

## ABNORMAL UTERINE BLEEDING IN WOMEN OF REPRODUCTIVE AGE

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### SAŽETAK

**Uvod:** Patološko krvarenje iz materice predstavlja jedan od najčešćih poremećaja zdravlja kod žena u reproduktivnom periodu. Uz to, predstavlja i značajan javno-zdravstveni problem. Cilj ovog rada je da se prikaže savremena podela, kao i osnovi dijagnostike i lečenja patoloških krvarenja iz materice.

**Metode:** U radu su prikazani podaci iz radova selektovanih pretraživanjem MEDLINE baze korišćenjem kombinacije ključnih reči: "menstrual bleeding", "abnormal uterine bleeding", "PALM-COEIN classification", "leiomyoma", "endometrial polyp", "adenomyosis", "gynecological malignancies", "coagulopathy", "diagnostics of abnormal uterine bleeding", i "treatment of abnormal uterine bleeding". Podaci prikupljeni iz odabranih radova upotrebljeni su i predstavljeni u ovom radu.

**Zaključak:** U cilju postizanja jedinstvene klasifikacije poremećaja menstrualnog ciklusa, usvojena je klasifikacija ovih poremećaja koja se naziva akronimom PALM-COEIN. Uzroci nabrojani u prvom delu akronima (PALM) imaju patološko-anatomski supstrat na nivou genitalnih organa koji se može dijagnostikovati primenom imidžing metoda i/ili histopatološkim pregledom. Uzroci nabrojani u drugom delu akronima (COEIN) uključuju difunkcionalne poremećaje i ne mogu se dijagnostikovati primenom imidžing metoda.

**Ključne reči:** krvarenje, materica, menstrualni ciklus

### ABSTRACT

**Introduction:** Abnormal uterine bleeding is one of the most common health disorders in women of reproductive age. In addition, it represents a significant public health problem. The aim of this paper is to present the modern classification, as well as the basis for diagnosis and treatment of abnormal uterine bleeding.

**Methods:** This paper presents data from publications selected from the MEDLINE database using a combination of keywords: "menstrual bleeding", "abnormal uterine bleeding", "PALM-COEIN classification", "leiomyoma", "endometrial polyp", "adenomyosis", "gynecological malignancies", "coagulopathy", "diagnostics of abnormal uterine bleeding", and "treatment of abnormal uterine bleeding". The collected data from the selected studies were used and presented in this review paper.

**Conclusion:** In order to achieve a unique classification of abnormal uterine bleeding, a classification was adopted under the name/acronym PALM-COEIN. The causes listed in the first part of the acronym (PALM) have a pathological/anatomical cause in the reproductive organs that can be diagnosed using imaging techniques and/or histopathological examination. The causes listed in the second part of the acronym (COEIN) represent a group of dysfunctional disorders and they cannot be diagnosed using imaging techniques.

**Key words:** bleeding, uterus, menstrual cycle

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## UVOD

Patološko krvarenje iz materice (engl. *abnormal uterine bleeding -AUB*) predstavlja svako krvarenje koje odstupa od normalne cikličnosti/učestalosti, dužine trajanja i obima menstrualnog krvarenja, i predstavlja jedan od najčešćih poremećaja zdravlja kod žena u reproduktivnom periodu [1,2]. Uz to, predstavlja i značajan javno-zdravstveni problem. Prema podacima iz literature, prevalencija ovih krvarenja iznosi 3 do 30% [3].

Precizno poznavanje osnova fiziologije menstrualnog ciklusa je uslov za postavljanje pravovremene dijagnoze i sprovođenje adekvatnog lečenja patološkog krvarenja iz materice. Normalan menstrualni ciklus se definiše kao regularno ciklično krvarenje, koje se javlja na prosečno 28 dana, traje 4 do 7 dana, uz prosečan gubitak krvi od oko 35 ml (Tabela 1). Ovaj ciklus je rezultat složene interakcije između hipotalamusa, prednjeg režnja hipofize, jajnika, i endometrijuma. Na svakom od ovih nivoa stvaraju se hormoni, koji omogućavaju ili sprečavaju oslobađanje hormona na drugim nivoima. Manje od 1,0% žena imaju regularne menstruacione cikluse koji traju kraće od 21 i duže od 35 dana [4].

**Tabela 1.** Karakteristike normalnog menstrualnog krvarenja

**Table 1.** Characteristics of normal menstrual bleeding

Interval između ciklusa / <i>Interval between cycles</i>	28 (21 - 35) dana / <i>days</i>
Dužina trajanja krvarenja / <i>Duration of bleeding</i>	4 - 7 dana / <i>days</i>
Obim krvarenja / <i>Bleeding volume</i>	35 (20 - 80) ml

Varijacije u dužini trajanja i intenzitetu menstrualnog krvarenja su uobičajene na početku i kraju reproduktivnog perioda - tokom adolescencije i pre nastupanja menopauze. Učestalost anovulatornih ciklusa je najveća pre 20-te godine života i posle 40-te godine života. Tokom 12 do 18 meseci nakon menarhe, menstruacioni ciklusi su iregularni, usled nezrelosti hipotalamo-hipofizno-ovarijalne osovine. Nekoliko godina nakon menarhe, dužina lutealne faze ciklusa postaje relativno konstantna (13 do 15 dana). Tokom 5 do 7 godina nakon menarhe, menstruacioni ciklusi postaju regularni i njihova dužina i trajanje se ne menjaju značajno tokom reproduktivnog perioda, iako se sa godinama dužina trajanja menstruacionih ciklusa polako smanjuje. Tokom perioda od 8 do 10 godina pre menopauze, učestalost ovulatornih ciklusa se smanjuje [1 - 4].

Ukoliko dođe do poremećaja funkcije hipotalamo-hipofizne osovine i/ili strukturalnog poremećaja materice (miomi, polipi, adenomioza, malignitet), ili poremećaja u koagulaciji krvi (koagulopatije, jatrogeni uzroci), remeti se normalan menstrualni ciklus i nastaje patološko krvarenje [5].

## INTRODUCTION

Abnormal uterine bleeding (AUB) is any bleeding that deviates from the normal cycle/frequency, length, and quantity of menstrual bleeding, and represents one of the most frequent health problems in women in the reproductive period [1,2]. Also, it is a significant public health issue. According to data from literature, the prevalence of this type of bleeding ranges from 3 to 30% [3].

Accurate knowledge of the physiology of menstrual bleeding is a prerequisite for establishing a timely diagnosis and administering appropriate treatment for abnormal uterine bleeding. A normal menstrual cycle is defined as regular cyclical bleeding, which occurs every 28 days, on average, and lasts from 4 to 7 days, with an average blood loss of around 35 ml (Table 1). This cycle is the result of a complex interaction between the hypothalamus, the anterior pituitary lobe, the ovaries, and the endometrium. At each of these levels, hormones are secreted, which enable or inhibit the release of hormones at other levels. Less than 1.0% of women have regular menstrual cycles that are shorter than 21 days or longer than 35 days [4].

Variations in the duration and intensity of menstrual bleeding are common at the beginning and at the end of the reproductive period - in adolescence and before menopause. The frequency of anovulatory cycles is the highest before 20 years of age and after 40 years of age. During 12 to 18 months after menarche, menstrual cycles are irregular, due to the immaturity of the hypothalamic-pituitary-ovarian axis. Several years after menarche, the length of the luteal phase of the cycle becomes relatively constant (13 to 15 days). During the period of 5 to 7 years following menarche, menstrual cycles become regular, and their length and duration do not significantly change during the reproductive period, although, over the years, the length of the menstrual cycle gradually shortens. During the period of 8 to 10 years before menopause, the frequency of ovulatory cycles gradually decreases [1-4].

If the function of the hypothalamic-pituitary-ovarian axis is disrupted, and/or if a structural abnormality of the uterus occurs (myomas, polyps, adenomyosis, malignancy), or if there is a disorder in blood coagulation (coagulopathies, iatrogenic causes), the normal menstrual cycle is disrupted and abnormal uterine bleeding occurs [5].

Abnormal uterine bleeding has a significant impact on physical and mental health, as well as on the emotional, sexual, and professional aspects of women's lives, as they diminish their quality of life. Also, this issue generates significant economic costs. It has been estimated that direct medical costs for the treatment of abnormal uterine bleeding in the United States of

Patološka krvarenja iz materice imaju značajan uticaj na fizičko i mentalno zdravlje, kao i na emotivni, seksualni i profesionalni aspekt života žena, smanjujući i njihov kvalitet života. Takođe, ova krvarenja uzrokuju značajne materijalne troškove. Procenjeno je da direktni troškovi njihovog lečenja u Sjedinjenim Američkim Državama iznose oko jednu milijardu dolara godišnje, dok indirektni troškovi koji proističu iz izostanka sa posla, smanjenja društvene i životne aktivnosti iznose oko 12 milijardi dolara godišnje [6].

Cilj ovog rada je da se prikaže savremena podela, kao i osnovi dijagnostike i lečenja patoloških krvarenja iz materice.

**METODE**

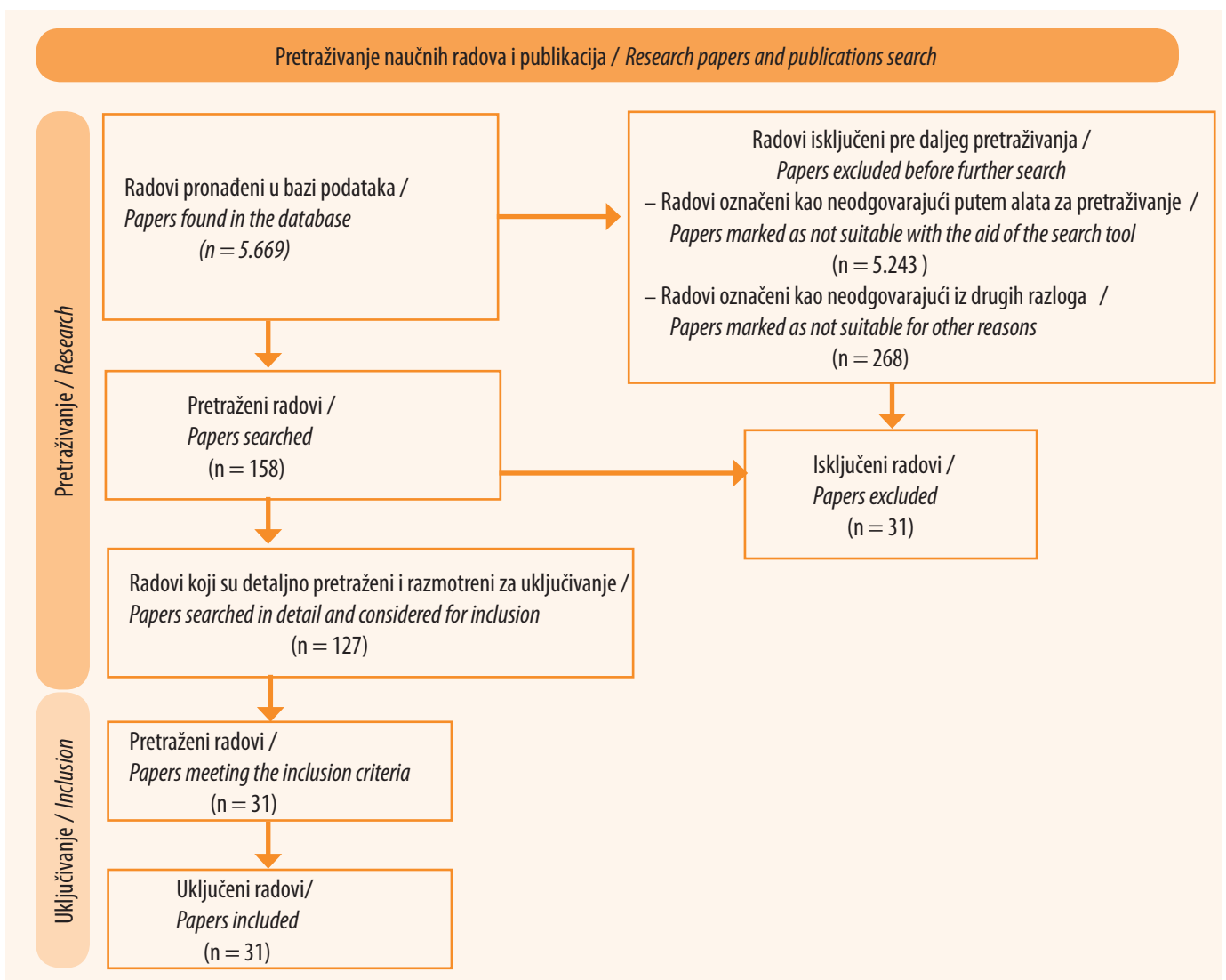
U radu su prikazani podaci iz radova selektovanih pretraživanjem PubMed baze korišćenjem kombinacije ključnih reči: "menstrual bleeding", "abnormal uterine bleeding", "PALM-COEIN classification", "leiomyoma", "en-

America amount to roughly 1 billion dollars per year, while indirect costs, stemming from absence from work and decrease in social and life activity, amount to approximately 12 billion dollars annually [6].

The aim of this paper is to present the current classification, as well as the bases of diagnosis and treatment of abnormal uterine bleeding.

**METHODS**

This paper presents data from publications selected from the PubMed database using a combination of keywords: "menstrual bleeding", "abnormal uterine bleeding", "PALM-COEIN classification", "leiomyoma", "endometrial polyp", "adenomyosis", "gynecological malignancies", "coagulopathy", "diagnostics of abnormal uterine bleeding", and "treatment of abnormal uterine bleeding". The database search and the method of publication selection and inclusion into this study are presented in Figure 1.



Slika 1. PRISMA dijagram pretraživanja i odabira publikacija

Figure 1. PRISMA diagram of the publications search and selection

*dometrial polyp*", "adenomyosis", "gynecological malignancies", "coagulopathy", "diagnostics of abnormal uterine bleeding", "treatment of abnormal uterine bleeding". Pretraživanje baze podataka, način odabira i uključivanja publikacija u ovaj rad prikazani su u **Grafikonu 1**.

### Savremena nomenklatura poremećaja menstrualnog ciklusa i patoloških krvarenja iz materice (FIGO 2011)

U cilju postizanja jedinstvene klasifikacije patoloških krvarenja iz materice, Međunarodna federacija ginekologa i akušera (engl. *International Federation of Gynecology and Obstetrics - FIGO*) je, 2011. godine, uvela klasifikaciju ovih poremećaja pod nazivom *PALM-COEIN* [1-3]. Sam akronim označava pojedine uzroke patološkog krvarenja iz materice. Uzroci nabrojani u prvom delu akronima (*PALM*) imaju patološko-anatomski supstrat na nivou genitalnih organa koji se može dijagnostikovati primenom imidžing metoda i/ili histopatološkim pregledom [1,2,4,7]. Uzroci nabrojani u grupi *COEIN* uključuju difunkcionalne poremećaje i ne mogu se dijagnostikovati primenom imidžing metoda [1-4].

#### Endometrijalni polip

Polip predstavlja promenu nastalu usled lokalizovanog rasta tkiva endometrijuma, sastavljenu od žlezda, strome i krvnih sudova, i pokrivenu epitelom. Najčešće se sreće kod žena u reproduktivnom periodu, a učestalost polipa se povećava sa godinama. Smatra se da estrogeni igraju ključnu ulogu u njihovom nastanku [8]. Patološko krvarenje uzrokovano polipima se manifestuje kao intermenstrualno krvarenje, hipermenoreja, metroragija ili postmenopausalno krvarenje, a može biti povezano i sa dismenorejom. Ipak, kao i miomi, polipi su najčešće asimptomatski [8,9]. Česti su kod infertilnih pacijentkinja i onih koje primaju tamoksifen. Najveći broj polipa endometrijuma su benigni, mada su u postmenopauzi u 1,5 do 4,5% slučajeva maligni [8,9]. Polipi manji od 1 cm mogu spontano regresirati. Dijagnostikuju se ultrazvukom ili histeroskopski. Polipi se leče hirurški-histeroskopskom resekcijom ili eksplorativnom kiretažom [9].

#### Adenomioza

Adenomiozu karakteriše prisustvo tkiva endometrijuma (žlezda i strome) u miometrijumu. Prisustvo ektopičnog endometrijalnog tkiva dovodi do hipertrofije okolnog miometrijuma, uzrokujući difuzno uvećanje materice. Javlja se fokalno ili difuzno u materici, a najveću učestalost ima u petoj deceniji života. Najznačajniji faktor za nastanak adenomioze je multiparitet, ali se smatra da svi faktori koji doprinose penetraciji endometrijalnih žlezda i strome kroz bazalni sloj endometrijuma, utiču na nastanak endometrioze (kiretaža materične šupljine,

### Current nomenclature of menstrual cycle disorders and abnormal uterine bleeding (FIGO 2011)

For the purpose of achieving a uniform classification of menstrual cycle disorders, in 2011, the International Federation of Gynecology and Obstetrics (FIGO) introduced a classification of these disorders under the name *PALM-COEIN* [1-3]. This acronym denotes individual causes of abnormal uterine bleeding. The causes listed in the first part of the acronym (*PALM*) have a pathological/anatomical cause in the reproductive organs that can be diagnosed using imaging techniques and/or histopathological examination [1,2,4,7]. The causes listed in the second part of the acronym (*COEIN*) represent a group of dysfunctional disorders and they cannot be diagnosed using imaging techniques [1-4].

#### Endometrial polyp

A polyp is a lesion which is formed as the result of localized endometrial tissue growth. It is composed of glands, stroma, and blood vessels, and is covered with epithelium. It is most commonly encountered in women in the reproductive period, and the frequency of the occurrence of polyps increases with age. It is believed that estrogens play a key role in their formation [8]. Abnormal uterine bleeding, caused by polyps, is manifested as intermenstrual bleeding, hypermenorrhea, metrorrhagia or postmenopausal bleeding, and may also be linked to dysmenorrhea. However, just like myomas, polyps are most commonly asymptomatic [8,9]. They are frequent in infertile patients and those treated with tamoxifen. Most of the endometrial polyps are benign, although, in postmenopause, in 1.5 to 4.5% of the cases, they are malignant [8,9]. Polyps smaller than 1 cm may spontaneously regress. They are diagnosed by ultrasound or with hysteroscopy. Polyps are treated by surgical-hysteroscopic resection or by explorative curettage [9].

#### Adenomyosis

Adenomyosis is characterized by the presence of endometrial tissue (glands and stroma) in the myometrium. The presence of ectopic endometrial tissue leads to hypertrophy of the surrounding myometrium, causing diffuse enlargement of the uterus. It occurs focally or diffusely in the uterus, and its greatest frequency is in women in their forties. The most significant factor for the occurrence of adenomyosis is multiparity, but it is believed that all factors contributing to the penetration of endometrial glands and the stroma through the basal layer of the endometrium, influence the development of endometriosis (curettage of the uterine cavity, cesarean section, miscarriage). Bleeding caused by adenomyosis occurs as the result of uterine contractility impairment. It

carski rez, spontani pobačaj). Krvarenje uzrokovano adenomiozom nastaje kao posledica poremećaja kontraktilnosti materice. Najčešće se manifestuje menorigijom i obično je povezano sa izraženom dismenorejom [10]. Adenomioza se dijagnostikuje ultrazvukom i nuklearnom magnetnom rezonancom. Definitivna dijagnoza se postavlja histopatološkim pregledom. Medikamentno lečenje uključuje primenu progesteronskih preparata, agonista gonadotropin-oslobađajućeg hormona (engl. *gonadotropin-releasing hormone - GnRH*) i inhibitora aromataze. Fokalna ognjišta adenomioze se mogu lečiti hirurškom resekcijom. Kod žena koje nisu zainteresovane za reprodukciju, lečenje je moguće sprovesti embolizacijom materičnih arterija [11].

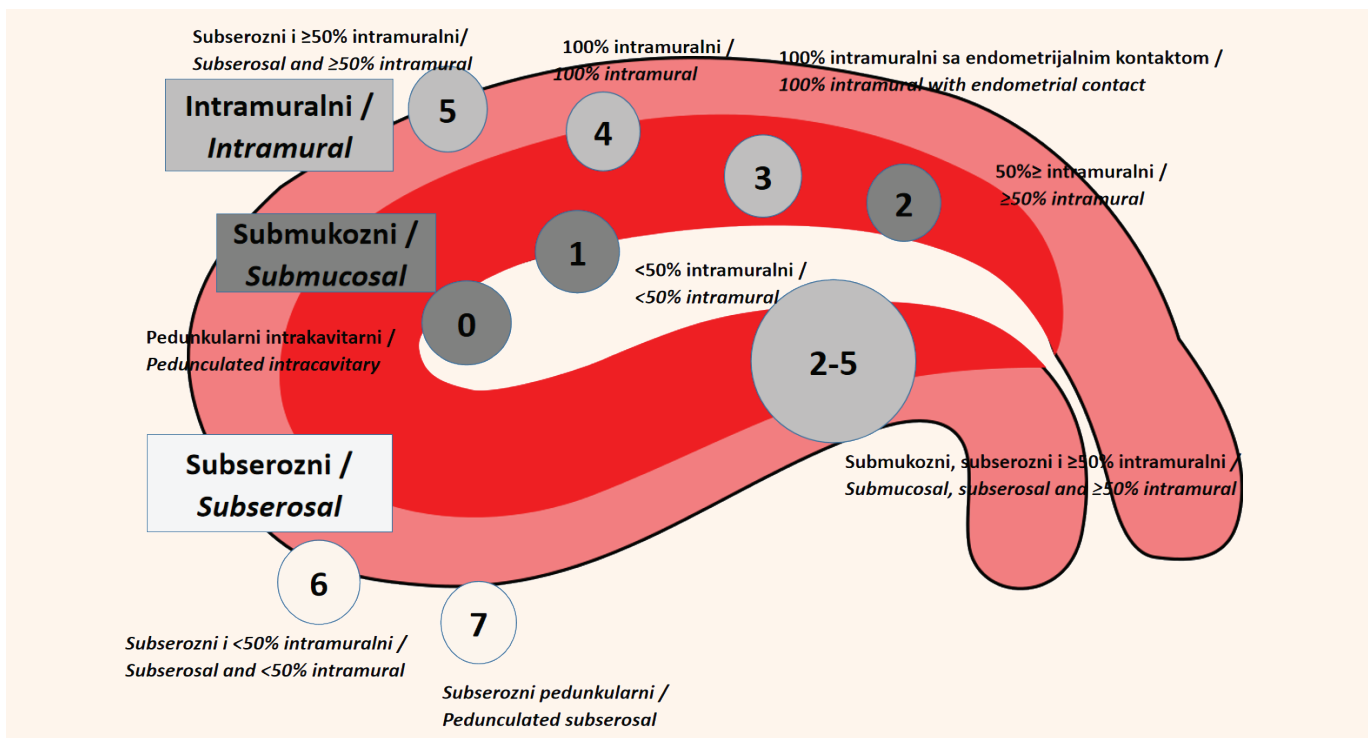
**Leiomiom**

Leiomiomi, miomi ili fibromi su benigni tumori poreklom od mišićnih ćelija miometrijuma. Predstavljaju najčešće benigne tumore ženskih reproduktivnih organa. Klinička slika varira od potpunog odsustva subjektivnih tegoba do brojnih simptoma, koji mogu imati značajan uticaj na zdravlje žene. Manje od 50,0% mioma su simptomatski, a najčešći simptom je patološko krvarenje iz materice [7,12–15]. Mogu biti pojedinačni ili multipli, a u oko 97,0% slučajeva su lokalizovani u telu materice. U odnosu na anatomske slojeve zida materice ovi tumori se dele na submukozne, intramuralne, subserozne, i intraligamentarne (miomi lokalizovani između listova širokih materičnih veza). Na Slici 2 prikazana je FIGO podela mioma na osnovu

most commonly manifests as menorrhagia and is usually connected to marked dysmenorrhea [10]. Adenomyosis is diagnosed with ultrasound and nuclear magnetic resonance imaging. Definitive diagnosis is established by histopathological examination. Medicamentous treatment includes the application of progesterone-based medicaments, gonadotropin-releasing hormone (GnRH) agonists, and aromatase inhibitors. Focal areas of adenomyosis can be treated with surgical resection. In women not interested in reproduction, it is possible to perform treatment by embolizing uterine arteries [11].

**Leiomyomas**

Leiomyomas, myomas or fibromas are benign tumors originating from muscular cells of the myometrium. They are the most common benign tumors of female reproductive organs. The clinical presentation varies from complete absence of subjective complaints to numerous symptoms, which may significantly affect the woman’s health. Less than 50.0% are symptomatic, and the most frequent symptom is abnormal uterine bleeding [7,12–15]. They can be solitary or multiple, and in around 97.0% of the cases, they are localized in the body of the uterus. In relation to the anatomical layers of the uterine wall, these tumors are classified as submucosal, intramural, subserosal, and intraligamentous (myomas localized between the leaves of the broad uterine ligaments). Figure 2 shows the FIGO classification of myomas based on localization [1-3]. The nomenclature of myomas, by type, based on this classification is presented in Table 2.



Slika 2. Tipovi mioma po FIGO klasifikaciji

Figure 2. Types of myomas according to the FIGO classification

**Tabela 1.** Karakteristike normalnog menstrualnog krvarenja

**Table 1.** Characteristics of normal menstrual bleeding

SM - submukozni / SM - submucosal	0	Intrakavitarni miomi na peteljci / <i>Intracavitary pedunculated myomas</i>
	1	<0% intramuralni / <50% intramural
	2	≥50% intramuralni / ≥50% intramural
0 - ostali/ 0 - other	3	U kontaktu sa endometrijumom, 100% intramuralni / <i>In contact with the endometrium, 100% intramural</i>
	4	Intramuralni / <i>Intramural</i>
	5	Subserozni ≥50% intramuralni / <i>Subserosal ≥50% intramural</i>
	6	Subserozni <50% intramuralni / <i>Subserosal &lt;50% intramural</i>
	7	Subserozni na peteljci / <i>Pedunculated subserosal</i>
	8	Drugi (cervikalni, intraligamentarni, paraziti) / <i>Other (cervical, intraligamentous, parasitic)</i>
Hibridni leiomiomi (u kontaktu kako sa endometrijumom, tako i sa serozom materice) / <i>Hybrid leiomyomas (in contact both with the endometrium and with the uterine serosa)</i>	Obeležavaju se sa dva broja odvojena crtom (-). Prvi broj označava odnos mioma sa endometrijumom, a drugi odnos mioma sa serozom materice. / <i>They are marked with two numbers separated by a hyphen (-). The first number marks the relation between the myoma and the endometrium, while the other one designates the relation between the myoma and the uterine serosa.</i> Na primer, miom 2-5 je submukozni i subserozni, pri čemu je manje od 50% volumena mioma u odnosu sa endometrijumom i peritonealnom šupljinom. / <i>For example, a myoma marked 2-5 is submucosal and subserosal, with less than 50% of the myoma volume in contact with the endometrium and the peritoneal cavity.</i>	

lokalizacije [1-3]. Nomenklatura mioma po tipovima na osnovu ove podele prikazana je u Tabeli 2.

Mehanizmi kojima miomi utiču na pojavu patoloških krvarenja iz materice su različiti, a u velikoj meri zavise i od njihove veličine, broja i lokalizacije. Kod žena sa patološkim krvarenjem iz materice, najčešće se dijagnostikuju intrakavitarni (miomi u šupljini materice), submukozni miomi i veliki intramuralni miomi [16]. Ovi miomi povećavaju ukupnu površinu šupljine materice prekrivenu endometrijumom, dovode do iregularne deskvamacije endometrijuma i iregularnih kontrakcija materice, izazivajući iregularna i obilna materična krvarenja [17]. Pored toga, novija saznanja ukazuju na značaj neoangiogeneze, povišenih nivoa vazoaktivnih supstanci i faktora rasta, kao i koagulacionih promena, koji zajednički utiču na pojavu patoloških krvarenja kod žena sa miomima [18]. Lečenje mioma je medikamentno (kombinovana oralna kontracepcija, GnRH agonisti i antagonisti) ili hirurško (miomektomija, histerektomija), u zavisnosti od karakteristika mioma, godina starosti i pariteta pacijentkinje [19]. Kod žena koje nisu zainteresovane za reprodukciju, lečenje je moguće sprovesti embolizacijom materičnih arterija [20].

### Malignitet i hiperplazija

Maligne bolesti ženskih reproduktivnih organa koje mogu uzrokovati krvarenje uključuju oboljenja vulve, vagine, grlića materice, endometrijuma, tela materice, jajnika i jajovoda. Najčešći uzroci patoloških krvarenja su maligniteti materice.

Karcinom grlića materice se manifestuje kontaktnim, intermenstrualnim ili potpuno acikličnim krvarenjem, te je isključivanje ovog oboljenja značajan deo

The mechanisms through which myomas affect the occurrence of abnormal uterine bleeding vary and depend, to a great extent, on the size of the myomas, their number, and localization. In women with abnormal uterine bleeding, the following myomas are most commonly diagnosed: intracavitary (myomas in the uterine cavity), submucosal, and large intramural myomas [16]. These myomas enlarge the overall surface of the uterine cavity covered with endometrium, lead to irregular desquamation of the endometrium and to irregular contractions of the uterus, thereby causing irregular and profuse uterine bleeding [17]. Also, recent discoveries indicate the significance of neoangiogenesis, elevated levels of vasoactive substances and growth factors, and of coagulation changes, which together affect the occurrence of abnormal bleeding in women with myomas [18]. Treatment of myomas is medicamentous (combined oral contraceptives, GnRH agonists and antagonists) or surgical (myomectomy, hysterectomy), depending on the characteristics of the myomas and on the age and parity of the patient [19]. In women not interested in reproduction, it is possible to perform treatment by embolizing uterine arteries [20].

### Malignancy and hyperplasia

Malignant diseases of female reproductive organs that may cause bleeding include malignancies affecting the vulva, the vagina, the cervix, the endometrium, the uterine body, the ovaries and the oviducts. The most common causes of abnormal uterine bleeding are uterine malignancies.

Cervical carcinoma manifests as contact, intermenstrual or completely acyclic bleeding, which is why it

postupka dijagnostike uzroka patoloških krvarenja iz materice [21]. Patološko krvarenje može biti uzrokovano različitim poremećajima endometrijuma, kao što su cistična i adenomatozna hiperplazija, endometrijalna intraepitelna neoplazija (EIN) i karcinom endometrijuma [4,22]. Najčešći simptom karcinoma endometrijuma je patološko krvarenje iz materice. Iako se najčešće javlja tokom sedme decenije života, u oko 15,0% slučajeva se sreće kod premenopausalnih žena, a u oko 3,0% do 5,0% slučajeva kod žena mlađih od 40 godina. Sarkomi materice se obično javljaju kod starijih žena u menopauzi, a klinički se manifestuju patološkim krvarenjem iz materice i progresivnim uvećanjem materice. Tumori jajnika koji produkuju estrogen (najčešće granulosa-ćelijski tumori) mogu se manifestovati patološkim krvarenjem iz materice [2-4,23].

### Koagulopatija

Patološko krvarenje iz materice može biti prva klinička manifestacija hematoloških oboljenja. Oko 13,0% žena sa obilnim menstrualnim krvarenjem ima neki koagulacioni poremećaj, od kojih je najzastupljenija von Willebrandova bolest [24]. Koagulopatija predstavlja jedan od najčešćih uzroka menoragije [25]. Oboljenja koja dovode do deficita trombocita, a mogu biti i uzrok patoloških krvarenja iz materice, uključuju leukemiju, teške oblike sepse, idiopatsku trombocitopenijsku purpuru. Hemofilija A i B su X-vezani recesivni deficiti faktora koagulacije VIII i faktora koagulacije IX [24-26]. Žene koje su prenosioci ovih bolesti imaju snižene nivoe faktora VIII i faktora IX, što se može manifestovati menoragijom. Ređe, nasledne koagulopatije koje uključuju poremećaj ostalih faktora koagulacije (V, VII, X, XI i XIII), mogu se manifestovati menoragijom. Poremećaji funkcije jetre kod alkoholizma, kao i njena hronična oboljenja mogu imati za posledicu poremećaj produkcije faktora koagulacije i nastanak patološkog krvarenja [24].

Oko 5,0% do 20,0% adolescentkinja kod kojih se pojavi patološko krvarenje iz materice imaju neku koagulopatiju. Zbog toga je ispitivanje koagulacionog statusa naročito značajno kod žena ovog životnog doba [25].

Detaljno ispitivanje koagulacionog statusa predstavlja neizostavni deo dijagnostičkog protokola kod žena sa patološkim krvarenjima iz materice, a lečenje je hematološko [24,25].

### Ovulatorna disfunkcija

Jedan od uzroka patoloških krvarenja, koja se javljaju u periodu nakon menarhe i u perimenopauzi, jeste ovulatorna disfunkcija. Nastaje kao posledica poremećaja funkcije hipotalamo-hipofizno-ovarijalne osovine, sa kontinuiranom produkcijom estrogena i izostankom

is important to rule out this disease, as a part of the process of diagnosing the cause of abnormal uterine bleeding [21]. Abnormal bleeding can be caused by different endometrial disorders, such as cystic and adenomatous hyperplasia, endometrial intraepithelial neoplasia (EIN), and endometrial carcinoma [4,22]. The most frequent symptom of endometrial carcinoma is abnormal uterine bleeding. Although it most frequently occurs in women in their sixties, in around 15.0% of the cases it is encountered in premenopausal women, and in 3.0% to 5.0% of the cases in women younger than 40 years. Uterine sarcomas usually occur in older women in menopause, and they clinically manifest as abnormal uterine bleeding and progressive enlargement of the uterus. Ovarian estrogen producing tumors (most commonly granulosa cell tumors) may manifest as abnormal uterine bleeding [2-4,23].

### Coagulopathy

Abnormal uterine bleeding may be the first clinical manifestation of hematological diseases. Around 13.0% of women with profuse menstrual bleeding have some form of coagulation disorder, of which the most common one is von Willebrand's disease [24]. Coagulopathy represents one of the most frequent causes of menorrhagia [25]. Diseases leading to platelet deficiency, which can be the cause of abnormal uterine bleeding, include leukemia, severe forms of sepsis, and idiopathic thrombocytopenic purpura. Hemophilia A and B are X-related recessive deficiencies of coagulation factor VIII and coagulation factor IX [24-26]. Women who are carriers of this disease have decreased levels of factor VIII and factor IX, which may manifest as menorrhagia. Less frequently, hereditary coagulopathies that include a disorder in other coagulation factors (V, VII, X, XI and XIII) may manifest as menorrhagia. Disorders of liver function in alcoholism, as well as chronic liver diseases, may result in a coagulation factor production disorder and the occurrence of abnormal bleeding [24].

Around 5.0% to 20.0% of adolescent young women who experience abnormal uterine bleeding have some form of coagulopathy. This is why coagulation status testing is especially significant in women of this age [25].

Detailed analysis of the coagulation status presents an indispensable part of the diagnostic protocol in women with abnormal uterine bleeding, and the treatment is hematological [24,25].

### Ovulatory dysfunction

One of the causes of abnormal uterine bleeding, which occurs in the period after menarche and in perimenopause, is ovulatory dysfunction. It develops as the result

ovulacije, formiranja žutog tela i sekrecije progesterona u jajniku. Estrogena stimulacija dovodi do kontinuirane proliferacije endometrijuma, koji u nekom trenutku, usled nedovoljne vaskularizacije, podleže nekrozi. Kao posledica ovog poremećaja nastaje tzv. probojno krvarenje. Ovakva anovulatorna krvarenja su najčešća tokom prvih nekoliko godina nakon menarhe i u perimenopauzi. U adolescenciji, uzrok anovulacija je nezrelost hipotalamo-hipofizno-gonadne osovine i izostanak pozitivne povratne sprege estradiola, koja uzrokuje pik LH-a (luteinizirajućeg hormona). U perimenopauzi, uzrok ove vrste krvarenja je ovarijalna insuficijencija. Narочito obilna krvarenja se javljaju nakon prolongiranog perioda ekspozicije endometrijuma estrogenima, što se obično sreće kod adolescentkinja nakon menarhe, pacijentkinja sa PCO (engl. *polycystic ovary*) sindromom, gojaznih, kao i perimenopauzalnih žena [4,26].

Ovulatorna disfunkcija se može manifestovati i amenorejom, a anovulatorna krvarenja oligomenorejom, intermenstrualnim krvarenjem ili hipermenorejom. Kod žena koje imaju regularne menstrualne cikluse u 20,0% slučajeva izostaje ovulacija.

Najčešći uzrok anovulatornih krvarenja tokom reproduktivnog perioda žene je sindrom policističnih jajnika (engl. *polycystic ovary syndrome* - PCOS). Ređi uzrok je poremećaj hipotalamo-hipofizne funkcije. Uz to, i drugi hormonski poremećaji mogu biti praćeni anovulatornim krvarenjem, kao što su oboljenja tiroidne žlezde (hipotireoidizam, hipertireoidizam), nadbubrežne žlezde i *diabetes mellitus* [27,28]. Hiperprolaktinemija i povišene vrednosti kortizola (Kušingov sindrom) takođe mogu dovesti do anovulacije. Ređe, uzroci su poremećaji ishrane (anoreksija, bulimija), hronične bolesti, alkoholizam, zloupotreba droga, kao i stres [4,27,28].

### Jatrogeni uzroci

Jatrogeno nastala patološka krvarenja iz materice nastaju kao posledica uzimanja medikamenata, najčešće oralnih kontraceptiva, selektivnih modulatora estrogenih receptora, GnRH agonista i antagonist, digitalisa i antikonvulziva. Lekovi izazivaju patološka krvarenja, bilo remeteći funkciju hipotalamo-hipofizno-gonadne osovine, bilo izazivajući fluktuacije cirkulišućih nivoa hormona.

Hiperprolaktinemija može biti posledica dejstva antipsihotika koji deluju kao dopaminski antagonisti na nivou centralnog nervnog sistema (risperidon) [4,29]. Patološka krvarenja ove vrste se mogu javiti kod korisnica kombinovane hormonske kontracepcije (flasteri, vaginalni prstenovi, pilula), ali i kod korisnica intrauterinih kontraceptivnih uložaka. Probojna krvarenja su česta tokom prva tri meseca upotrebe oralnih

of a disturbance in the functioning of the hypothalamic-pituitary-ovarian axis, with continuous production of estrogen and absence of ovulation, corpus luteum formation and progesterone secretion in the ovaries. Estrogen stimulation leads to continuous proliferation of the endometrium, which, at some point, due to insufficient vascularization, necrotizes. As the result of this disorder, so-called breakthrough bleeding occurs. Such anovulatory bleeding is most frequent during the first few years after menarche and in perimenopause. In adolescence, the cause of anovulation is the immaturity of the hypothalamic-pituitary-gonadal axis and the absence of positive feedback by estradiol, which causes peak LH (luteinizing hormone). In perimenopause, the cause of this type of bleeding is ovarian insufficiency. Especially profuse bleeding occurs after a prolonged period of endometrial exposure to estrogens, which is usually found in adolescent young women after menarche, patients with polycystic ovary (PCO) syndrome, obese, and perimenopausal women [4,26].

Ovulatory dysfunction can manifest as amenorrhea, while anovulatory bleeding may manifest as oligomenorrhea, intermenstrual bleeding or hypermenorrhea. In women with regular menstrual cycles, ovulation is absent in 20.0% of the cases.

The most common cause of anovulatory bleeding during the reproductive period in women is the polycystic ovary syndrome (PCOS). A disturbance of the hypothalamic-pituitary function is a less common cause. Additionally, other hormonal imbalances may be accompanied by anovulatory bleeding, such as diseases of the thyroid gland (hypothyroidism, hyperthyroidism), diseases of the adrenal glands, and *diabetes mellitus* [27,28]. Hyperprolactinemia and elevated levels of cortisol (Cushing's syndrome) can also lead to anovulation. Less frequently, the causes can be eating disorders (anorexia, bulimia), chronic disease, alcoholism, drug abuse, and stress [4,27,28].

### Iatrogenic causes

Abnormal uterine bleeding resulting from iatrogenic causes is the consequence of taking medication, most commonly oral contraceptives, selective modulators of estrogen receptors, GnRH agonists and antagonists, digitalis, and anticonvulsants. Drugs cause abnormal bleeding, either by disrupting the function of the hypothalamic-pituitary-gonadal axis or by causing fluctuations in the levels of circulating hormones.

Hyperprolactinemia may be the result of the effect of antipsychotics acting as dopamine antagonists at the level of the central nervous system (risperidone) [4,29]. This type of abnormal bleeding may occur in patients who use combined hormonal contraception



hormonskih kontraceptiva i javljaju se kod 30,0% do 40,0% korisnica. Ova vrsta krvarenja najčešće se sreće kod korisnica oralnih kontraceptivnih pilula i hormonske supstitucije u perimenopauzi [30]. Većina krvarenja se manifestuje menoragijom.

Važno je ukazati na to da sva krvarenja kod pacijentkinja koje koriste hormonsku kontracepciju nisu posledica hormonskih faktora. Rezultati novih istraživanja ukazuju na to da pacijentkinje koje koriste oralne kontraceptive i imaju patološka krvarenja imaju visoku prevalenciju infekcije *Chlamydia-om trachomatis*, koja uzrokuje pojavu krvarenja kod ovih pacijentkinja. Skrining na polno prenosive bolesti treba razmotriti kod pacijentkinja koje imaju patološka krvarenja i koriste hormonsku kontracepciju [30].

### Endometrijalni uzroci

U ovu kategoriju se svrstavaju krvarenja u odsustvu patoloških promena endometrijuma, ranije nazivana „ovulatorna disfunkcionalna krvarenja“. Patološka krvarenja iz materice mogu biti manifestacija poremećaja mehanizama reparacije endometrijuma. Kod ovih pacijentkinja prisutni su povišeni nivoi vazodilatatornih supstanci (prostaciklin I2 i prostaglandin E2) i sniženi nivoi vazokonstriktornih supstanci (endotelin-1 i prostaglandin 2α). Ovi poremećaji mogu biti primarni i sekundarni, uzrokovani inflamacijom ili infekcijom endometrijuma [4]. Menoragija može biti prvi znak endometritisa kod žena, kod seksualno prenosivih bolesti. Patološka krvarenja iz materice česta su u slučajevima subkliničke infekcije uzrokovane *Chlamydia-om trachomatis*. Ostali uzroci uključuju smanjenje nivoa estrogena tokom terapije antibioticima i antikonvulzivima [29,31]. Takođe, u ovu grupu poremećaja spadaju krvarenja koja se javljaju tokom terapije steroidnim hormonima, kao što je, na primer, probojno krvarenje.

Endometrijalni uzroci patoloških krvarenja iz materice kod žena u reproduktivnom periodu se dijagnostikuju tek nakon isključivanja ostalih patoloških procesa i potvrde postojanja normalnih ovulacija.

### Neklasifikovani uzroci

U ovu grupu patoloških krvarenja se ubrajaju krvarenja koja nisu obuhvaćena prethodno opisanim uzrocima, kao što su krvarenja uzrokovana stranim telom (tampon, pesar) ili traumom. Ostali uzroci krvarenja iz ove grupe su hronični endometritis i arterio-venske malformacije [4].

### Dijagnoza patoloških krvarenja iz materice

Pre sprovođenja bilo koje dijagnostičke procedure neophodno je isključiti postojanje neprepoznate trudnoće određivanjem nivoa β-HCG-a u serumu pacijentkinje.

(patches, vaginal rings, contraceptive pills), but also in women using intrauterine contraceptive implants. Breakthrough bleeding is common in the first months of using oral hormone contraceptives and occur in 30.0% to 40.0% of the women using them. This type of bleeding is most commonly encountered in women using oral contraceptive pills and hormonal substitution in perimenopause [30]. Most bleeding manifests as menorrhagia.

It is important to note that all bleeding in patients using hormonal contraceptives is not caused by hormonal factors. The results of recent studies have shown that patients using oral contraceptives and experiencing abnormal uterine bleeding also have a high prevalence of *Chlamydia trachomatis* infection, which causes bleeding in these women. Screening for sexually transmitted diseases should be considered in patients with abnormal uterine bleeding who use hormonal contraceptives [30].

### Endometrial causes

Bleeding occurring in the absence of pathological changes to the endometrium fall under this category and was earlier referred to as 'ovulatory dysfunctional bleeding'. Abnormal uterine bleeding may be a manifestation of the disruption in the endometrial repair mechanism. In these patients, elevated levels of vasodilatory substances (prostacyclin I2 and prostaglandin E2) are present, as well as decreased levels of vasoconstrictory substances (endothelin-1 and prostaglandin 2α). These disorders may be primary and secondary, caused by inflammation or infection of the endometrium [4]. Menorrhagia may be the first sign of endometritis in women, in sexually transmitted diseases. Abnormal uterine bleeding is frequent in cases of subclinical infection caused by *Chlamydia trachomatis*. Other causes include a decrease in the level of estrogen during treatment with antibiotics and anticonvulsants [29,31]. Also, this group of disorders includes bleeding occurring during steroid hormone treatment, such as, for example, breakthrough bleeding.

Endometrial causes of abnormal uterine bleeding in women in the reproductive period are diagnosed only after excluding other pathological processes and confirming the existence of normal ovulations.

### Unclassified causes

Types of abnormal uterine bleeding not covered by the above-mentioned causes fall under this category, such as bleeding caused by a foreign body (tampon, pessary) or trauma. Other causes of bleeding from this group are chronic endometritis and arteriovenous malformations [4].

Dijagnostički protokol zavisi od anamnestičkih podataka i kliničkog nalaza, kao i od godina starosti, pariteta, pri čemu se mora imati u vidu i eventualno prisustvo faktora rizika za postojanje endometrijalne hiperplazije i maligniteta. U svim slučajevima kontaktnog krvarenja, neophodno je uraditi i kolposkopski i citološki pregled po metodi Papanikolau, a po potrebi i dopunsku dijagnostiku, u cilju isključivanja postojanja karcinoma grlića materice.

Prvi korak u dijagnostici jeste uzimanje detaljne lične i porodične anamneze (dužina trajanja, cikličnost i obim menstrualnog krvarenja; pojava modrica po koži; krvarenja iz nosa; krvarenja desni; krvarenje posle porođaja ili operativnih zahvata; uzimanje lekova - hormonski preparati, antikoagulansi, antipsihotici, antidepresivi; postojanje pratećih znakova i simptoma - promena telesne težine, fizička aktivnost, premenstrualni sindrom, dismenoreja, dispareunija, galaktoreja, hirzutizam, akne). Iako subjektivan, podatak o upotrebi tampona, odnosno uložaka tokom ciklusa, može pružiti procenu obima krvarenja. Podatak o promeni tampona, odnosno uložaka češće od jednom na tri sata, kao i upotreba više od 20 tokom jednog ciklusa, potreba za promenom tampona ili uložaka tokom noći, izbacivanje ugrušaka većih od 2,5 cm, te krvarenje duže od 7 dana, ukazuju na obilno patološko krvarenje iz materice.

Klinički pregled omogućava evaluaciju patoloških promena grlića materice, uterusa i adneksa. Njime se prvenstveno potvrđuje da li se radi o iregularnom krvarenju iz materice.

Nakon toga se izvodi ultrazvučni pregled male karlice, odnosno evaluacija materice, debljine endometrijuma i ovarijuma. Ovim pregledom se takođe mogu dijagnostikovati endometrijalni polipi i submukozni miomi. U slučaju nejasnih nalaza, radi se sonohisterografija ili histeroskopija, a po potrebi i frakcionirana eksplorativna kiretaža. U nekim slučajevima, naročito kod adolescentkinja i pacijentkinja sa intaktnim himenom, radi se pregled nuklearnom magnetnom rezonancom.

Ukoliko se ovim pregledima isključi postojanje patoloških promena endometrijuma, miometrijuma i jajnika, neophodno je ispitivanje ovulatorne funkcije, kao i postojanja drugih endokrinopatija i koagulacionih poremećaja, kao i mikrobiološko ispitivanje (cervikalni i vaginalni bakteriološki bris, brisevi na *Chlamydia*-u *trachomatis*, *Ureaplasma*-u *urealyticum*, *Mycoplasma*-u *hominis*).

Određivanjem serumskog progesterona između 22. i 24. dana ciklusa kod žena sa ciklusom na 28 dana, može se dokumentovati postojanje ovulacije, a vrednosti veće od 3 ng/ml ukazuju na postojanje ovulacije. Kod žena starijih od 40 godina, neophodno je uraditi dijagnostičku kiretažu u cilju isključivanja karcinoma endometrijuma [1,2,4,5].

## Diagnosis of abnormal uterine bleeding

Before carrying out any diagnostic procedure it is necessary to exclude the existence of an unrecognized pregnancy by determining the  $\beta$ -HCG level in the serum of the patient.

The diagnostic protocol depends on anamnestic data and the clinical finding, as well as on the age and parity of the patient. At the same time the presence of possible risk factors for the existence of endometrial hyperplasia and malignancy must also be taken into consideration. In all cases of contact bleeding, it is necessary to perform colposcopy as well as cervical cytology by Pap smear, and, if necessary, additional diagnostics, for the purpose of excluding the existence of cervical carcinoma.

The first step in the diagnostics is taking a detailed personal and family medical history (length, cyclicality, and volume of menstrual bleeding; occurrence of bruises on the skin; nosebleeds; bleeding of gums; postpartum bleeding or bleeding after surgical procedures; drugs that the patient is on – hormonal medicaments, anticoagulants, antipsychotics, antidepressants; existence of accompanying signs and symptoms – change in body weight, physical activity, premenstrual syndrome, dysmenorrhea, dyspareunia, galactorrhea, hirsutism, acne). Although subjective, information on the use of tampons or menstrual pads during menstruation may offer an estimation on the volume of bleeding. Information on the change of tampons or pads more often than once in every three hours, as well as the use of more than 20 menstrual pads during one menstrual cycle, the need for changing pads or tampons during the night, discharging clots larger than 2.5 cm, bleeding lasting longer than 7 days, indicate profuse abnormal uterine bleeding.

Clinical examination enables evaluation of pathological changes in the cervix, uterus, and adnexa. It primarily confirms whether there is irregular uterine bleeding.

The next step is ultrasound examination of the lesser pelvis, i.e., the evaluation of the uterus, the thickness of the endometrium, and the ovaries. Endometrial polyps and submucosal myomas can also be diagnosed with this examination. In case of unclear findings, sonohysterography or hysteroscopy is performed, and, if necessary, fractional explorative curettage. In some cases, especially in adolescent patients and patients with an intact hymen, a nuclear magnetic resonance imaging examination is performed.

If these examinations exclude the existence of pathological changes in the endometrium, the myometrium, and ovaries, it is necessary to examine the ovulatory function, as well as to test for other

## Lečenje patoloških krvarenja iz materice

Najvažniji korak u lečenju patološkog krvarenja je dijagnostika uzroka krvarenja. Terapija je ekspektativna, medikamentna i hirurška. Ekspektativna terapija se savetuje u slučaju pojave probojnih krvarenja, tokom prva tri meseca korišćenja oralnih kontraceptiva. Lečenje polipa je hirurško, a metoda izbora je histeroskopska polipektomija. Miomi se mogu lečiti medikamentno i hirurški (miomektomija, histerektomija, embolizacija krvnih sudova, GnRH analozi). Maligne bolesti se leče u skladu sa onkološkim protokolima, u zavisnosti od lokalizacije primarnog tumora, histološkog tipa i FIGO stadijuma bolesti. Kod žena u reproduktivnom periodu sa anovulatornim krvarenjima, savetuje se primena kombinovanih oralnih kontraceptiva ili intrauterinih uložaka sa levonorgestrelom. U slučaju anovulatornih krvarenja kod žena starije životne dobi, koje nisu zainteresovane za rađanje, dolazi u obzir ablacija endometrija i histerektomija. Hirurško lečenje se primenjuje kod pacijentkinja kod kojih medikamentno lečenje nije dalo željene rezultate [1,4,5].

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endocrinopathies and coagulation disorders, and to perform microbiological testing (cervical and vaginal bacterial culture swabs, swabs for *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Mycoplasma hominis*).

Establishing the level of serum progesterone between day 22 and day 24 of the menstrual cycle in women whose cycle is 28 days, can facilitate the documenting of the existence of ovulation, with values above 3 ng/ml indicating the existence of ovulation. In women above the age of 40 years, it is necessary to perform diagnostic curettage for the purpose of excluding endometrial carcinoma [1,2,4,5].

## Treatment of abnormal uterine bleeding

The most important step in treating abnormal uterine bleeding is the diagnosis of the cause of the bleeding. The therapy is expectative, medicamentous, and surgical. Expectative therapy is advised in case of breakthrough bleeding occurring in the first three months of using oral contraceptives. Polyp treatment is surgical, and the method of choice is hysteroscopic polypectomy. Myomas can be treated with medication as well as surgically (myomectomy, hysterectomy, blood vessel embolization, GnRH analogs). Malignant diseases are treated according to oncological protocols, depending on the localization of the primary tumor, the histological type, and the FIGO stage of the disease. In women in their reproductive period who experience anovulatory bleeding, it is recommended to apply combined oral contraceptives or intrauterine devices with levonorgestrel. In cases of anovulatory bleeding in older women not interested in reproduction, performing endometrial ablation or a hysterectomy is an option. Surgical treatment is performed in patients in whom medicamentous treatment did not provide the desired results [1,4,5].

**Conflict of interest:** None declared.

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