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## THE ROLE OF IMMUNOLOGICAL FACTORS IN THE DEVELOPMENT OF ABNORMAL UTERINE BLEEDING IN WOMEN OF REPRODUCTIVE AGE WITH EXTRAGENITAL DISORDERS

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The **aim** of the study was to assess the role of immunological factors in the development of abnormal uterine bleeding in women of reproductive age with extragenital disorders.

**Materials and methods.** The study involved 100 women with abnormal uterine bleeding and accompanying extragenital disorders (main group) and 50 somatically healthy women (control group). Autoimmune antibodies to platelets, phagocytic activity of neutrophil granulocytes, concentration of circulating immune complexes (CICs), total level of membranotropic cytotoxic factors, content of CD4<sup>+</sup>T-helper subpopulations and cytotoxic CD8<sup>+</sup>T-killer lymphocytes were evaluated as immunological markers.

**Results of the study.** The study showed that thrombocytopenia, caused by the presence of autoimmune antibodies to their own platelets, can be one of the pathogenic factors of bleeding in women with AUB. In 41 % of women with AUB, phagocytic reactions were found to be intense, which was expressed by an increase in chemotaxis and adhesion functions, and in 46 % of women by an increase in the absorption capacity of phagocytes. In the main group, 48 % of the examined women had insufficient phagocyte enzymatic activity, which was evidenced by a decrease in the index of completion of phagocytosis. In 79 % of women of the main group, violations of the formation and elimination of circulating immune complexes were detected. The formation of low-molecular-weight CICs in 82 % of women of this cohort contributed to the induction of autoimmune reactions. The total content of membranotropic cytotoxic factors, which was evaluated according to the lymphocytotoxic test, exceeded the reference values in 88 % of women of the main group. In the main group, the average content of CD4<sup>+</sup> T-helpers was 23 % lower, and the content of suppressor CD8<sup>+</sup> T-lymphocytes was twice as low compared to the control group, resulting in a significant increase in the immunoregulatory index by 30 %.

**Conclusion.** The women of the main group with abnormal uterine bleeding were found to have a violation of the functional activity of cellular factors of innate immunity, accompanied by changes in the absorption and digestive capacity of phagocytic cells. Assessment of secondary adaptive reactions showed induction of humoral sensitization and formation of autoimmune reactions (presence of antiplatelet autoantibodies, increase in CICs and LCT, decrease in the subpopulation of CD8<sup>+</sup>-suppressor T-lymphocytes). The detected violations indicate the pathogenic role of immunological reactions in women with abnormal uterine bleeding

**Keywords:** abnormal uterine bleeding, immune system, antiplatelet autoantibodies, phagocytic reactions, humoral sensitization

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### 1. Introduction

According to modern notions, abnormal uterine bleeding (AUB) is a comprehensive term encompassing any uterine bleeding that does not meet the parameters of normal menstruation in women of reproductive age [1].

In the structure of gynecological diseases, uterine bleeding at puberty is observed in 10–15 %, AUB of reproductive period in 25–30 %, in late reproductive age in 35–55 %, in menopause up to 55–60 %, i.e., the incidence of AUB increases with age [2, 3]. Such a wide range of AUB incidence is due to the fact that studies of this abnormality are conducted in different clinical conditions [4, 5]. Thus, the incidence of AUB detection

in women aged 30 to 49 by a general practitioner was 5 %, by a gynecologist – up to 30 % [6].

Despite the achievements of modern medicine, even in the developed countries, the frequency of surgical interventions in case of uterine bleeding remains high [7]. The lifestyle of modern women has reduced the duration of physiological amenorrhea. Due to the influence of adverse environmental conditions and nutrition, there was an increase in menstrual disorders, which led to a rise in AUB prevalence and a decrease in reproductive function [8, 9]. Given the high relevance of this abnormality, identifying the causes of AUB can prevent the development of complications and long-

term consequences such as infertility and / or malignant neoplasms.

The causes of AUB could be different: both uterine and ectopic, in particular, extragenital disorders. Uterine bleeding is largely related to the condition of the endometrium, which is significantly affected by the metabolism of sex hormones, as well as hormonal status in general [10]. According to modern ideas, the leading role in the implementation of hemostasis in the endometrium is played by the platelet link of the hemostasis system [11]. Primary coagulopathies are found in a significant number of patients: most often Willebrand's disease (7–20 %), as well as platelet dysfunction (up to 20 %) [12].

A complete structure of the vascular wall, normal functioning of the vascular-platelet link [13, 14] and blood coagulation factors have been found to be necessary for the timely cessation of physiological menstruation [15, 14]. The process of hemocoagulation is known to be regulated by the humoral system with the participation of coagulation factors and various hormones, as well as the autonomic nervous system by stimulating or inhibiting the processes of hemocoagulation [16]. Thus, the processes of hypercoagulation occur due to the predominance of the tone of the sympathetic division of the autonomic nervous system, the predominance of the tone of the parasympathetic division causes the opposite effect. The autonomic nervous system affects the production by the vascular wall of substances involved in hemocoagulation. In addition, platelets contain adrenoceptors that have the opposite effect on platelet aggregation. During physiological menstruation, estrogens affect the process of hemostasis, thus contributing to the restoration of the endometrium due to the activation effect on the production of specific factors – prostaglandin F<sub>2α</sub> and endothelin1, characterized by vasoconstrictive properties [17]. Weakening of vasoconstriction also affects the volume and duration of menstrual blood loss [18]. As a result, under physiological conditions, the duration of uterine bleeding is associated with the coordinated action of vascular, cellular and tissue factors.

Changes that occur in the lining of the uterus, directly or indirectly, due to the metabolism of local factors, are associated with certain hormonal alterations. The duration and intensity of functional uterine bleeding depend on the initial concentration of sex hormones in the blood, the rate and degree of reduction of their level. Any violation of hormonal status negatively affects the process of rejection of the functional layer of the endometrium [19, 20]. Under such conditions, hormonal and immunological hemostasis are interrelated, as the immune system affects the receptor apparatus of the uterus [21].

Thus, uterine bleeding of reproductive age is caused by many factors, mainly resulting from hormonal and immunological changes. However, the effect of immune status on the development of AUB in women of reproductive age has not been fully identified, which substantiates the need for further research in this area.

**The aim.** To study the role of immunological factors in the development of abnormal uterine bleeding in women of reproductive age with extragenital disorders.

## 2. Materials and methods

The study was conducted at the Department of Obstetrics, Gynecology and Pediatric Gynecology of Kharkiv national medical university (clinical base of CNP “City Maternity Hospital No. 1” of KhCC (“CMH No. 1”). The study involved examination of 150 women of reproductive age, who were divided into clinical groups: Clinical group I (main) – 100 women with abnormal uterine bleeding and concomitant extragenital disorders, Clinical group II (control) – 50 somatically healthy women who came for a routine checkup. The patients of the main group were treated in the gynecological department of “CMH No. 1”. In accordance with the provisions of the Helsinki Declaration of the World Medical Association last revision, all patients involved in the study signed an informed consent to the use of survey data for scientific purposes. Minutes No. 2, dated September 17, 2019, of the meeting of the commission on ethics and bioethics of Kharkiv National Medical University.

Exclusion criteria from the study were: pregnancy as a possible cause of metrorrhagia, concomitant somatic diseases in the stage of decompensation and cancer, hormonal treatment at the time of examination.

All women underwent a complete clinical and laboratory examination.

The presence of autoimmune antibodies to platelets, phagocytic activity of neutrophilic granulocytes, concentration of circulating immune complexes (CIC), total level of membranotropic cytotoxic factors, level of CD4+T-CD-cytocytocytic subtypes were assessed as immunological markers of abnormal bleeding.

Studies of the presence of autoimmune antibodies to platelets were performed by indirect immunofluorescence using Thrombocytes IIFT sets, EUROIMMUN (Germany).

Phagocytic activity of peripheral blood neutrophils was determined by their ability to endocytose yeast cells, followed by microscopy. The effectiveness of phagocytosis was assessed by the functions of chemotaxis and adhesion, which characterize the phagocytic index (PHI) – the percentage of neutrophils involved in phagocytosis of their total number; phagocytic number (PHN) characterizes the absorbing function – the amount of antigen, in particular *Saccharomyces cerevisiae* cells, captured by one active phagocyte; the effectiveness of endocytosis was evaluated by the phagocytosis completion index (PHCI), which is the result of the ratio of PHN after 30 minutes and 120 minutes, and characterizes the effectiveness of digestive function with lysosomal enzymes (oxygen-dependent phagocytosis).

Serum CIC content was assessed spectrophotometrically after incubation of samples in borate buffer and polyethylene glycol at room temperature. During incubation, the CIC precipitated on PEG (polyethylene glycol), which changed the optical density of the samples. The optical density was measured spectrophotometrically at a wavelength of  $\lambda=450$  nm against borate buffer. The CIC constant (CIC-k) was determined by a method based on selective CIC precipitation in a PEG density gradient.

The lymphocytotoxicity test (LCT) was performed by the Terasaki method. Cell counting was performed using a light microscope. The level of membra-

neotropic cytotoxic factors was assessed by the percentage of living and dead cells.

The level of subpopulations of CD4+, CD8+ lymphocytes was determined using monoclonal antibodies (MCAT). The principle of the method is to specifically bind MCATs labelled with the FITC fluorescent dye to the corresponding surface antigens of immunocompetent cells. The percentage of cells in the corresponding subpopulation was calculated using a fluorescence microscope.

Statistical data were processed using the general-purpose software package Statistic 6.0 with correlation tables and the Pearson  $\chi^2$  criterion.

### 3. Results

The study showed that in the main group the absolute content of platelets was lower than in the control group by 24.6 % (Fig. 1). In women of the main group the platelet content was on average  $(196.4 \pm 6.8) \cdot 10^9/l$ , while in women of the control group the number of platelets averaged  $(267.8 \pm 37.5) \cdot 10^9/l$ .

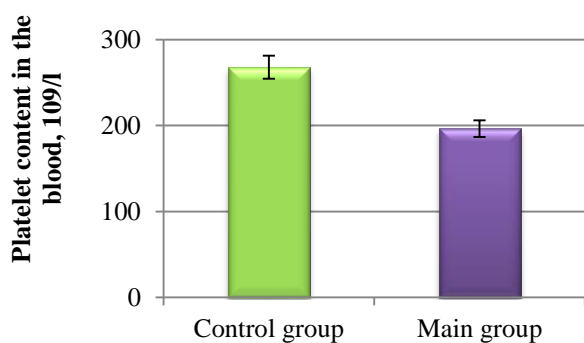


Fig. 1. The content of blood platelets in women of the studied groups

It is known that thrombocytopenia can be caused by the presence of autoimmune antibodies. Thus, in the screening study of blood sera of patients of the main group, 28 % of those surveyed were found to have autoimmune antibodies to their own platelets (Fig. 2).

Phagocytic cells are known to be the first line of defense against pathogens. The course and consequences of any infectious or inflammatory process are determined by the reaction of neutrophilic granulocytes, which is based on their ability to absorb and digest microbial antigens.

In most women in the control group (94 %) phagocytic reactions corresponded to the physiological norm (Table 1). In 6 % of the examined women of the control group the functions of chemotaxis and adhesion of neutrophilic granulocytes were lower than the reference interval, and 4 % of the women of the control group were found to have a slight decrease in digestive function of phagocytes, as evidenced by phagocytosis completion index below 1.09 (Table 1).

In 41 % of women in the main group phagocytic reactions were intense, which was expressed by increased functions of chemotaxis, adhesion, and 46 % of women were shown to have an increase in the absorption capacity of phagocytes. However, in the examined patients of this group the efficiency of phagocytic reactions

was insufficient, as evidenced by the decrease in the value of the phagocytic index (34 %) and phagocytosis completion index (48 %) (Table 1).

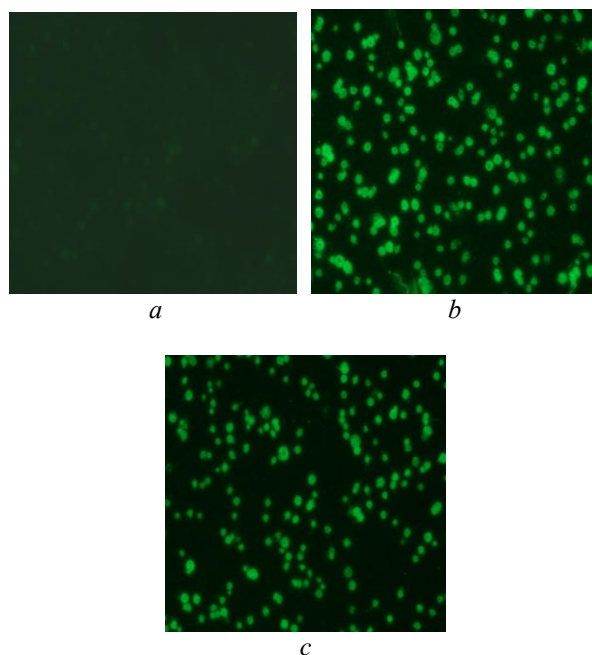


Fig. 2. Fluorescence microscopy of drugs: *a* – negative control; *b* – positive control; *c* – antiplatelet antibodies in the serum of patient I (case history No. 116) of the main group (magnification  $\times 1000$ )

In addition to the factors of innate immunity, the study revealed changes in the humoral part of the immune system.

In 96 % of women in the control group, the content of circulating immune complexes (CIC), which is the result of the interaction of antigens with antibodies that are normally eliminated from the body by phagocytes after prior opsonization with immunoglobulins and proteins of the complement system, corresponded to physiological norms. In 2 % of women serum CIC concentration was slightly outside the reference range. The total content of membranotropic cytotoxic factors, which was assessed by lymphocytotoxic test, significantly exceeded the reference values in 88 % of women in the main group (Table 2).

In the control group, the degree of lymphocytotoxicity was increased in 16 % of women surveyed, while in the main group this figure was 88 % (Table 3).

Such membranotropic cytotoxic structures derived from pathogens or damaged own cells, along with low molecular weight CICs, are an additional factor of tissue alteration and an inducer of autoimmune reactions.

The study of subpopulations of lymphocytes in women of both groups showed that in the main group the average content of CD4+T-helpers was lower by 23 % than in women of the control group (Fig. 3). There was also a twofold decrease in the content of suppressor CD8+T-lymphocytes relative to the control group. Violation of the ratio of subpopulations of CD4+T-helpers to CD8+T-cells caused a significant increase in the immunoregulatory index to the value  $(3.06 \pm 0.08)$  at  $(2.10 \pm 0.09)$  in the control group.

Table 1  
Efficacy of phagocytic reactions in healthy women of the control group and women with abnormal uterine bleeding (main group)

Index	Parameters	Frequency of detection in groups, as a percentage of n (%) / abs. number of women	
		Control (n=50)	Main (n=100)
Phagocytic index, %	Reference interval (70–90)	94 % / 47	25 % / 25
	Increased ( $\geq 91$ )	–	41 % / 41
	Decreased ( $\leq 69$ )	6 % / 3	34 % / 34
Phagocytic number	Reference interval (2.5–4.0)	98 % / 49	42 % / 42
	Increased ( $\geq 4.1$ )	–	46 % / 46
	Decreased ( $\leq 2.4$ )	2 % / 1	12 % / 12
Phagocytosis completion index	Reference interval (1.1–1.22)	96 % / 48	64 % / 64
	Increased ( $\geq 1.23$ )	–	–
	Decreased ( $\leq 1.09$ )	4 % / 2	36 % / 36

Table 2  
The content of circulating immune complexes in the serum of healthy women in the control group and patients with abnormal uterine bleeding (main group)

Index	Parameters	Frequency of detection in groups, as a percentage of n (%) / abs. number of women	
		Control (n=50)	Main (n=100)
CIC, s.u.	Reference interval (70–100)	96 % / 48	21 % / 21
	Increased ( $\geq 101$ )	2 % / 1	38 % / 38
	Decreased ( $\leq 69$ )	2 % / 1	41 % / 41
CIC-k, s.u.	Reference interval (1.1–1.5)	96 % / 48	18 % / 18
	Increased ( $\geq 1.6$ )	–	–
	Decreased ( $\leq 1.0$ )	4 % / 2	82 % / 82

Table 3  
The degree of lymphocytotoxicity of blood serum of healthy women in the control group and patients with abnormal uterine bleeding (main group)

Index	Parameters	Frequency of detection in groups, as a percentage of n (%) / abs. number of women	
		Control (n=50)	Main (n=50)
LCT, %	Reference values ( $\leq 30$ )	84 % / 42	12 % / 12
	Increase ( $\geq 31$ )	16 % / 8	88 % / 88

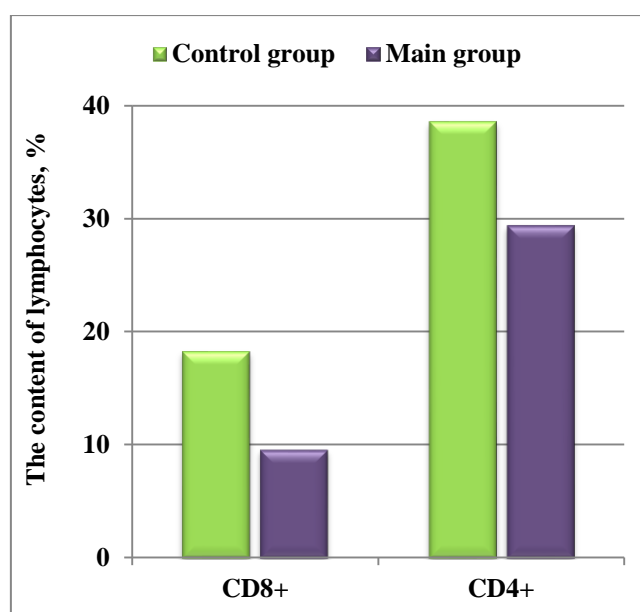


Fig. 3. The ratio of the main subpopulations of T-lymphocytes (helper CD4+-T-lymphocytes and suppressor CD8+-T-lymphocytes) in women of the control and main groups



#### 4. Discussion

Numerous studies over many decades have recognized that menstrual bleeding is not only an endocrine process caused by a change in the secretion of ovarian hormones, but also includes a series of significant changes in immunoresistance with the involvement of cellular and humoral factors of immunity [22, 23].

Scientific information available today about changes in immunoreactivity in women with abnormal bleeding is contradictory. Some authors indicate that women with heavy menstrual bleeding have abnormalities in the number, distribution, and functions of immune cells [21]. Other authors did not find pronounced violations of cellular immunity in patients with a similar disorder. Quantitative changes in T-lymphocytes and their subpopulations are characterized by the authors as immunocompensation [24].

The question of the role of thrombocytopenia as a pathogenic factor of abnormal uterine bleeding also remains debatable. Most researchers believe that uterine bleeding is more severe in women with disorders of the blood coagulation system, in particular with thrombocytopenia [25]. Some authors indicate that moderate menorrhagia is observed when the number of platelets is  $< 20\text{--}30 \cdot 10^9/l$ , which is easy to correct [26]. However, these data do not correspond to the results of our research. We found that the absolute content of platelets in patients with AUB is a quarter lower than in healthy women. Therefore, we believe that abnormal uterine bleeding in women of reproductive age may be a consequence of thrombocytopenia or a defect in platelet function.

Autoimmune processes can be singled out among the large number of pathogenic factors leading to thrombocytopenia. A decrease in the number of platelets in peripheral blood could be caused by autoimmune antibodies (AAB) attacking platelets and megakaryocytes [27, 28]. In view of this, we carried out a qualitative determination of antiplatelet AAB in the blood serum of women in the control and main groups, which showed that 28 % of women in the main group with AUB had autoimmune antibodies to their own platelets. Therefore, we believe that one of the pathogenic factors of bleeding in women of this cohort may be the presence of antibodies to their own platelets.

Thrombocytopenia caused by the presence of antiplatelet autoantibodies indicates the involvement of immune mechanisms in the pathological process. The changes in immunoresistance in women with AUB revealed in this study show an imbalance of immunological links in the immune system, which increases the risk of developing autoimmune conditions in this cohort of patients.

Assessment of phagocytic function of peripheral blood neutrophil granulocytes demonstrated that almost half of the examined women of the main group had enhanced chemotaxis, adhesion, and endocytosis functions secondary to low digestive capacity of phagocytes. A low index of completion of phagocytosis indicates depletion of the functional reserve of neutrophils due to prolonged stress, which contributes to the formation of autoimmune reactions [29].

An increase in the cytotoxicity of blood serum was detected in the humoral chain of immunity, which

was characterized by a change in the content of low molecular weight immune complexes (CICs) and membranotropic lymphocytotoxic factors (LCT) relative to the physiological norm. The reason for the low level of CICs in the blood serum of women with AUB may be insufficient intensity of their formation due to a violation of antigen “recognition” mechanisms, a deficiency of opsonizing humoral factors that participate in the formation of CICs (in particular, general and species-specific immunoglobulins, proteins of the complement system that form membrane-attacking complex, etc. [30–32]. In addition, a decrease in the relative physiological norm of the level of CICs in the blood serum of 41 % of the examined women of the main group may be a consequence of their accumulation in tissues, which was facilitated by the low molecular weight of CICs in 82 % of patients with uterine bleeding.

Low molecular weight immune complexes are known to be able to accumulate in various organs and tissues [33]. The tropism of CIC to the endothelium of vessels causes damage to biological structures and the induction of autoimmune reactions [34]. A decrease in the content of CICs in blood serum could occur because of their fixation on platelets and endothelium, which is characteristic of pathological CICs with a low molecular weight [35]. Immune complexes, binding to the complement CR2 receptor on the surface of the B-lymphocyte, induce the production of immunoglobulins by these cells, including autoimmune antibodies [36]. In view of this, it can be concluded that the violation of the formation of CICs, which was detected in the blood serum of 79 % of women of the main group, contributed to the induction of immunopathological autoimmune reactions.

In the cellular chain of immunity, the study of the main subpopulations of T-lymphocytes revealed a decrease in the suppressive function of CD8+T-lymphocytes, which also indicates the formation of autoimmune disorders in women of the main group. There is also evidence in the literature that women with progression of endometrial hyperplasia develop pronounced changes in the subpopulation composition of immunocompetent cells [37]. Our data are consistent with the results of Witkiewicz A.K. et al. (2010), who showed that in women with atypical endometrial tissue morphology, the number of regulatory T cells is increased, and the number of cytotoxic subpopulations of lymphocytes, represented mainly by CD8+ (80 %), decreases [38].

Therefore, the findings of our own study indicate the presence of an imbalance in the immune system of women with abnormal uterine bleeding. The presence of an imbalance of immunological links in the immune system increases the risk of developing autoimmune conditions in this cohort of patients.

**Limitations of the study.** The study did not include women with pregnancy, as a possible cause of metrorrhagia, with accompanying somatic and gynecological oncology, and on the background of hormonal treatment at the time of examination.

**Prospects for further research.** Prospects for further research. The authors assume that the study of the role of immunological factors in the pathogenesis of abnormal uterine bleeding in women of reproductive age with extragenital pathology will provide an opportunity to predict their

occurrence and influence certain links of pathogenesis to prevent serious complications in this category of patients. This assumption requires additional research.

### 5. Conclusion

The women of the main group with abnormal uterine bleeding were found to have a violation of the functional activity of cellular factors of innate immunity, accompanied by changes in the absorption and digestive capacity of phagocytic cells. Assessment of secondary adaptive reactions showed induction of humoral sensitization and formation of autoimmune reactions (presence

of antiplatelet autoantibodies, increase in CICs and LCT, decrease in the subpopulation of CD8<sup>+</sup>-suppressor T-lymphocytes). The detected violations indicate the pathogenic role of immunological reactions in women with abnormal uterine bleeding.

### Conflicts of interest

The authors declare that they have no conflicts of interest.

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