

# The influence of infections and immune disorders on the development of intra-uterine pathology in women with antenatal fetal death in the anamnesis

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Reproductive losses remain an urgent problem among the female population, of which antenatal fetal death (AFD) takes a leading place. The pathogenesis of this pathology is multifactorial, but at the same time, it is impossible to accurately determine the single cause of AFD.

Analyzing the frequency of AFD in the world, a tendency towards repeated episodes of AFD or AFD combined with reproductive losses in early pregnancy has been established. The literature has presented data on causal relationships with existing endometrial pathology, among which the inflammatory process in the endometrium takes the leading position, and pregnancy losses with inadequate immune system response.

**The objective:** to determine the state of the immune system, infectious profile and features of the immunohistochemical state of the endometrium in women with a history of AFD at the stage of prepregnancy preparation.

**Materials and methods.** A clinical examination was performed on 30 patients with a history of AFD who had applied to the antenatal clinic of the municipal non-profit enterprise "Kyiv City Maternity Hospital No. 3" regarding planning their next pregnancy. A general clinical examination, a detailed analysis of the general, gynecological anamnesis, and data on the course of the previous pregnancy and childbirth were performed.

All patients underwent microscopic examination of vaginal discharge stained with Gram and assessed according to the Hay-Ison criteria. The state of the endometrium was studied by microscopic examination and immunohistochemical analysis with the determination of CD-138 and CD-56. The state of the immune system was assessed by determining the activity of the cellular component (T- and B-lymphocytes) and cytokine proteins (IL-1 $\alpha$ , IL-6, IL-8,  $\gamma$ -INT, TNF- $\alpha$ ).

**Results.** According to the somatic anamnesis, a high percentage of morbidity of the urinary system of an infectious-inflammatory nature (53.3%) and pathology of the cardiovascular system (63.3%) was determined. Among gynecological pathology inflammatory diseases of the genital tract (53.3%) and uterine leiomyoma (33.3%) predominated. In the obstetric anamnesis the spontaneous miscarriage was detected in almost every second woman (46.7%) and in every seventh woman – AFD (13.3%). During microscopic examination of vaginal discharge, the majority of women were diagnosed with stage III and IV according to the Hay-Ison criteria. During microscopic examination of the endometrium, disorders of its proliferation was detected in 2/3 of the patients, and during immunohistochemical examination – a positive reaction of CD-138 and an increased concentration of CD-56. During the study of the state of the immune system a decreased level of T-suppressors, B-lymphocytes were observed, with increased in T-killers and pro-inflammatory cytokines.

**Conclusions.** Women with a history of antenatal fetal death have certain features of the regulatory mechanisms of the immune system both at the local and generalized levels, which prompts a detailed study and diagnosis at the pre-gravid stage when determining further reproductive plans. Research of extragenital pathology, infectious profile and the state of local immunity in the uterine cavity is especially necessary.

**Keywords:** antenatal fetal death, immunity, infection, CD-138, CD-56, Pipelle biopsy, pregnancy, endometritis, T-lymphocytes.

## Вплив інфекцій та імунних порушень на розвиток внутрішньоматкової патології у жінок з антенатальною загибеллю плода в анамнезі

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Актуальною проблемою серед жіночого населення залишаються репродуктивні втрати, з них антенатальна загибель плода (АЗП) посідає провідне місце. Патогенез виникнення цієї патології є мультифакторним, але, у той самий час, неможливо точно визначити єдину причину АЗП.

Аналізуючи частоту АЗП у світі, встановлено тенденцію до повторних епізодів АЗП або АЗП, поєднану із репродуктивними втратами у ранній термін вагітності. У літературі зареєстровано дані про причинно-наслідкові зв'язки із наявною патологією ендометрія, серед яких лідируючі позиції займає запальний процес в ендометрії, і втратами вагітності за неадекватної відповіді імунної системи.

**Мета дослідження:** визначення стану імунної системи, інфекційного профілю та особливостей імуногістохімічного стану ендометрія у жінок з АЗП в анамнезі на етапі прегравідарної підготовки.

**Матеріали та методи.** Здійснено клінічне обстеження 30 пацієнток з АЗП в анамнезі, які звернулись до жіночої кон-

сультації комунального некомерційного підприємства «Київський міський пологовий будинок № 3» щодо планування наступної вагітності. Проведені загальноклінічне дослідження, детальний аналіз загального, гінекологічного анамнезу, даних перебігу попередньої вагітності та розродження.

Усім пацієнткам виконано мікроскопічне дослідження вагінальних виділень, зафарбованих за Грамом та оцінених за критеріями Нау–Ison. Вивчення стану ендометрія здійснено методом мікроскопічного дослідження та за допомогою імуногістохімічного аналізу з визначенням CD-138 та CD-56. Стан імунної системи оцінювали шляхом визначення активності клітинної ланки (Т- та В-лімфоцитів) і протеїнів цитокінового ряду (IL-1 $\alpha$ , IL-6, IL-8,  $\gamma$ -INT, TNF- $\alpha$ ).

**Результати.** Згідно з даними соматичного анамнезу, встановлено високий відсоток захворюваності сечовидільної системи інфекційно-запального характеру (53,3%) та патології серцево-судинної системи (63,3%). Серед гінекологічної патології анамнестично переважали запальні захворювання статевих шляхів (53,3%) та лейоміома матки (33,3%). В акушерському анамнезі майже у кожній другій жінки виявляли мимовільний викидень (46,7%) та у кожній сьомій – АЗП (13,3%). Під час мікроскопічного дослідження вагінальних виділень у більшій частині встановлено III і IV ступені за критеріями Нау–Ison. Під час мікроскопічного визначення стану ендометрія у 2/3 пацієнток встановлено порушення його проліферації і під час імуногістохімічного дослідження – позитивну реакцію CD-138 та збільшену концентрацію CD-56. Під час вивчення стану імунної системи спостерігалось зниження рівня Т-супресорів, В-лімфоцитів за збільшення вмісту Т-кілерів та прозапальних цитокінів.

**Висновки.** Жінки з антенатальною загибеллю плода в анамнезі мають певні особливості регуляторних механізмів імунної системи як на локальному, так і на генералізованому рівні, що спонукає до детального вивчення і діагностики на прегравідарному етапі під час визначення подальших репродуктивних планів. Особливо потребує дослідження екстрагенітальна патологія, інфекційний профіль і стан локального імунітету у порожнині матки.

**Ключові слова:** антенатальна загибель плода, імунітет, інфекція, CD-138, CD-56, пайпель-біопсія, вагітність, ендометрит, Т-лімфоцити.

The problem of miscarriage remains a topical issue among the female population [24, 31, 35, 39]. The frequency of miscarriage varies from 10% to 30% of the total number of pregnancies and there is no tendency to decrease. In particular, the frequency of spontaneous miscarriages is 15–25% of the total number of pregnancies, including 12% in the II trimester [22, 26]. Antenatal fetal death (AFD) occurs in up to 2 children per 1,000 live births in countries with an average and high level of development and up to 8 cases per 1,000 live births in countries with a low level of development [4, 29]. In Ukraine, the frequency of stillbirths is 5–6 cases per 1000 live births [6, 7].

The main problem related to the study of the pathogenesis of pregnancy loss is due to the polyetiological component, which is combined with an imbalance in the immune system and hormonal homeostasis in the early stages of pregnancy [10, 44]. At the same time, the immune system plays an important role as a regulator of stability of homeostasis and supports the development of pregnancy. In particular, during pregnancy due to the balance of proteins of the cytokine series, namely interleukin 10 (IL-10) and tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), the recognition of the embryo and the emergence of tolerance of the mother's body to the fetus occur, preventing the phenomenon of "rejection" [23, 38]. Progesterone affects the increase of T-lymphocytes, which contributes to the inhibition of the immune cells activity [32].

According to the literature, one of the factors of immune disorders during pregnancy can be oxidative stress, the destructive effect of which is an important factor in the development of inflammatory and autoimmune processes in the body, which is associated with disorders in the hemostasis system [16, 41]. Recently, many publications have appeared indicating the pathogenetic influence of changes in the hemostasis system, namely hypercoagulation, on the occurrence of a missed pregnancy in the II and III trimesters of pregnancy and directly or indirectly related to a violation of the implantation process [13, 40]. After all, the trophoblast acts as one of the regulators of favorable implantation and maintenance of the viability of the embryo due to rapid integration with

the endometrium and the formation of immunological "masking", when the fetus is actually protected from the influence of the maternal immune system [42].

According to the literature, during the study of endometrial tissues in cases of habitual miscarriage, changes in the morphofunctional state of the mucous membrane due to opportunistic pathogens are recorded [2, 12, 18, 36].

In the sources of the world literature, there are registered data on the violation of the receptive apparatus of the endometrium during a missed pregnancy in a short period of time [27]. These changes are associated with the occurrence of a chronic inflammatory process and a violation of the index of the ratio of estradiol and progesterone receptors [5]. Especially pronounced changes are observed in the stroma. During pregnancy, which occurred against the background of chronic endometritis, there is a violation of implantation due to changes in the work of the immune system, such as: an increase in the concentration of B-lymphocytes, cellular and mediator imbalance, suppression of the phagocytic activity of leukocytes [25, 30, 34]. Similar results were demonstrated in the study by K. Kitaya, in which in women with chronic endometritis, pregnancy loss related to implantation disorders was registered in every third case [19, 43].

NK cells (CD-56) are diagnostic markers of the endometrium state, which play a leading role in the regulation of trophoblast cell invasion, vascular remodeling, and cytotoxicity [11]. In a normal pregnancy, the cytotoxicity of CD-56 decreases, which contributes to the progression of pregnancy. With high levels of CD-56, the prognosis of a favorable course of pregnancy decreases, and with the decompensation of adaptive mechanisms, the pregnancy missed [17, 28, 37]. The CD-138 protein plays an important role in the implantation process. Data on the direct dependence of the presence of CD-138 and the occurrence of reproductive losses are recorded in the literature. This has been demonstrated by many studies not only during the use of assisted reproductive technologies, but also during spontaneous pregnancy [14, 15, 20, 37]. An increase in CD-138 levels in early pregnancy is an unfavorable prognostic factor for pregnancy outcome [33].

Therefore, in our opinion, the determination of the main markers of the chronic inflammatory process of the endometrium after a missed pregnancy, especially in the second half of gestation, is of great importance for the implementation of the woman's further reproductive plans.

**The objective:** to determine the state of the immune system, infectious profile and features of the immunohistochemical portrait of the endometrium in women with a history of antenatal fetal death at the stage of prepregnancy preparation.

### MATERIALS AND METHODS

To achieve the goal, we conducted a clinical examination and study of the expression of CD-138 and CD-56 in the endometrium of 30 patients with a history of AFD who were planning the next pregnancy on the basis of the women's consultation of the Kyiv maternity hospital No. 3 in the period from 2021 to 2023. The average value of the intergenetic interval in women of the examined group was  $4.4 \pm 0.3$  years.

During the clinical examination, data on hereditary anamnesis, extragenital pathology, anamnesis of gynecological diseases, parity, gestational age and features of the course of pregnancy before AFD, features of childbirth and the postpartum period with AFD were taken into account.

The microbiocenosis of the genital tract was studied using Gram-stained vaginal smear microscopy and evaluated using the Hay-Ison criteria, which distinguish 5 types of vaginal biotope [3].

I – normal vaginal microflora with *Lactobacillus* spp. dominance.

II – mixed bacterial microflora with *Lactobacillus* spp. and conditionally pathogenic microorganisms.

III – absent or in insignificant amount of *Lactobacillus* spp., conditionally pathogenic microorganisms prevail.

IV – *Lactobacillus* spp. were not detected, Cocci and pathogenic microorganisms prevail.

Real-time polymerase chain reaction (PCR) was used to determine the composition of microorganisms in vaginal secretions.

Samples of the endometrium for research were selected after general clinical methods of examination with the help of Pipelle biopsy on the 7th - 10th day of the menstrual cycle. Aspirate biopsy was performed in an outpatient department using the Pipelle system (JS Medical Materials, Ukraine), the procedure did not require additional anesthesia.

Syndecan-1 CD-138 (CD-138) is a membrane protein that interprets the work of plasma cells and acts as the "gold standard" in the diagnosis of chronic endometritis, which was determined using CD138 immune serum (Dako, USA).

CD-56 is a prototypic marker of NK cells. NK cells are natural killers with a heterogeneous population of immune system lymphocytes with cytolytic activity. According to its functional activity, it refers to a local marker of inflammation and an apoptosis factor.

The study of the immune system was carried out by determining the activity of the cell line in aspirate from the uterine cavity, total level of leukocytes namely general level lymphocytes and T-lymphocytes (CD3+, CD4+, CD8+, CD16+) and B-lymphocytes (CD22+) using the method of current cytofluorimetry on a NAVIOS cytometer (Beckman Coulter, USA). The immunoregulatory index (IRI) was determined by the ratio of the number of T-helpers (CD4+) to the number of T-suppressors (CD8+). Proteins of the cytokine series (pro-inflammatory – IL-1 $\alpha$ , IL-6, IL-8,  $\gamma$ -INT) and anti-inflammatory – TNF $\alpha$ ) were determined with the help of enzyme immunoassay on the analyzer "EL 808" ("Bio Tech Instruments", China).

Statistical data processing was carried out on a personal computer using Microsoft Excel 2013 software and further verification of the obtained data in the Statistica for Windows program and Microsoft Excel 13.0.

### RESULTS AND DISCUSSION

The age of patients with AFD varied from 24 to 39 years. The average age of patients with AFD was  $31.5 \pm 1.8$  years.

Analyzing the data of the somatic history, it was established that every second patient with AFD has a history of chronic pathology of the urinary system of an infectious nature 16 (53.3%); pathology of the cardiovascular system occurred in 19 (63.3%) patients. Predominant were vegetative-vascular dystonia 11 (36.7%), arterial hypertension 5 (16.7%), mitral valve prolapse 2 (6.7%), chronic endocarditis 1 (3.3%), etc. Varicose veins disease of the lower extremities were observed in 14 (43.3%) of patients with a history of AFD (Table 1).

Every fourth patient has a history of chronic tonsillitis (8 (26.7%) women) as a chronic source of secondary infection, and 3 (10.0%) patients underwent tonsillectomy due to recurrent paratonsillar abscesses.

Among gynecological pathologies in the anamnesis, the leading place was occupied by inflammatory diseases of the genital tract (16 – 53.3%) with detection of specific (9 (30.0%) and non-specific microflora (13 – 43.3%) (Table 2).

Benign diseases of the uterine body, namely uterine leiomyoma, were registered in every third woman's history (10 – 33.3%); adenomyosis occurred in every fourth patient (8 – 26.7%).

Among pregnancy parity, it was found that for 11 (36.7%) patients, the pregnancy that ended with AFD was the first, every third patient with AFD in anamnesis (10 (33.3%) women) had artificial abortions, in almost half of the women (14 (46.7%) patients) had a history of miscarriage. 4 (13.3%) patients had a history of repeated stillbirths.

Table 1

#### Extragenital pathology in patients with AFD in anamnesis, abs. number (%)

Nosology	Number of patients in the examined group, n = 30
Diseases of the urinary system	16 (53.3)
Varicose veins disease of the lower extremities	13 (43.3)
Pathology of the thyroid gland	8 (26.7)
Diabetes	4 (13.3)
Metabolic syndrome	5 (16.7)
COVID-19	5 (16.7)
Connective tissue pathology	3 (10.0)

**Table 2**  
**Obstetrics and gynecology pathology in patients with history of AFD, abs. number (%)**

Nosology	Number of patients in the examined group, n = 30
Inflammatory diseases of genital organs	16 (53.3)
Sexually transmitted infections	9 (30.0)
Non-specific vulvovaginitis	13 (43.3)
Uterine leiomyoma	10 (33.3)
Adenomyosis	8 (26.7)
Endometrial polyp	5 (16.7)
Cervical dysplasia	5 (16.7)
Polycystic ovary syndrome	2 (6.7)
Infertility	2 (6.7)
Repeated pregnancy losses	14 (46.7)
Repeated antenatal fetal death	4 (13.3)
Premature birth	7 (23.3)
Artificial abortion	10 (33.3)

The distribution of women with AFD depending on the gestation period did not establish a reliable difference: in the 22–28<sup>th</sup> week of gestation, AFD of the fetus was registered in every third woman (8 (26.7%) patients); 28–34 weeks – 6 (20.0%) women; 34–37 weeks – 7 (23.3%) women; ≥ 37 weeks – 9 (30.0%) patients ( $p > 0.005$ ).

The method of delivery was determined according to the obstetric situation and in the presence of violations in the main vital indicators. After all, additional injury and infection of the uterus can provoke an increased immune response in the uterine cavity [8, 9]. Thus, in 27 (90.0%) patients, childbirth took place through the natural birth canal; 3 (10.0%) – by caesarean section, the indications for which were: premature detachment of the placenta – 1 (3.3%) patient with subsequent development of the decimated intravascular coagulation syndrome; severe preeclampsia with a history of operated uterus – 2 (6.7%) women. The frequency and structure of complications during childbirth and in the postpartum period are presented in the table 3.

Among the patho-anatomical causes of antenatal fetal death, intrauterine infection of the fetus was on the first place – 11 (36.7%) cases; on second place – extragenital pathology of the mother – 7 (23.3%) cases, premature placental abruption – 1 (3.3%); umbilical cord anomalies – 8 (26.7%); severe preeclampsia – 2 (6.7%) women; fetal malformations – 2 (6.7%). It is worth noting that in 11 (36.7%) cases a combination of several causes was established, but in 4 (13.3%) cases the cause could not be established.

Given the presence in the structure of extragenital and gynecological pathology of conditions that contribute to chronic infection or its manifestation, a study was conducted to determine the microbiocenosis of the genital tract and the immunological status of these patients.

The results of the study of vaginal microbiocenosis according to the Hay–Ison criteria showed a significant decrease in the number of *Lactobacillus* spp. At the same time, every third patient has stage I and II according to the Hay–Ison criteria (stage I – 4 (13.3%); stage II – 7 (23.3%) patients) (Table 4).

**Table 3**  
**Peculiarities of the course of childbirth and the postpartum period with AFD in examined women, abs. number (%)**

Indicator	Number of patients in the examined group, n = 30
Abnormalities of the contractile activity of the uterus	5 (16.7)
Bleeding in labor	3 (10.0)
Episio-, perineotomy	7 (23.3)
Placental tissue defect	11 (36.7)
Hypotonic bleeding in the postpartum period	4 (13.3)
Thrombosis of the ovarian vein	1 (3.3)
Chorionamnionitis	5 (16.7)
Postpartum endometritis	4 (13.3)

**Table 4**  
**The state of the microbiocenosis of the genital tract in the examined women when evaluated according to the Hay–Ison criteria, abs. number (%)**

Grade according to the Hay–Ison criteria	Number of patients in the examined group, n = 30
I (Normal state)	4 (13.3)
II (Intermediate state)	7 (23.3)
III (Bacterial vaginosis)	11 (36.7)
IV (Aerobic vaginitis)	8 (26.7)

Grade III according to the Hay–Ison criteria was found in a third (11 (36.7%)) of patients, which corresponded to bacterial vaginosis, and Grade IV – in 8 (26.7%) patients. Among the detected microorganisms, the following prevailed: *Ureaplasma urealiticum* – 10 (33.3%); *Enterococcus faecalis* – 9 (30.0%); *Gardnerella vaginalis* – 8 (26.7%); *Escherichia coli* – 8 (26.7%); *Staphylococcus aureus* – 7 (23.3%); *Candida* spp. – 7 (23.3%); *Streptococcus agalactiae* – 5 (16.7%). Only 2 (6.7%) patients noted discomfort in the genital area.

Analyzing the results of the pathohistological examination, which consisted of two main parts: a microscopic description and an immunohistochemical examination, we established that the majority of examined patients had signs of chronic endometritis (23 (76.7%) women).

During the microscopic description, the following results were obtained: a normal type of endometrial proliferation was found in every fifth woman with a history of AFD (7 (23.3%) patients) (Table 5).

Violation of endometrial proliferation was manifested in the form of: micropolyps (6 (16.7%) women); focal stroma fibrosis (2 (6.7%) women); sclerosis (2 (6.7%) women) and thrombosis (1 (3.3%) women) of arterial walls.

Lympholeucocytic infiltration was found in more than half of the patients (17 (56.7%) women), which is the dominant sign of inflammation of the mucous layer of the uterus. The detected infiltrates consisted of lymphocytes and plasma cells, and in some cases with admixtures of leukocytes and histiocytes located around blood vessels and individual uterine glands.

Table 5

**Variants of microscopic description of the endometrium, abs. number (%)**

Microscopic features of the endometrium	Number of patients in the examined group, n = 30
Normal endometrial proliferation	7 (23.3)
Violated proliferation:	23 (76.7)
- Micropolyps	6 (16.7)
- Lymphocytic infiltration	17 (56.7)
- Clubs of spiral arteries	7 (23.3)
- Plasma cells	11 (36.7)
- Focal fibrosis of the stroma	2 (6.7)
- Sclerosis of arterial walls	2 (6.7)
- Thrombosis of spiral arteries	1 (3.3)

Table 6

**Indicators of cellular immunity in examined women, M±m**

Indicators of cellular immunity	Women with a history of AFD	Reference value
Leukocytes, 10 <sup>9</sup> /l	9.7 ± 0.8	4.0–9.0
Lymphocytes, %	18.0 ± 1.3	18–40
CD3+, %	61.4 ± 4.8	60–89
CD4+, %	33.7 ± 2.8	31–61
CD8+, %	12.7 ± 1.2	14–36
CD16+, %	30.8 ± 2.7	4–26
CD22+, %	5.3 ± 0.5	11.1–37
IRI, %	9.1 ± 0.6	1.0–3.5

Plasma cells are located mainly in single clusters or diffuse growths and were found in every third woman (11 (36.7%) women).

Therefore, in our opinion, these changes indicated the presence of signs of chronic endometritis and required a detailed immunohistochemical examination of the endometrium to determine the local immunological profile of the endometrium in this category of patients.

According to the results of immunohistochemical examination of the endometrium, a positive reaction of CD-138 (DAKO, clone MI15) was established in 19 (63.3%) in a significant number of plasma cells; in every fourth (8 (26.7%) of patients) women, a positive CD-138 reaction was noted in a moderate number of plasma cells; in 3 (10.0%) women, a positive CD-138 reaction was determined in single plasma cells.

The number of natural killer cells (CD-56) in an increased concentration was found in every third patient with a history of AFD (11 (36.6%) women). At the same time, every fourth woman (7 (23.3%) women) showed a decrease in the number of CD-56, which means the presence of immune hyporeactivity and reduced protection against viral damage to the endometrium.

Analyzing the cellular link of the immune system in the aspirate from the uterine cavity, in almost all patients with a history of AFD (26 (86.7%) women), the concentration of T-suppressive cells – CD8+ decreased and was 12.7 ± 1.2% (Table 6).

However, persistence of chronic endometrial inflammation was established in 20 (66.7%) women. Natural killers – CD16+ were found in concentration 30.8 ± 2.7% and exceeds the levels of reference values, which confirms the immune response to the inflammatory process in the uterine cavity. The relative number of B-lymphocytes (CD22+) was found to be reduced by almost two times, which confirms the exhaustion of the immune response in the uterine cavity and requires further careful treatment and preparation for the onset of the next pregnancy.

There is no doubt that AFD has a systemic effect on the body, disrupting the work of the endocrine, nervous and immune systems. Coordination of actions between systems is ensured by specific peptides – cytokines, which regulate intercellular and intersystem interactions, such as: cell development, stimulation and inhibition of growth, apoptosis and functional activity.

When studying the state of the immune system in women with a history of AFD, attention was also paid to the level of pro-inflammatory and anti-inflammatory interleukins in the aspirate from the uterine cavity. In 22 (73.3%) patients, pro-inflammatory cytokines – IL-10 – prevailed. The level of IL-1 constituted 29.5 ± 2.1 pg/ml (reference values: 0–10 pg/ml), IL-6 – 22.3 ± 2.9 pg/ml (reference values: < 0–10 pg/ml), which is a marker of intrauterine infection. These changes, in our opinion, may indicate chronic inflammation in the uterine cavity and activation of specific immunization.

Draws attention that the concentration of IL-10 was registered 37.3 ± 3.2 pg/ml (reference values: < 0–10 pg/ml), which is not typical and differs from the indicators of immunity in a missed pregnancy in a short term [1, 21].

The concentration of TNF-α, as one of the main regulators of the body's hereditary resistance, in women with AFD in history was 17.7 ± 1.3 pg/ml which exceeded the reference value of the indicator by almost 2 times (reference value: < 8.1 pg/ml). Clinically, in our opinion, this is due to the presence in the anamnesis of diseases of the cardiovascular system (19 (63.3%) women) and endocrinopathies (5 (16.7%) patients) and a chronic inflammatory response manifested by inflammatory diseases genital tract (16 (53.3%) patients).

Therefore, analyzing the state of the immune system in patients with AFD, a significant difference was established in the indicators of cellular immunity due to a decrease in T-suppressors and an increase in T-killers, a decrease in B-lymphocytes.

## CONCLUSIONS

1. According to the somatic anamnesis data, it was established that half of the patients with antenatal fetal death have a history of pathology of the urinary system of an infectious nature, and a fourth of the patients have chronic inflammatory diseases of the otorhinolaryngology organs. Among gynecological pathologies in the anamnesis, inflammatory diseases of the genital tract (53.3%) and uterine leiomyoma (33.3%) prevailed.

2. Analyzing the data of the obstetric anamnesis, we found that the majority of women from the examined group had repeated pregnancy losses in the anamnesis (46.7%). As for births with AFD, in 90.0% of cases they occurred through natural birth canals, and in every third case – with a defect of the placental tissue, and in every seventh – with postpartum septic diseases of the uterus (13.3%).

3. According to the results of the conducted microscopic examination according to the Hay-Ison criteria, 2/3 of patients with AFD with a history of III and IV degree of biotope of vaginal secretions with a predominance of microorganisms causing aerobic vaginitis were established (26.7%).

4. When analyzing the morphofunctional characteristics of the endometrium, every fifth woman with AFD (23.3%) had normal endometrial proliferation. With the pathological type of proliferation, the leading place was occupied by lymphocytic infiltration (56.7%); increased number of plasma cells (36.7%); micropolyposis (16.7%), which are symptoms of a chronic inflammatory process of the endometrium.

5. Analyzing the cellular link of the immune system in the aspirate from the uterine cavity, in almost all patients with APD in history (26 (86.7%) women), the concentration of T-suppressive cells – CD8+ decreased and

amounted to  $12.7 \pm 1.2\%$ . Natural killers – CD16+ were detected at a concentration of  $30.8 \pm 2.7\%$ , which exceeds the reference values, and confirms the immune response to the inflammatory process in the uterine cavity.

In 22 (73.3%) patients, pro-inflammatory cytokines – IL-10 – prevailed. The level of IL-1 was  $29.5 \pm 2.1$  pg/ml, IL-6 was  $22.3 \pm 2.9$  pg/ml. These changes, in our opinion, may indicate chronic inflammation in the uterine cavity and activation of specific immunization which confirms the increased immune response to the inflammatory process in the uterine cavity.

6. Therefore, women with a history of antenatal fetal death have certain peculiarities in the regulatory mechanisms of the immune system both at the local and generalized level and require a detailed study and diagnosis at the pre-gravid stage during subsequent reproductive plans.

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Стаття надійшла до редакції 23.09.2024. – Дата першого рішення 27.09.2024. – Стаття подана до друку 23.10.2024