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HEMOSTASIS DISORDERS WITH ABNORMAL UTERINE BLEEDING AND THEIR TREATMENT TACTICS

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To determine the specifics of hemostasis disorders in abnormal uterine bleeding, we examined 130 women, of which 110 were female patients who made up the main group. The control group included 20 healthy women without menstrual cycle disorders. It was found that abnormal uterine bleeding in the reproductive age, in the absence of etiopathogenetic treatment, leads to the development of posthemorrhagic anemia. The severity and nature of bleeding are determined by defects in the platelet link system of the hemostasis system that violate the aggregation function of platelets. The study of the overall hemostatic potential, primary hemostasis, and the state of intravascular coagulation in patients with abnormal uterine bleeding using methods for assessing the amount of platelet aggregation allowed us to identify and differentiate disorders in the hemostasis system. The application of modern principles of management of women with abnormal uterine bleeding and the use of fibrinolysis inhibitors allows for an increase in the activity of the blood coagulation system and to stop bleeding for 2–5 days altogether.

Key words: abnormal uterine bleeding, disorders of the coagulation system, overall hemostatic potential, fibrinolysis inhibitors.

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ПОРУШЕННЯ СИСТЕМИ ГЕМОСТАЗУ ПРИ АНОМАЛЬНИХ МАТКОВИХ КРОВОТЕЧАХ ТА ЇХ ЛІКУВАЛЬНА ТАКТИКА

Для з'ясування особливостей порушень в системі гемостазу при аномальних маткових кровотечах нами обстежено 130 жінок, з яких, 110 пацієнток, які склали основну групу спостереження. Контрольну групу склали 20 здорових жінок без порушення менструального циклу. З'ясовано, що аномальні маткові кровотечі в репродуктивному віці, при відсутності етіопатогенетичного лікування, призводять до розвитку постгеморагічної анемії. Тяжкість і характер кровотеч визначається наявністю дефектів в тромбоцитарної ланки системи гемостазу з порушенням агрегаційної функції тромбоцитів. Дослідження загального коагуляційного потенціалу, первинного гемостазу і стану внутрішньосудинної гемокоагуляції у пацієнток з аномальними матковими кровотечами з використанням методів оцінки кількості агрегації тромбоцитів дозволяє виявити і диференціювати порушення в системі гемостазу. Застосування сучасних принципів ведення жінок з аномальними матковими кровотечами та застосування інгібіторів фібринолізу дозволяє домогтися підвищення активності системи згортання крові і повною зупинки кровотечі на 2–5 добу.

Ключові слова: аномальні маткові кровотечі, порушення системи згортання крові, загальний коагуляційний потенціал, інгібітори фібринолізу.

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Abnormal uterine bleeding (AUB) is a pathological process that regulates the menstrual cycle and is associated with the development of coagulopathy, ovulation disorders, or the functional state of the endometrium [1].

AUB is abnormal bleeding from the uterus, not related to systemic diseases or organic pathology of the pelvic organs and leads to changes in the ratio of steroid hormones in the blood and changes in the state of the endometrium. They are accompanied by a violation of the gonadotropic function of the pituitary gland and a decrease in the activity of the ovaries, which leads to anovulatory cycles with insufficient luteal phase. It is a medical and social problem that contributes to the development of dyshormonal disorders at the level of the hypothalamic-pituitary-adrenal-ovarian systems, the development of coagulation changes in the blood system, and often requires the necessary urgent care [12].

Uterine hemostasis during menstruation is associated with platelet aggregation, fibrin formation, tissue regeneration, prostaglandin inhibition of platelets, vasodilation, and fibrinolysis. With this pathology, endocrine changes occur, a hormonal disorder that leads to a disorder of the ovulation process in the ovaries.

The leading role in the pathogenesis of AUB belongs to the inflammatory process of the genitals, under the influence of which the sensitivity of ovarian receptors to the action of gonadotropic hormones, as well as the sensitivity of endometrial receptors to estrogens and progesterone, changes [6].

In the late reproductive period, there is a fading of the hypothalamic centers, which cease to respond to the action of steroid hormones, as a result of which the pituitary gland's production of gonadotropins in the ovaries increases. As a result of the gradual depletion of ovarian function, luteal

insufficiency is formed, which leads to hyperestrogeny. These hormonal changes lead to hyperproliferation and secretory transformation of the endometrium [8].

Increased secretion of adrenocorticotropic hormone (ACTH) leads to suppression of the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). At the same time, the synthesis of estrogens and progesterone increases in the ovaries. There is an increase in the production of neurotransmitters (norepinephrine, dopamine, serotonin). It leads to a decrease in endogenous opioid peptides (endorphin) and an increase in gonadotropin-releasing hormone (GnRH), with a subsequent reduction in the LH/FSH ratio. As a result, ovulation does not occur. Follicle persistence occurs with increased estradiol secretion and decreased progesterone secretion.

Patients with AUB have an increased risk of developing increased intravascular coagulation with the formation of numerous fibrin microclots and aggregates of blood cells (platelets, erythrocytes) that block microcirculation in organs and tissues, including the uterus and endometrium [5]. To date, there is no complete picture reflecting the state of the coagulant system of hemostasis, immunological status, and cytokines in the development of ABU. However, these processes are of great importance for elucidating the main pathogenetic mechanisms of bleeding and determining prognostic markers preceding the hemostasis system and immunological regulation.

The purpose of the study was to analyze the hemostasis system disorders in women with abnormal uterine bleeding and the feasibility of using fibrinolysis inhibitors in their treatment.

Material and methods. To find out the specifics of disorders in the hemostasis system during uterine bleeding, we examined 110 women with ABU, who made up the main study group. The control group included 20 healthy women without menstrual cycle disorders. Patients were examined in Municipal Non-Commercial Enterprise “City Maternity Hospital No. 1” Of Kharkiv City Council in 2021–2024.

Women in the main group were divided into 3 subgroups according to the etiology of bleeding. The 1st subgroup included 41 (37.3 %) women with an ovulatory cycle, the second – 36 (32.7 %) patients with an anovulatory cycle, and the 3rd – 33 (30.0 %) patients with uterine bleeding of unknown etiology.

To assess the condition of the female genital organs according to the ultrasound examination (ultrasound), the size of the uterus, ovaries, and the thickness of the endometrium were determined. This made it possible to exclude the presence of uterine fibroids, adenomyosis, endometritis, and other gynecological pathology as a cause of dysfunctional uterine bleeding (DUB) development.

All women were of reproductive age (from 20 to 48 years old) and had disorders of menstrual function such as menorrhagia and menometrorrhagia.

Endometrium condition was assessed by the size of the inner layer of the uterus, which provides changes in the level of steroid hormones in the peripheral blood.

All medical and preventive measures were carried out by the Order of the Ministry of Health of Ukraine dated 13.04.2016 No. 353 (as amended on 09/23/2016 No. 994) “Unified clinical protocol of primary, secondary (specialized) and tertiary (highly specialized) medical care for abnormal uterine bleeding”.

When clarifying the anamnesis, particular importance was attached to the time of onset and nature of the menstrual function, the formation of the menstrual cycle and its disturbances, the duration and pain during menstruation, the amount of menstrual blood loss and the presence of recurrent bleeding in patients with AUB.

When examining women, standard clinical examination methods, indicators of overall hemostatic potential, primary hemostasis, state of intravascular hemocoagulation, indicators of the fibrinolytic system, and antiplasmin potential of blood were used. Laboratory tests carried out the determination of plasma hemostasis parameters: activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), Fibrinogen (Fg), plasma recalcification time (PRT, sec.), soluble fibrin monomer complex (SFMC), which were determined with the help of sets of reagents of the research and production company “Simko-LTD”, Lviv. The state of platelet-vascular hemostasis was assessed by the percentage of adherent platelets (AP) and by the index of spontaneous platelet aggregation (ISPA). Determination of antithrombin III (AT-III) in plasma was carried out by incubating diluted citrate plasma with a standard amount of thrombin. The residual activity of thrombin was determined based on the coagulation time of fibrinogen. Further control and results of coagulation hemostasis therapy were carried out directly at the time of bleeding. During treatment on days 5–7 of the menstrual cycle, defects in the hemostasis system were identified, which became the primary criterion for distinguishing two forms of abnormal uterine bleeding: combined and isolated.

Treatment measures performed for patients with AUB were selected etiopathogenetically and individually. When choosing a treatment method, the intensity of bleeding, the degree of anemia, and

coagulogram indicators were considered. Step-by-step treatment involves stopping bleeding, regulating the menstrual cycle, and then preventing it.

For statistical evaluation, all data were entered into Excel spreadsheets. The obtained digital data were processed using mathematical statistics and variational and alternative analyses. The results were analyzed using licensed statistical programs Microsoft Excel and Statistics 6.0. At the same time, the mean values of each indicator were calculated using the Student's T-test, the mean square deviation, the mean error of the arithmetic mean, and the estimation of the distribution of values. Mean and standard error (M±SE) were used for changes that followed a normal distribution.

Results of the study and their discussion. At the time of admission of the patients to the hospital, the duration of bleeding was on average from 5–7 days to 1–2 months, while in the majority of patients of the main group – 78 (73.3 %), the duration of bleeding was no more than 11–14 days. In subgroup 1, the duration of bleeding was 13.9±0.5 days. In the 2nd subgroup, the duration of bleeding was 9.5±0.3 days; in the 3rd subgroup, 11.3±0.4 days, respectively.

Upon admission to the hospital, the volume of blood loss in the 1st subgroup amounted to more than 180 ml – in 35 (88.5 %) patients; the amount of blood loss was 165 ml in 17 (47.2 %) patients of the 2nd subgroup, and in the 3rd subgroup – 150–160 ml – in 21 (63.3 %) patients.

Based on this, it can be concluded that more abundant bleeding from the genital tract occurred in patients with uterine bleeding in the 1st observation subgroup ($p < 0.05$), which was the main reason for the development of complications in the form of posthemorrhagic anemia.

A complication in the form of anemia was detected in 27 (85.8 %) patients with AUB in the 1st subgroup, of which mild anemia was detected in 13 (48.2 %) patients, and moderate anemia was diagnosed in 9 (33.3 %) patients, severe – in 5 (18.5 %) patients. In the 2nd follow-up subgroup, anemia was observed in 32 patients, with a mild degree in 19 (59.4 %), a moderate degree in 8 (25.0 %), and severe anemia – in 5 (15.6 %) patients. No cases of severe anemia were detected in the 3rd subgroup.

In 26 (92.9 %) patients of the 1st subgroup (Table 1), the hemoglobin level was below the norm and amounted to 70±5.6 g/l, in the 2nd subgroup – 80±5.3, in the 3rd subgroup – on average, it was 85–90±4.4 g/l).

Table 1

Hematological indices in examined patients with AUB (M±m)

Groups of patients	White blood cells, 10^9g /L	Lymphocytes %	Monocytes %	Eosinophils, mcL	Red blood cells, 10^{12}/L
Subgroup 1 (n=41)	8.4±0.1*	28.7±0.1	7.8±0.1*	5.9±0.1*	3.1±0.1*
Subgroup 2 (n=36)	6.6±0.1	26.2±0.2	5.4±0.1	3.8±0.1	4.4±0.1
Subgroup 3 (n=33)	7.2±0.1*	34.2±0.1*	8.6±0.1*	5.5±0.1*	3.2±0.1*
Control group (n=20)	5.2±0.1	29.8±0.1	6.1±0.1	3.6±0.1	5.7±0.1

Note * – differences are significant compared to the control group, $p < 0.05$.

A decrease in total protein in blood serum and serum iron concentration was found in patients with anemia. White blood cells, monocytes, and eosinophils were significantly higher in AUB's 1st and 3rd subgroups than in the corresponding control group. The number of red blood cells in all groups of patients with AUB was significantly reduced compared to the control group.

To identify the features of the functioning of the hemostasis system in those examined with AUB, a Hemostatic Screening Test was conducted with a study of the overall hemostatic potential, platelet-vascular hemostasis, anticoagulation, and fibrinolytic subsystems. The hemostasis system was studied using the following indices: overall hemostatic potential, plasma recalcification time, prothrombin time, and thrombin time. Parameters of the overall hemostatic potential of blood in women with AUB are shown in Table 2.

APTT is considered the most sensitive test for displaying blood coagulation activity [2], which indicated an increase in hemocoagulation potential ($p<0.05$). A more pronounced decrease in APPT in AUB indicates a clear development of permanent hypercoagulation, which correlates with the severity of blood loss.

PT, which reflects the activity of factors of the external pathway of blood coagulation, practically did not change. Regarding TT, the diagnostic value of determining the state of fibrinogenesis also did not increase compared to the control in the main group ($p<0.05$**).**

TT, the diagnostic value of determining the state of fibrinogenesis, was significantly increased in AUB women compared to controls ($p<0.01$).

The concentration of fibrinogen was also increased in all subgroups compared to the control (4.5±0.3 g/L in 1st, 4.3±0.2 g/L in the 2nd, and 4.0±0.4 g/L in the 3rd; in the control – 3.6±0.1 g/L). PRT, which characterizes the internal path of blood coagulation, tended to increase in all subgroups of patients examined with AUB compared to controls ($p<0.05$). The number of blood platelets in subgroups 1, 2, and 3 was significantly reduced compared to the control (244.6±2.6) and was 215.6±1.3x10^9/L ($p<0.01$) and 220.2±1.7x10^9/L and 227.6±1.3*, respectively ($p<0.05$). When studying the main component of the anticoagulation system of the blood (AT-III)), a decrease in its activity was noted in the examined women of the main group with AUB ($p<0.05$). Thus, the analysis of the conducted studies showed that patients with AUB have an increased overall coagulation potential. In addition, with prolonged blood loss, a subclinical form of the chronic syndrome of disseminated intravascular coagulation (DIC) of blood develops.

Table 2

Features of the hemostasis system functioning in women with AUB

Parameters	Subgroup 1 (n=41)	Subgroup 2 (n=36)	Subgroup 3 (n=33)	Control group (n=20)
Parameters of the overall hemostatic potential in the examined patients				
APTT, sec	24.4±2.3*	31.4±2.1 *	28.4±2.2*	41.7±2.3
PT, sec	22.5±1.4	21.7±1.5	20.8±1.3	22.2±1.7
TT, sec	19.3±1.3*	18.6±1.1*	20.1±1.4*	16.5±1.1
Fg, g/L	4.5±0.3	4.3±.0.2	4.0±0.4	3.6±0.1
PRT, sec	84.2±1.2*	85.6±2.1*	90.1±1.8*	96.2±1.5
Tc x10^9/L	215.6±1.3**	220.2±1.7*	227.6±1.3*	244.6±2.6
AT-III, %	72.0±2.2*	76.1±2.3*	72.3±2.1	82.6+2.1
Parameters of primary hemostasis and state of intravascular coagulation in patients with AUB				
ISPA, units	18.6±1.5*	16.6±1.2*	15.8±1.4*	5.7±1.6
PAP, %	73.3±3.1*	64.4±3.2*	66.4±2.1*	44.4±2.2
SFMC, µg/mL	35.4±1.5*	22.7±2.2*	25.2±2.2*	8.6±2.4
FDP, µg/mL	7.1±1.4 *	5.1±1.2*	4.8±1.2*	1.6±0.1
Parameters of the fibrinolytic system in the examined women				
GFC, E440/mL/hour	16.5±1.6**	14.2±1.8	15.5±1.4	9.6±0.5
PPA, minutes	22.4±1.5	19.2±1.3	21.2±1.6	20.54±1.3
HFDF, minutes	17.3±1.4 *	20.4±12	19.2±1.5	21.4±1.3
Parameters of antiplasmin potential of blood in examined patients				
APP, %	121.1±3.5*	119.8±6.5*	120.5±4.4*	107.96±2.4
FAAP, %	118.4±1.6*	119.1±2.2*	117.9±2.8*	99.4±1.4
SAAP, %	112.5±2.3 *	114.3±3.1*	113.8±2.6*	102.3±2.1

Note: the significance of subgroups 1, 2, and 3 differences compared to the control group, * $p<0.05$; ** – $p<0.01$; *** – $p<0.001$.

It can be assumed that the initiating mechanisms of the development of DIC syndrome in this group of examinees are related to a violation in other links of the system of regulation of the aggregate state of the blood. According to the authors' data, the development of DIC blood syndrome in patients with AUB is often associated with primary hemostasis activation [13]. The results of indicators of primary hemostasis and the state of intravascular hemocoagulation in women with AUB complicated by anemia are presented below.

In AUB, the spontaneous platelet aggregation index significantly exceeded the control data in all follow-up groups ($p<0.05$), and the percentage of adherent platelets (PAP) also significantly exceeded the control data from 1.4 to 1.7 times. The indicators of ISPA and PAP were the highest in anemia caused by ovulatory uterine bleeding ($p<0.05$). The state of intravascular hemocoagulation was assessed by the plasma concentration of pathological hematological coagulants – soluble fibrin monomer complex (SFMC) and fibrin and fibrinogen degradation products (FDP).

In ovulatory AUB, an increase in the content of SFMC in blood plasma was observed compared to the control group. In contrast, the concentration of FDP increased in subgroup 1 by 5.6 times and in subgroups 2 and 3 from 3.5 to 3.8 times compared to the control group. The results indicate a high level of thrombocythemia and intravascular activation of blood coagulation in all patients with AUB.

Determination of global fibrinolytic capacity (GFC), potential plasminogen activity (PPA), and Hageman-factor-dependent fibrinolysis (HFDF).

GFC in blood plasma increased in patients of the subgroup 1 compared to controls (GFC − 16.5±1.6 and in controls, 9.6±0.5, $p<0.01$). The potential activity of plasminogen in the examined patients was practically unchanged compared to the control, and the value of HFDF reached the level of reliability ($p<0.05$).

Its increase characterized antiplasmin potential (APP) in examined women with AUB. It was due to an increase in slow-acting antiplasmin (SAAP) since the activity of fast-acting antiplasmin (FAAP) in subgroups 1, 2, and 3 of patients was probably increased. The obtained results indicate the activation of the antiplasmin system in the examined women with DUB without a clear preference for FAAP or SAAP.

Studies have shown that women with AUB develop a subclinical form of chronic DIC of the blood. Its primary development link is the activation of platelet-vascular hemostasis with subsequent involvement in the process of coagulation potential caused by a decrease in the indicators of the blood's anticoagulation system [11].

Considering the data obtained in patients with AUB, we believe that the development of uterine bleeding in all subgroups occurred at the level of relative hypercoagulation. Analysis of the state of the hemostatic system in patients with recurrent AUB allowed us to identify various defects and specific patterns in the mechanisms of development and stopping of uterine bleeding. Patients with AUB were treated with antifibrinolytic and non-steroidal anti-inflammatory drugs to reduce menstrual blood loss, reduce anemia, and prevent the recurrence of bleeding [7].

The tranexamic acid was prescribed in a dosage of 3000 mg per day, 2 days before the start of the expected menstruation and until the last day of menstruation (on average 7–8 days). Aminocaproic acid blocks plasminogen activators and partially suppresses the action of plasmin, thereby providing a specific hemostatic effect during bleeding [4].

Against the background of taking drugs with AUB, the measures taken led to the cessation of bleeding. The bleeding stopped for 2–5 days. The cessation of uterine bleeding occurred at approximately the same level as the overall hemostatic potential indices.

Considering prostaglandins' role in the pathogenesis of AUB, therapy with inhibitors of their synthesis is quite effective in patients with ovulatory bleeding.

Hormonal therapy is the most justified method of treatment for AUB, which is prescribed differently depending on the pathogenetic variant. In the luteal phase for 3–6 months or intrauterine system (IUS) “Mirena”. For anovulatory bleeding, combined oral contraceptives (Zhanin, Yaryna) are used for 3–6 months in the presence of endometrial hyperplasia – progestogens from the 5th to the 25th day [3].

The drugs of choice for the treatment of both ovulatory and anovulatory AUB are GnRH agonists, which are prescribed for 3–4 months. Numerous studies have proven the high efficiency of progestogens in treating AUB. By suppressing ovulation, danazol (200 mg) causes a decrease in estrogen levels more effectively than oral contraceptives and antifibrinolytics. The effectiveness of the method is 60–80 %. Side effects (weight gain of 2–4 kg, phenomena of hyperandrogenemia, irritability, fatigue, myalgia, recurrence of bleeding after withdrawal of the drug) limit its use.

Treatment with GnRH agonists leads to a decrease in the sensitivity of adenohypophysis cell receptors to GnRH, which causes a reduction in the secretion of gonadotropins with the subsequent development of hypoestrogeny. GnRH agonists (zoladex, buserelin, decapeptyl-depot, diferelin, etc.) are used as injections, subcutaneous implants, and endonasal sprays. The effectiveness of the method reaches 90 %. Still, the high cost and side symptoms of estrogen deficiency (hot flashes, dyspareunia, demineralization of bone tissue, etc.) limit the use of these drugs in the treatment of DUB [9].

Hysteroscopic endometrial ablation and hysterectomy are surgical methods of treating AUB. Endometrial ablation (resection of the uterine mucosa) is performed with a laser, a resectoscope, a loop, and a ball electrode under the control of hysteroscopy [10].

To prevent repeated surgical interventions, prostaglandin synthesis inhibitors were prescribed (nimesulide 100 mg 2 times/day, ibuprofen 200 mg 2–3 times/day) in the first 3 days of menstruation. Their purpose is essential, as it is the prevention of inflammatory complications, damage to the receptor apparatus of the endometrium, and the formation of hormone resistance. Iron preparations, multivitamins, and mineral preparations were prescribed for treating anemia and, in severe cases, blood substitutes and blood preparations. All patients with detected disorders in the hemostasis system underwent a repeat examination of the hemostasis system within the next 6–12 months after the treatment on the 3–7 day of the menstrual cycle. After the therapy, the parameters of the functional activity of platelets normalized in these patients. After the treatment, including hormonal therapy, against the background of normalization of menstrual function, the indicators of aggregation activity of platelets

remained approximately at the same level as at the time of bleeding in patients with AUB. Therefore, after carrying out coagulation studies, patients with AUB and detected disorders in the hemostasis system were prescribed the drug tranexamic acid for 5 days.

Thus, changes in the parameters of the coagulation potential indicate an increase in the activity of the blood coagulation system against the background of tranexamic acid treatment. The positive effect of the therapy on patients with AUB was observed in 89.9 % and led to the cessation of uterine bleeding.

Conclusion

AUB in the reproductive age leads to the development of posthemorrhagic anemia. The severity and nature of bleeding are determined by defects in the platelet link system of the hemostasis system that violate the aggregation function of platelets.Pathological activation of the hemostasis system contributes to the increase of the overall hemostatic potential, primary hemostasis, and the state of intravascular hemocoagulation using methods for assessing the amount of platelet aggregation. It makes it possible to identify and differentiate disorders in the hemostasis system.

Using fibrinolysis inhibitors makes it possible to increase the activity of the blood coagulation system and completely stop bleeding for 2–5 days.

The development of the subclinical form of chronic DIC, the activation of platelet-vascular hemostasis affects the reduction of indicators of the anticoagulation system of the blood with the involvement of the coagulation potential in the process due to the decrease of the indicators of the anticoagulation system of the blood. A high frequency of AUB can affect the level of endogenous fibrinolysis and significantly increase the risk of thrombotic complications.

References

1. Byrchak IV. Osoblyvosti rehulyatsiyi ahrehatnoho stanu krovi zhinok na tli dysfunktsionalnykh matkovykh krovotech reproduktyvnoho viku. Bukovynskyy medychnyy visnyk, 2014, 18.2 (70). 209–210 [in Ukrainian].
2. Burka OA, Tutchenko TM, Shumytskyy AV. Rol laboratornykh doslidzhen u diahnostytsi prychyn anomalnykh matkovykh krovotech. Zdorovya zhinky, 2019, 3 (139): 49–52. doi: https://doi.org/10.15574/HW.2019.139.49 [in Ukrainian].
3. Vovk IB. Osoblyvosti zastosuvannya kombinovanykh oralnykh kontratseptyviv z kontratseptyvnoyu ta likuvalno-profilaktychnoyu metoyu. Medychni aspekty zdorovya zhinky. 2018. №4(117). 5–12. [in Ukrainian].
4. Pyrohova LV, Chernyshenko TM, Kolesnikova IM, Platonova TM, Bereznytskyy HK, Makohonenko YeM, et al. Riven zahalnoho hemostatychnoho, zhortayuchoho i fibrynolitychnoho potentsialu u plazmi krovi donoriv i khvorykh pry riznykh zakhvoryuvannyakh. Ukr. biokh. zhurn. 2016. T.88. №2. 56–65. [in Ukrainian].
5. Tatarchuk TF, Kosey NV, Tutchenko TM. Suchasna diahnostyka ta likuvannya anomalnykh matkovykh krovotech. Reproduktyvna endokrynolohiya. 2018. № 1(3). 74–78. [in Ukrainian].
6. Bradley LD, Gueye NA. The medical management of abnormal uterine bleeding in reproductive-aged women. Am J Obstet Gynecol. 2016 Jan;214(1):31–44. doi: 10.1016/j.ajog.2015.07.044.
7. Goldstein SR, Lumsden MA. Abnormal uterine bleeding in perimenopause. Climacteric. 2017 Oct;20(5):414–420. doi: 10.1080/13697137.2017.1358921.
8. Guasch E, Gilsanz F. Massive obstetric hemorrhage: Current approach to management. Med Intensiva. 2016 Jun-Jul;40(5):298–310. doi: 10.1016/j.medin.2016.02.010.
9. Lambalk CB, Banga FR, Huirne JA, Toftager M, Pinborg A, Homburg R, et al. GnRH antagonist versus long agonist protocols in IVF: a systematic review and meta-analysis accounting for patient type. Hum Reprod Update. 2017 Sep 1;23(5):560–579. doi: 10.1093/humupd/dmx017.
10. Leal CRV, Vannuccini S, Jain V, Dolmans MM, Di Spiezio Sardo A, Al-Hendy A, et al. Abnormal uterine bleeding: The well-known and the hidden face. J Endometr Uterine Disord. 2024 Jun; 6:100071. doi: 10.1016/j.jeud.2024.100071.
11. Steiner RA, Fink D. Menstruationsstörungen [Abnormal menstrual bleeding]. Praxis (Bern 1994). 2002 Nov 13;91(46):1967–1974. German. doi: 10.1024/0369-8394.91.46.1967.
12. Wang L, Guan HY, Xia HX, Chen XY, Zhang W. Dydrogesterone treatment for menstrual-cycle regularization in abnormal uterine bleeding – ovulation dysfunction patients. World J Clin Cases. 2020 Aug 6;8(15):3259–3266. doi: 10.12998/wjcc.v8.i15.3259.
13. Wouk N, Helton M. Abnormal Uterine Bleeding in Premenopausal Women. Am Fam Physician. 2019 Apr 1;99(7):435–443. PMID: 30932448.

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