the following symptoms: bruising from one to two times a month, nosebleeds from one to two times a month, frequent bleeding gums and a family history of heavy bleeding [19, 20]. Previously, by agreement, persons with AUB who took anticoagulant therapy were classified as AUB associated with coagulopathy. However, such AUBs are currently considered iatrogenic [4].

Table 2 – Main changes in the PALM-COEIN classification (2020 revision) [9]

Category	Changes
AUB-A	Improved criteria for ultrasound diagnosis
AUB-L	Definition of type 3 node as a submucous uterine myoma Definitions and differences between nodes are introduced: Type 0 and 1; 6 and 7 Type 2 and 3; 4 and 5
AUB-C	Does not include AUB associated with agents disrupting blood coagulation, now belongs to AMA-I
AUB-I	Now includes AUB associated with any iatrogenicity, including the use of anticoagulants and agents affecting ovulation
AUB-O	New diagnostic threshold changes in the characteristics of normal bleeding and cycle, given earlier, have been introduced. No longer includes ovulatory disorders associated with agents disrupting ovulation
AUB-N	The category “Not yet classified” is replaced by “Does not belong to any of the categories”

Ovulatory dysfunction (AUB-O) occurs with anovulation and the absence of the corpus luteum. In this situation, there is progesterone deficiency and uncontrolled secretion of estrogens, resulting in continuous proliferation of the endometrium caused by low progesterone levels. The endometrium is fragile and lacks sufficient stromal support. Various situations are known to cause anovulation: polycystic ovary syndrome, hyperprolactinemia and thyroid disease, as well as premature ovarian failure. However, anovulation can also occur physiologically, especially during adolescence (due to immaturity of the hypothalamic-pituitary axis) or during perimenopause, when ovulation disorders precede menopause [21].

Endometrial dysfunction (AUB-E) can be considered after excluding structural causes, anovulation or coagulopathy. According to some data, the primary dysfunction of the endometrium causes AUB. The primary disease may be associated with a deficiency of local production of vasoconstrictors (endothelin-1 and prostaglandin F<sub>2a</sub>), accelerated endometrial clot lysis (excess production of plasminogen activator) or with an increase in local production of prostaglandin E<sub>2</sub> and prostacyclin (I<sub>2</sub>). AUB-E can also be caused by infection or inflammation of the endometrium [22]. According to the FIGO consensus, there are no informative diagnostic tests in this situation.

AUB associated with the use of systemic pharmacotherapy or intrauterine systems/devices is classified as iatrogenic (AUB-I). In addition to gonadal steroids such as estrogens, progestins, and androgens, and agents that directly affect their production or local function, this category now includes nonsteroidal drugs that promote ovulation disruption, as well as drugs that affect dopamine metabolism, in particular, phenothiazines and tricyclic antidepressants. In the initial classification of women with AUB associated with the use of anticoagulants, this type of bleeding was classified as coagulopathy (AUB-C). In the modern review, they are considered iatrogenic and classified as AUB-I. Thus, rivaroxaban has a greater effect on the volume of menstrual bleeding than traditional vitamin K antagonists [20].

An unclassified AUB (AUB-N) was created in the original system for reasons that occur infrequently or are not well defined. These include (but are not limited to) arteriovenous malformations [23], uterine scar or "isthmocele", which often occur due to prior caesarean section and are sometimes considered the cause of AUB [24]. As new data is received, it can be allocated to a separate category or defined in those categories that already exist.

To choose a rational management tactic, it is necessary to establish the cause of AUB and assign it to one of the indicated categories according to the PALM-COEIN classification [25, 26]. The amount of blood loss is assessed according to clinical indicators or a point scale (menstrual blood loss pictogram); an objective alkaline-hematin test is used during scientific research [7].

According to international recommendations [27, 28], in the case of AUB, laboratory diagnosis should consist of the following stages: determining the level of  $\beta$ -HCG in blood serum (in case of suspected pregnancy); examination for the presence of anemia (clinical blood test, in particular, platelets); coagulogram, if hemostasis abnormality is suspected, hematologist consultation

and special examination (in the case of Willebrand disease, determination of factor VIII, ristocetin factor, Willebrand factor antigen). Hormonal examination is carried out in case of irregular menstruation and risk of hypothyroidism (determination of TSH, progesterone level); research on chlamydial infection (in case of high infection risk); a Pap test is performed to rule out cervical disorder.

The recommendations of the American and Canadian College of Obstetricians and Gynecologists (2013) provide an algorithm for the examination of patients with AUB [2]. Transvaginal ultrasound examination (US) of the pelvic organs is considered as a first-line diagnostic procedure for assessing the state of the endometrium (higher informativeness in postmenopause). Doppler provides only additional information about the nature of the disorder of the endometrium and myometrium. Sonohysterography, which is performed in case of insufficient information of transvaginal ultrasound to clarify focal intrauterine disorder, has a high diagnostic significance. MRI is not considered as a first-line diagnostic procedure in the case of AUB, but is recommended for multiple uterine fibroids to clarify the topography of the nodes before myomectomy, uterine artery embolization, FUS ablation, as well as suspected adenomyosis or in cases of poor visualization of the endometrium. Hysteroscopy and endometrial biopsy are still considered the "gold standard" for the diagnosis of intrauterine abnormalities, primarily for the exclusion of precancerous lesions and endometrial cancer. Recommended for suspected endometrial disorders, presence of risk factors for uterine cancer (obesity, polycystic ovary syndrome, diabetes, family history of colon cancer), in patients with AUB after 40 years of age. Office hysteroscopy and aspiration biopsy are preferred as less traumatic and more economical procedures.

#### Conclusions.

1. Abnormal uterine bleeding in women of reproductive age is the reason for frequent visits to primary care doctors and emergency departments.

2. Clinicians should carefully assess the health status of a woman with AUB to ensure that the bleeding is not related to pregnancy and trauma to the external genitalia.

3. A structured history should be taken, including the woman's age, regularity of menstrual cycles and associated menstrual problems (e.g., dysmenorrhea), onset and frequency of AUB, and symptoms or signs of bleeding tendency, bruising, hemorrhaging, and family history. If it is impossible to completely rule out hemostasis disorders, it is necessary to consult with hematologists.

4. After taking a complete history and ruling out pregnancy, clinicians can begin evaluating AUB using the PALM-COEIN terminology. The choice of a pathogenetically justified therapy of AUB is possible only after exclusion of structural causes (PALM) and determination of the level and nature of reproductive system dysregulation from the COEIN category.

5. The choice of long-term treatment of AUB is determined by the wishes and needs of the patient, primarily her reproductive plans – the choice of a group of drugs depends on this. This makes it possible not only to save a woman from heavy and irregular menstruation, but also to improve her quality of life, increase compliance and avoid complications.

**Prospects for further research.** The study of the features of the clinical course of AUB in women of reproductive age is relevant and promising. A clear definition of the cause of AUB, optimization of treatment methods will improve the quality of life of a woman and reduce social costs for this category of patients.

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### ОСОБЛИВОСТІ КЛІНІЧНОГО ПЕРЕБІГУ АНОМАЛЬНИХ МАТКОВИХ КРОВОТЕЧ У ЖІНОК РЕПРОДУКТИВНОГО ВІКУ

Благовещеньський Р. Є.

**Резюме.** Аномальна маткова кровотеча (АМК) є актуальною клінічною проблемою, що на сьогодні вивчена не до кінця. АМК впливають на якість життя, є причиною репродуктивних втрат, вимагають значних витрат на лікування. *Метою роботи* є викладення й узагальнення основних принципів діагностики та перебігу АМК у жінок репродуктивного віку на основі аналізу літератури та міжнародних рекомендацій. Проведено літературний огляд світових баз цитування (MEDLINE, EMBASE, Cochrane) за останні 10 років. Було визначено поняття нормального менструального циклу та АМК. Наведено класифікацію International Federation of Gynecology and Obstetrics. Визначено основні патологічні стани, які є причиною АМК. Для вибору раціональної тактики ведення пацієнтів необхідно встановити причину АМК та віднести її до однієї з категорій за класифікацією PALM-COEIN, за якою виділяють дві основні групи АМК: пов'язані та не пов'язані з органічною патологією

матки. Морфологічна причина (PALM) може бути діагностована за допомогою методів візуалізації та/або гістології, тоді як група COEIN пов'язана з причинами, які неможливо візуалізувати (неморфологічні).

Згідно з міжнародними рекомендаціями, у пацієнок з АМК лабораторна діагностика складається з певних етапів: з'ясування рівня  $\beta$ -ХГ в сироватці крові; обстеження на наявність анемії; визначення коагулограми. Гормональне обстеження проводиться в разі нерегулярного ритму менструацій та ризику гіпотиреозу; дослідження на хламідійну інфекцію – за високого інфекційного ризику; для виключення патології шийки матки проводиться ПАП-тест.

Гістероскопію та біопсію ендометрія вважають «золотим стандартом» діагностики внутрішньоматкової патології, насамперед для виключення передракових уражень та раку ендометрія.

**Ключові слова:** аномальна маткова кровотеча, менструальний цикл, морфологічні та неморфологічні причини, внутрішньоматкова патологія.

### FEATURES OF CLINICAL PRESENTATION OF ABNORMAL UTERINE BLEEDING IN WOMEN OF REPRODUCTIVE AGE Blagoveshchensky R. E.

**Abstract.** Abnormal uterine bleeding (AUB) is an urgent clinical problem that has not been fully studied at this stage. AUB affects the quality of life, causes reproductive losses, and requires significant health care costs. *The purpose of the study* is to outline and generalize the basic principles of diagnosis and presentation of AUB in women of reproductive age based on literature analysis and international recommendations. A literature review of world citation databases (MEDLINE, EMBASE, Cochrane) over the last 10 years was conducted. The concept of a normal menstrual cycle and AUB is defined. The classification of the International Federation of Gynecology and Obstetrics is presented. The main pathological conditions resulting in AUB have been determined. To choose a rational strategy for patient management, it is necessary to establish the cause of AUB and assign it to one of the categories according to the PALM-COEIN classification. PALM-COEIN classification distinguishes two main groups of AUB, related and not related to organic disorders of the uterus. A morphologic cause (PALM) can be diagnosed by imaging and/or histology, while the COEIN group is associated with causes that cannot be visualized (non-morphologic). According to international recommendations, laboratory diagnosis of patients with AUB involves certain stages: determination of the level of  $\beta$ -HCG in blood serum; examination for the presence of anemia; determination of the coagulogram. Hormonal examination is carried out in case of irregular menstrual rhythm and risk of hypothyroidism; tests on chlamydial infection (in case of high infection risk); a Pap test is performed to rule out cervical diseases. Hysteroscopy and endometrial biopsy are considered the “gold standard” for the diagnosis of intrauterine abnormalities, primarily to exclude precancerous lesions and endometrial cancer.

**Key words:** abnormal uterine bleeding, menstrual cycle, morphological and non-morphological causes, intrauterine abnormalities

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**A** – Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article.

**Received 10.03.2022**

**Accepted 09.08.2022**