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Comprehensive molecular and morphological study of abortion material in missed abortion of the first trimester

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BACKGROUND: Missed abortion is the main cause of reproductive loss in the first trimester, and genetic causes come first in the etiology of this disease. The immunological aspects of the mother-fetus system are currently widely discussed. In this regard, the study of the immunological relationship between the mother's body and the fetus in missed abortion, depending on the chorion karyotype, as well as after suffering reproductive loss, is a topical task, as it can optimize the methods of examining patients with missed abortion and identify factors that contribute to the development of recurrent miscarriage.

AIM: The aim of this study was to investigate the morphological and immunohistochemical characteristics of abortion material in missed abortion, depending on the presence of chorionic chromosomal abnormalities and the patient's history of reproductive losses.

MATERIALS AND METHODS: We performed a comprehensive morphological and immunohistochemical study (CD56, HLA-DR-II) of abortion material in 273 cases of missed abortion. Group 1 consisted of patients with different variants of chorionic chromosomal abnormalities (n = 169); group 2 included subjects with a normal karyotype of the chorion (n = 104). The data analysis was carried out taking into account the anamnesis of patients, depending on the presence of reproductive losses.

RESULTS: We revealed the morphological features of the abortion material in missed abortion in cases with chromosomal abnormalities of the chorion: pronounced edema, sclerosis, necrosis of chorionic villi, more pronounced inflammatory changes in the form of moderate and severe macrophage infiltration of the decidual tissue and endometrium, and accumulations of leukocytes as microabscesses. It has been proven that the severity of inflammatory changes in abortuses depends only on the chorion karyotype and does not depend on either the duration of the presence of an unviable fetal egg in the uterine cavity, or the patient's history of reproductive losses. It was shown that the CD56 and HLA-DR-II expressions in the abortion material depend on the patient's history of reproductive losses, regardless of the chorion karyotype.

CONCLUSIONS: In patients with an unburdened obstetric and gynecological history in the first missed abortion, it is advisable only to determine the chorion karyotype in order to identify the cause of missed abortion. The immunohistochemical study of the abortion material with the determination of the CD56 and HLA-DR-II expressions is important in repeated missed abortions, regardless of the chorion karyotype.

Keywords: missed abortion; chromosomal abnormalities of the chorion; reproductive loss; immunohistochemical study; endometrium; CD56; HLA-DR.

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Результаты комплексного молекулярно-морфологического исследования абортного материала при неразвивающейся беременности первого триместра

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Обоснование. Неразвивающаяся беременность является главной причиной репродуктивных потерь I триместра, а генетические причины выходят на первое место в этиологии данного заболевания. В настоящее время широко обсуждаются иммунологические аспекты системы мать – плод. В связи с этим изучение особенностей иммунологических взаимоотношений между организмом матери и плодом при неразвивающейся беременности в зависимости от кариотипа хориона, а также после репродуктивных потерь является актуальной задачей, так как может оптимизировать методы обследования пациенток с замершей беременностью и выявить факторы, способствующие развитию привычного невынашивания беременности.

Цель — изучить морфологические и иммуногистохимические особенности абортусов при неразвивающейся беременности в зависимости от наличия хромосомных аномалий хориона и анамнеза пациенток по репродуктивным потерям.

Материалы и методы. Проведено комплексное морфологическое и иммуногистохимическое исследование (CD56, HLA-DR-II) абортного материала 273 случаев неразвивающейся беременности. Первую группу составили пациентки с различными вариантами хромосомных аномалий хориона (n = 169), вторую — с нормальным кариотипом хориона (n = 104). Данные анализировали с учетом анамнеза пациенток в зависимости от наличия репродуктивных потерь.

Результаты. В исследовании выявлены морфологические особенности абортного материала при неразвивающейся беременности в случаях с хромосомными аномалиями хориона: значительный отек, склероз, некроз ворсин хориона, более грубые воспалительные изменения в виде умеренной и выраженной лимфоцитарно-макрофагальной инфильтрации децидуальной ткани и эндометрия, наличие в них скоплений лейкоцитов по типу микроабсцессов. Доказано, что на степень выраженности воспалительных изменений абортусов влияет только кариотип хориона и не влияет длительность нахождения нежизнеспособного плодного яйца в полости матки и наличие в анамнезе у пациентки репродуктивных потерь. Показано, что уровень CD56 и HLA-DR II класса в абортном материале зависит от анамнеза пациентки по репродуктивным потерям и не зависит от кариотипа хориона.

Заключение. Таким образом, у пациенток с неотягощенным акушерско-гинекологическим анамнезом при первой неразвивающейся беременности для выявления причины замершей беременности целесообразно только установление кариотипа хориона, а иммуногистохимическое исследование абортного материала с определением маркеров CD56 и HLA-DR II класса имеет значение при повторных неразвивающихся беременностях независимо от кариотипа хориона.

Ключевые слова: неразвивающаяся беременность; хромосомные аномалии хориона; репродуктивные потери; иммуногистохимическое исследование; эндометрий; CD56; HLA-DR.

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BACKGROUND

The maintenance of women's reproductive health is an urgent task of contemporary obstetrics and gynecology and has not only medical but also social significance. Approximately 80% of antenatal losses occur in the first trimester of pregnancy, including missed miscarriage, which ranks first, accounting for 40%–85%, according to different authors [1–3]. An important role in the etiology of missed miscarriage in the first trimester (>50%) is played by chorionic chromosomal abnormalities that occur *de novo*. A previously missed miscarriage negatively affects the reproductive health of a woman, increases the risk of repeated interruption of subsequent pregnancies, and causes chronic endometritis formation. The inadequate uniform standards for examining patients who have had a missed miscarriage determine the scientific and practical interest in this issue.

Histological examination of abortion material in case of missed miscarriage is currently routine; however, literature data on the aspects of abortuses morphology, depending on the chorion karyotype, are few and contradictory. Immunohistochemical examination complements the histological one and improves the diagnostic quality of endometrial pathological processes.

The immunological aspects of implantation are currently widely discussed. Normal pregnancy is known to proceed in a state of local immunosuppression concerning the trophoblast from the endometrium. The study of the aspects of the immunological relationship between the mother's body and the fetus in case of missed miscarriage, depending on the chorion karyotype, as well as reproductive losses, is not only of scientific interest but also of great practical importance since it can optimize the examination methods of patients with missed miscarriage and identify the factors contributing to the development of habitual miscarriage. An important role in this direction is assigned to natural killer (NK) cells and the major histocompatibility complex system involved in antigen recognition.

NK cells have been proven to represent the most numerous population of lymphocytes in the endometrium [4–6]. At the onset of pregnancy, they account for 70%–80% of the total count of lymphocytes [6–8]. Uterine NK cells perform a regulatory function and actively express CD56, in contrast to cytotoxic peripheral blood NK cells that highly express CD16 [6, 7, 9]. There is no consensus on the role of NK cells during pregnancy. However, most authors agree that uterine NK cells make an important contribution to maintaining pregnancy, as they form immunotolerance in the mother–fetus system, regulate the depth of trophoblast invasion during implantation, protect the placental bed from infectious factors, and participate in angiogenesis and remodeling of helical arteries [4, 9, 10].

In the major histocompatibility complex system, the human leukocyte antigen–DR isotype (HLA-DR) represents the class II genes, with their main function of antigen recognition. For the first time, their essence was studied and described at the end of the XX century in a group of patients who underwent organ transplantation [11]. A pronounced expression of HLA-DR has been proven to reject transplanted organs, and even the withdrawal of immunosuppressive therapy does not cause a transplant rejection reaction at a low level [12, 13]. In obstetrics and gynecology, HLA-DR is also actively studied, which revealed a significant increase in the blood level of this marker during pregnancy [14]. The study of the role of HLA-DR in the endometrium during pregnancy is undoubtedly of great importance for elucidating the local mechanisms of immunological rejection of the ovum.

This study aimed to analyze the morphological and immunohistochemical aspects of abortuses in missed miscarriage, depending on the chorion karyotype and the patient's history of reproductive losses.

MATERIALS AND METHODS

An observational retrospective cohort study was conducted at the Department of Obstetrics and Gynecology at the Clinic of Gynecology of the Mechnikov North-Western State Medical University of the Ministry of Health of the Russian Federation and the central clinic of "AVA PETER." The study included 273 patients with missed miscarriages during the first trimester of pregnancy, from 2005 to 2008 and from 2015 to 2019 in St. Petersburg. The diagnosis was established based on the ultrasound examination results. The inclusion criteria were the reproductive age of the patients, gestational age up to 12 weeks, and independent pregnancy that occurred without the use of assisted reproductive technologies. Exclusion criteria were gynecological diseases, such as clinically significant uterine fibroids and endometriosis, and sexually transmitted infections diagnosed during the current pregnancy.

The study was approved by the ethics committee of the Mechnikov North-Western State Medical University of the Ministry of Health of the Russian Federation (protocol No. 10 of 11/07/2018). All patients signed a voluntary informed consent.

The clinical part of the study included the analysis of case histories and the questioning of patients using a specially designed questionnaire containing questions regarding patient complaints, aspects of obstetric-gynecological and somatic anamnesis, the course and outcomes of previous pregnancies, heredity from close relatives, and symptoms indicating the possible presence of hereditary thrombophilia. All patients underwent standard preoperative clinical and laboratory studies.

Surgical treatment included uterine cavity curettage. When examining visually scrapings from the uterine cavity, chorionic villi were taken, which were placed in an isotonic sodium chloride solution for further genetic testing and a polymerase chain reaction to identify the main pathogenic microorganisms. The remaining scraping was fixed with 10% formalin for 24–48 h, passed through a series of isopropyl alcohol, and embedded in paraffin for further histological examination.

Cytogenetic study of chorionic villi was performed by karyotyping (Q-banding) using an accelerated direct method. According to the karyotyping results, patients were distributed into groups; Group 1 with various variants of chorionic chromosomal abnormalities (169 patients) and Group 2 with a normal chorionic karyotype (104 cases).

The infectious factor was ruled out from the abortion material study by polymerase chain reaction with DNA detection of *Chlamydia trachomatis*, *Mycoplasma genitalium*, *Ureaplasma urealyticum*, cytomegalovirus, and herpes simplex virus types 1 and 2.

Sections of 5–6 μm thick were made from paraffin blocks for histological examination, which were stained with hematoxylin and eosin. During the morphological examination under the microscope, Mik Med at a magnification of ×100, chorionic villi, decidual tissue, and endometrium were studied in detail. The degree of lymphocytic-macrophage infiltration of the endometrium and decidual tissue was assessed at a microscope magnification of ×100 using Avtandilov's morphometric grid. Mild infiltration was considered when up to 20 leukocytes were detected in the field of view, moderate infiltration when 21–60 leukocytes were detected, and severe infiltration in cases of over 61 leukocytes.

Patients without a history of inflammatory diseases of the uterus and appendages were selected, as well as those with no sexually transmitted infections, according to the study results of abortion material using a polymerase chain reaction, and with the most common variants of chromosomal abnormalities (polyploidies, trisomies for chromosomes 15 and 16) for immunohistochemical study.

Immunohistochemical staining was performed using immune sera to CD56 markers (Daco clone 123C3 — M7304) and HLA-DR-II (Leica clone LN-3 — NCL-LN3). A positive reaction was recorded by the brown color of the cell membranes. The results were quantitatively analyzed by counting the positively stained cells at ×400 magnification in ten fields of view and determining the average value with the calculation of the error of the mean. Micrographs of histological and immunohistochemical studies were made using a Nikon digital camera.

Statistical analysis of the obtained clinical and morphological results was performed using the STATISTICA 10.0 program from StatSoft. The frequency characteristics of the qualitative parameters were compared using the Yates-corrected χ^2 test and the Fisher's test. Quantitative indicators were presented as an arithmetic mean and standard deviation and compared using the Kolmogorov–Smirnov, Mann–Whitney, and median χ^2 tests. The critical level of significant differences for all types of analysis was determined as $p < 0.05$.

RESULTS

The analyses of the structure of chorionic chromosomal anomalies in case of missed miscarriage revealed that aneuploidies rank first with 129 cases (76.33%), followed by polyploidies (26 out of 169; 15.38%), and chorionic mosaic karyotype in 8.28% of cases (14 out of 169). Polyploidies were represented by triploidies in 76.92% of cases (20 out of 26) and by tetraploidies in 23.08% (6 out of 26) of cases. In the structure of aneuploidies, trisomy accounted for 88.37% (114 out of 129) and monosomy for 11.63% (15 out of 129). Trisomies were distributed as follows: 26.32% of all trisomies (30 out of 114) were trisomies on chromosome 16, 14.03% (16 out of 114) on chromosome 22, and trisomies on chromosomes 21 and 13 with a frequency of 13.16% (15 out of 114) and 12.28% (14 out of 114), respectively; mixed trisomies and trisomies on chromosome 15 were less common with 8.77% (10 out of 114) and 7.02% (8 out of 114), respectively. Other variants of trisomy were noted in isolated cases.

The clinical and anamnestic data analyses of patients revealed that the group with chorionic chromosomal abnormalities consisted of older patients aged 33.7 ± 6.09 years, with a median of 34 (LQ 29; UQ 38) years. In the group with a normal chorionic karyotype, the mean age was significantly lower and amounted to 31.66 ± 4.99 years, the median was 32 (LQ 28; UQ 36) years ($p < 0.05$). The terms when the pregnancy stopped developing did not significantly differ between the groups, namely at weeks 7.11 ± 1.83 in the group with chromosomal abnormalities (median 6.5 [LQ 6; UQ 8] weeks) and at weeks 6.85 ± 1.92 in the normal karyotype group (median 6.5 [LQ 5; UQ 8.25] weeks) ($p > 0.05$). The duration of the presence of ovum in the uterine cavity from the moment of its vital activity termination to surgical treatment revealed no differences between the groups, weeks 2.54 ± 1.75 with chorionic chromosomal abnormalities (median 2 [LQ 1; UQ 3.5] weeks) and weeks 2.34 ± 1.56 with a normal karyotype (median 2 [LQ 1; UQ 3.5] weeks) ($p > 0.05$).

The obstetric anamnesis structure revealed that the groups were homogeneous; approximately one-fourth of the patients were primigravidas, namely 24.85% (42 out of 169) with chromosomal abnormalities and 27.88% (29 out of 104) with a normal chorionic karyotype ($p > 0.05$), the rest of the patients had 1–7 pregnancies in history. No significant differences were found between

Table 1. The severity of edema and sclerosis of the chorionic villi in the studied groups

Sign	Chromosomal abnormalities of the chorion, *n* = 169		Normal chorion karyotype, *n* = 104		*p*
	n	%	*n*	%	
Chorionic villus edema:					
no edema	46	27.22	15	14.42	0.041
mild	34	20.12	24	23.08	
moderate	61	36.09	51	49.04	
severe	28	16.57	14	13.46	
Chorionic villus sclerosis:					
no sclerosis	71	42.01	61	58.65	0.026
mild	45	26.63	20	19.23	
moderate	30	17.75	17	16.35	
severe	23	13.61	6	5.77	
Severity of fibrinoid necrosis:					
no necrosis	126	74.56	93	89.42	0.019
mild	16	9.47	5	4.81	
moderate	17	10.06	4	3.85	
severe	10	5.92	2	1.92	

the groups, while the previous pregnancy ended in childbirth in 58.58% (99 out of 169) of patients in Group 1 and 52.88% (55 of 104) in Group 2. Losses of previous pregnancies occurred with a frequency of 31.73%–37.28% in both groups, but habitual miscarriage (loss of two or more pregnancies) in history with a normal chorionic karyotype was significantly more often registered (8.65%; 9 out of 104) than in the group with chromosomal abnormalities (1.18%; 2 out of 169) ($p < 0.05$).

The villous chorion in both groups was morphologically represented by hypoplastic, mostly avascular villi. With a normal karyotype, mild and moderate edema of the stroma of the villi and minor sclerotic changes were revealed (Table 1). More severe structural changes in the stroma in the form of severe edema and sclerosis of the villi were registered in the group with chorionic chromosomal abnormalities (Table 1). Additionally, trophoblast necrosis and clusters of fibrinoid necrosis fields in the intervillous space in the group with chromosomal abnormalities were detected 2.4 times more often than in the euploid group ($p < 0.05$) (Table 1, Fig. 1). Such changes, according to the literature, may be indirect signs of the immunological rejection reaction of pregnancy [1].

The decidual tissue in both groups was characterized by the presence of hyalinosis of the walls of the spiral arteries in 68.27%–69.23% of cases. Lymphocyte-macrophage infiltration in the euploid group was often moderate in 51.92% and mild in 25% of cases (Table 2). The group with different variants of chromosomal anomalies of the chorion significantly differed with more pronounced lymphocytic-macrophage infiltration (pronounced infiltration in 30.18% and moderate infiltration in 67.46% of cases) (Table 2). Additionally, microabscess-type

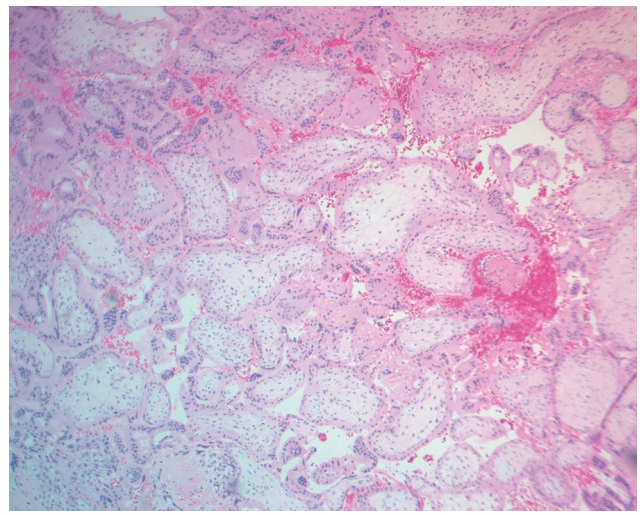

Fig. 1. Chorionic villi with chromosomal abnormalities: a combination of severe sclerosis and edema, trophoblast necrosis, and fibrinoid necrosis fields in the intervillous space. Staining with hematoxylin and eosin, magnified at ×100

clusters of leukocytes and necrotic changes in the decidual tissue were significantly more often detected with chromosomal abnormalities (Fig. 2).

The endometrium, in the group with chorionic chromosomal abnormalities in most cases (88.13%), was characterized by moderate and severe lymphocytic-macrophage infiltration (Table 3). Concurrently, microabscess-type clusters of leukocytes were formed approximately 3 times more often than in the euploid group ($p < 0.001$) (Fig. 3). The group with normal karyotype was characterized by an insufficient gravid transformation in approximately one-third of cases, as well as mild or moderate inflammatory infiltration (Table 3).

Table 2. Morphology of decidual tissue in the studied groups

Sign	Chromosomal abnormalities of the chorion, *n* = 169		Normal chorion karyotype, *n* = 104		*p*
	n	%	*n*	%	
Severity of lymphocytic-macrophage infiltration:					
mild	4	2.37	26	25.00	<0.001
moderate	114	67.46	54	51.92	<0.001
severe	51	30.18	24	23.08	<0.001
Microabscess-type clusters of leukocytes	84	49.70	38	36.54	0.033
Severity of necrosis:					
no necrosis	14	8.28	29	27.88	<0.001
mild	35	20.71	36	34.62	<0.001
moderate	77	45.56	21	20.19	<0.001
severe	43	25.44	18	17.31	<0.001

Table 3. Morphology of the endometrium in the study groups

Sign	Chromosomal abnormalities of the chorion, *n* = 169		Normal chorion karyotype, *n* = 104		*p*
	n	%	*n*	%	
Severity of lymphocytic-macrophage infiltration:					
mild	19	11.24	32	30.77	<0.001
moderate	103	60.95	41	39.42	<0.001
severe	47	27.81	31	29.81	<0.001
Microabscess-type clusters of leukocytes	72	42.60	16	15.38	<0.001
Insufficiency of gravid transformation of the endometrium	23	13.61	37	35.58	<0.001

The described inflammatory changes in the abortion material were registered regardless of the pregnancy duration and the duration of the presence of a non-viable ovum in the uterine cavity before the surgical intervention.

Inflammatory changes in the endometrium are often associated with a history of reproductive losses. The literature revealed that chronic endometritis in miscarriage is diagnosed in 60.5%–86.7% of cases [15, 16]. Therefore,

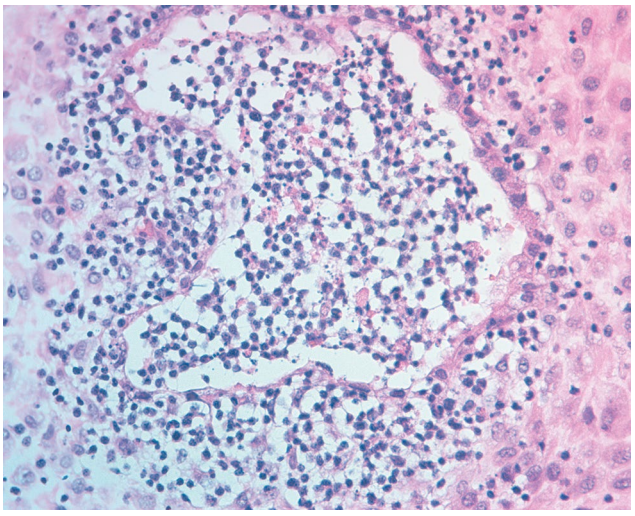

Fig. 2. Decidual tissue with a chorionic chromosomal abnormality (microabscess). Stained with hematoxylin and eosin, magnified at ×100

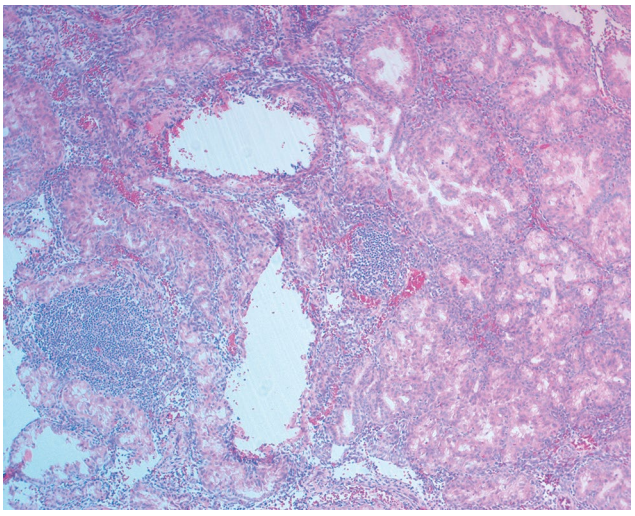

Fig. 3. Microabscesses of the endometrium with a chorionic chromosomal abnormality o. Stained with hematoxylin and eosin, magnified at ×100

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Table 4. Morphological assessment of scrapings from the uterine cavity based on patient's history of reproductive losses

Sign	First pregnancy loss, *n* = 177		History of reproductive losses, *n* = 96		*p*
	n	%	*n*	%	
Severity of lymphocytic-macrophage infiltration of decidual tissue:					
mild	21	11.86	9	9.38	>0.05
moderate	112	63.28	56	58.33	>0.05
severe	44	24.86	31	32.29	>0.05
Microabscess-type clusters of leukocytes in the decidual tissue	78	44.07	44	45.83	>0.05
Severity of decidual tissue necrosis:					
no necrosis	85	48.02	46	47.92	>0.05
mild	50	28.25	29	30.21	>0.05
moderate	30	16.95	19	19.79	>0.05
severe	12	6.78	2	2.08	>0.05
Severity of lymphocytic-macrophage infiltration of the endometrium:					
mild	34	19.21	17	17.71	>0.05
moderate	90	50.85	54	56.25	>0.05
severe	53	29.94	25	26.04	>0.05
Microabscess-type clusters of leukocytes in the endometrium	60	33.90	28	29.17	>0.05

Table 5. Results of immunohistochemical studies depending on the chorion karyotype

Marker	Chromosomal anomalies of the chorion, *n* = 169			Normal karyotype of the chorion, *n* = 104			*p*
	min	max	*M* ± *m*	min	max	*M* ± *m*	
CD56:							
in endometrium	28.17	265.00	164.00 ± 90.47	37.67	247.50	115.43 ± 87.16	>0.05
in decidual tissue	17.00	230.50	128.25 ± 82.07	5.67	254.33	96.79 ± 86.36	>0.05
HLA-DR-II:							
in endometrium	28.50	415.67	135.92 ± 143.80	29.33	204.50	107.64 ± 69.50	>0.05
in decidual tissue	1.00	82.50	26.06 ± 29.18	11.00	99.00	40.13 ± 32.86	>0.05

a comparative analysis of the histological examination results of abortion material in patients with the first pregnancy loss and those with a history of pregnancy loss was performed. Based on the obtained results, no significant relationship was found between reproductive losses in history and the degree of lymphocytic-macrophage infiltration of the endometrium and decidual tissue (Table 4).

In an immunohistochemical study, CD56 in the endometrium was found mainly in clusters of leukocytes in the cytogenic stroma, as well as around the endometrial glands, both a scattered arrangement of positively stained cells and clusters in microabscesses were noted in the decidual tissue. HLA-DR class II was mainly registered near the endometrial glands, often in clusters, and mostly scattered in the endometrial stroma and decidual tissue. When comparing the level of these markers in patients of the studied groups, no significant differences were found in the chorion karyotype (Table 5).

The results analysis of an immunohistochemical study, considering the obstetric anamnesis of patients, revealed a significant relationship between the history of reproductive losses and the level of CD56 and HLA-DR class II.

In primigravida patients, regardless of the chorion karyotype, the CD56 content was significantly higher. In some preparations, NK cells covered all visual fields in the decidual tissue, and they were mainly located in clusters of leukocytes in the stroma and all around the glands in the endometrium. With a history of reproductive losses, a significant decrease

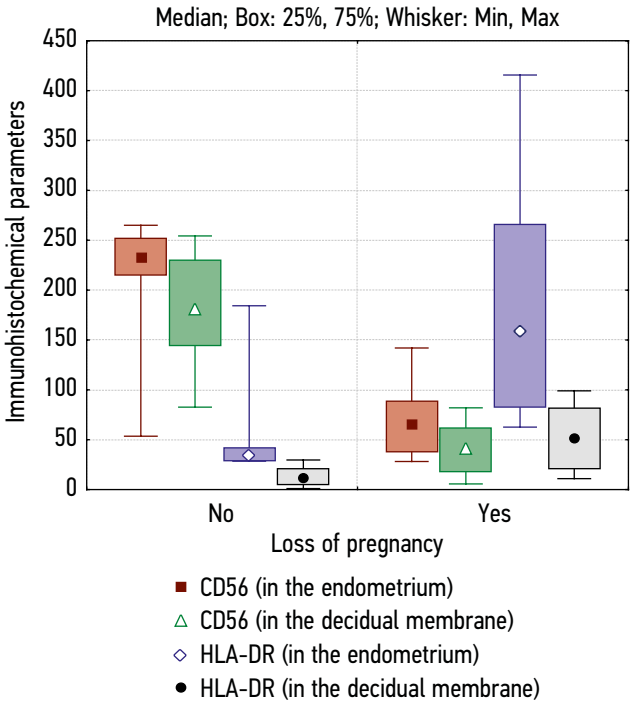

Fig. 4. Immunohistochemical study of CD56 and HLA-DR class II in the endometrium and decidual tissue in missed miscarriage in patients with reproductive losses in history

was found in the number of CD56 in the endometrium (71.61 ± 11.92) and decidual tissue (42.39 ± 6.59) compared with primigravida patients (207.82 ± 20.48 and 182.65 ± 5.41, respectively) ($p < 0.001$) (Fig. 4, 5).

The study of HLA-DR class II showed opposite results, thus the level of HLA-DR class II was significantly elevated both in the endometrium (184.99 ± 23.8) and in the decidual tissue (52.83 ± 2.95) in patients with a history of reproductive losses compared with the group of primigravidas (58.57 ± 10.62 and 13.35 ± 0.15, respectively) ($p < 0.001$) (Fig. 4, 6).

DISCUSSION

The study results revealed that missed miscarriages associated with chorionic chromosomal abnormalities occurred in patients with a predominantly non-aggravated obstetric and gynecological history. Missed miscarriage with euploid chorion karyotype was registered in women with a more aggravated obstetric and gynecological history. Additionally, habitual miscarriage in history was significantly more often diagnosed in patients of this group. Despite these anamnestic data and the absence of significant differences between

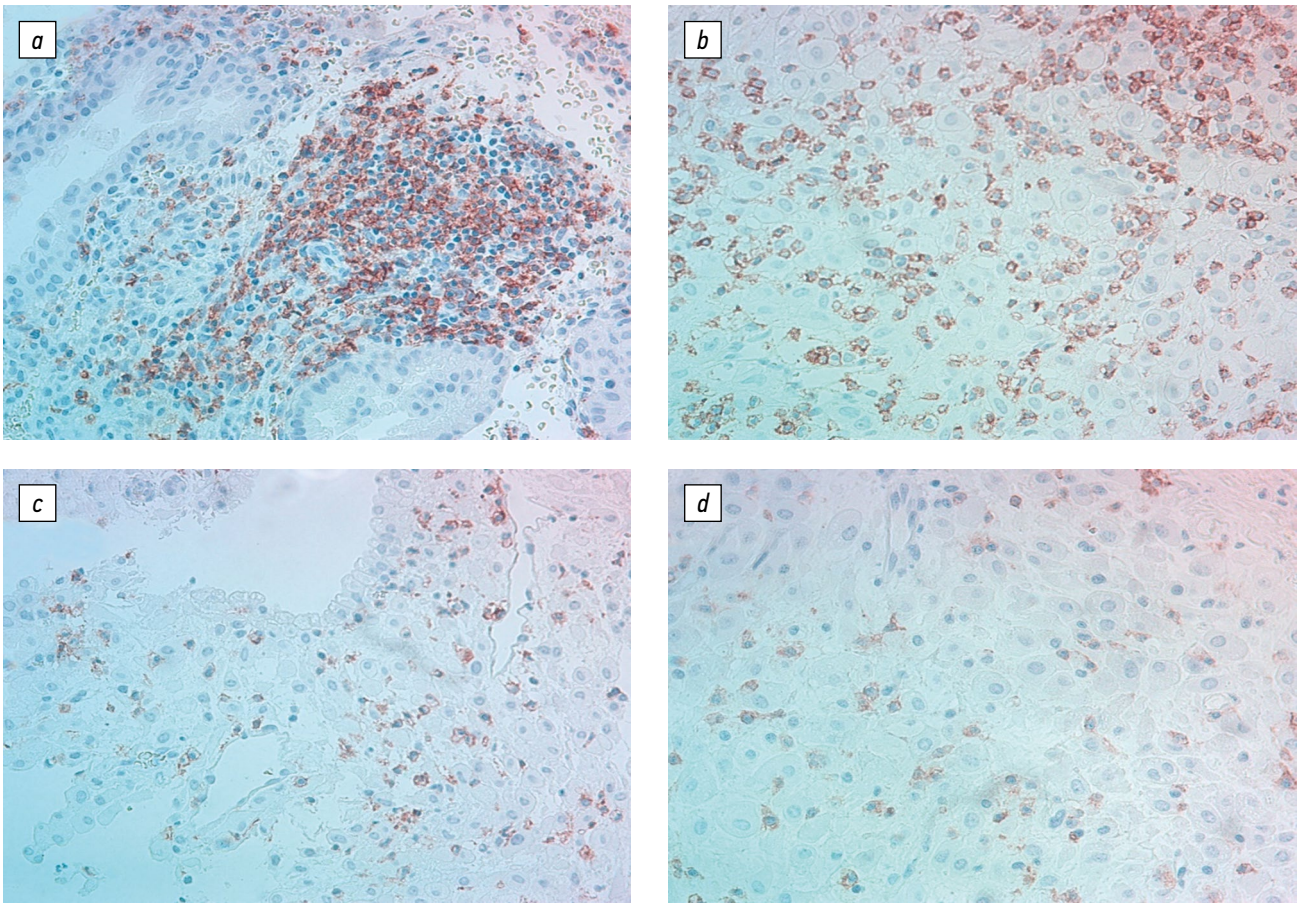

Fig. 5. Micrographs of the immunohistochemical study of CD56: *a* — in the endometrium of a patient with a first missed miscarriage; *b* — in the decidual tissue of a patient with the first missed miscarriage; *c* — in the endometrium of a patient with a history of reproductive losses; *d* — in the decidual tissue of a patient with a history of reproductive losses. The immunohistochemical study was magnified at ×400

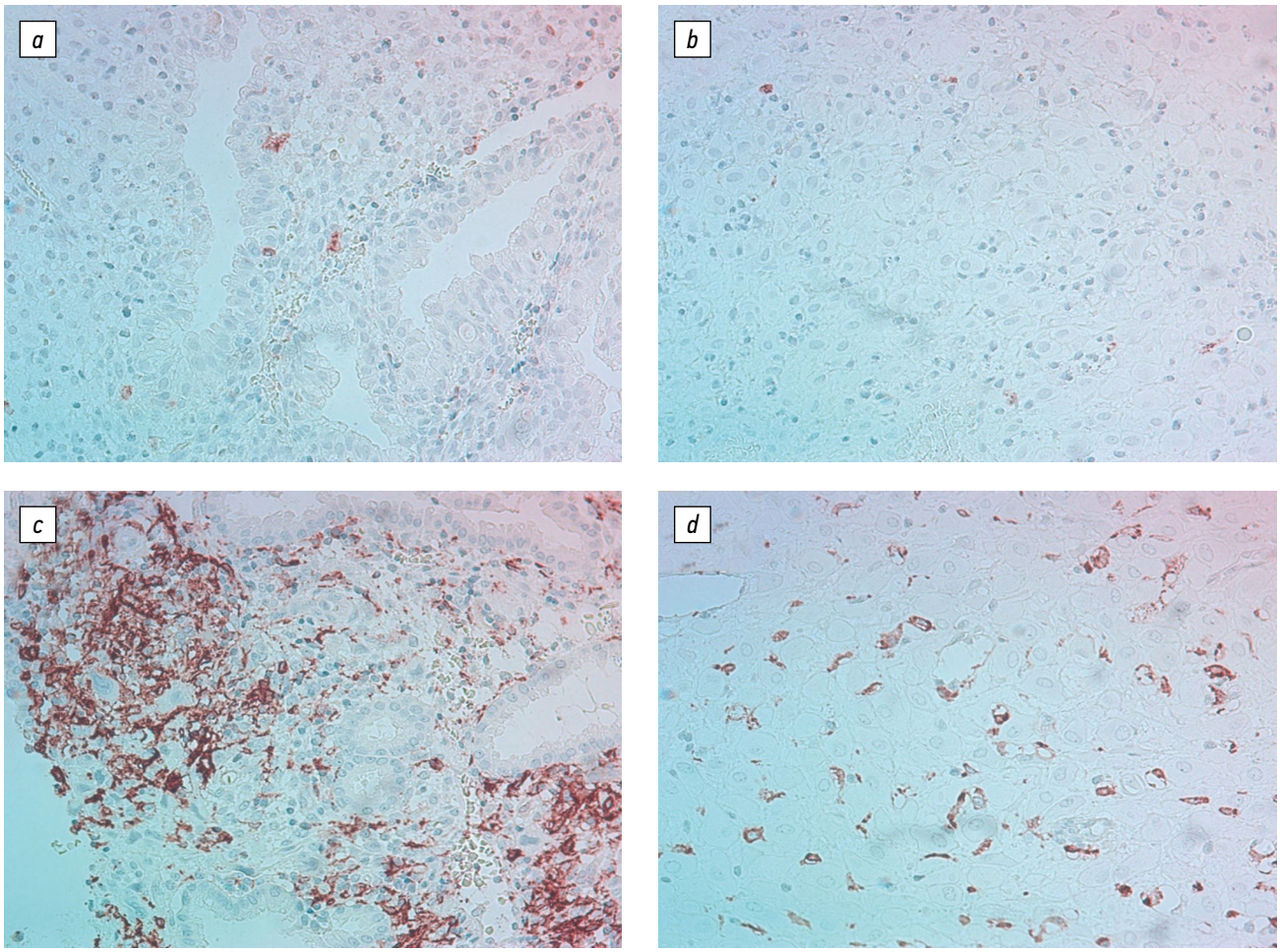

Fig. 6. Micrographs of the immunohistochemical study of HLA-DR class II: *a* — in the endometrium of a patient with a first missed miscarriage; *b* — in the decidual tissue of a patient with the first missed miscarriage; *c* — in the endometrium of a patient with a history of reproductive losses; *d* — in the decidual tissue of a patient with a history of reproductive losses. The immunohistochemical study was magnified at ×400

the groups in terms of gestational age and the duration of the non-viable ovum in the uterine cavity, more pronounced inflammatory infiltration of the endometrium and decidual tissue were noted in cases with chromosomal abnormalities of the chorion, coarser structural, and necrotic changes in the chorion villi. Lymphocyte-macrophage infiltration of the endometrium is an indicator of the inflammatory process; and in combination with plasma cells, it indicates a chronic inflammatory process [1, 17]. Morphological changes in the villous chorion, such as edema and trophoblast hypoplasia, are associated with chromosomal abnormalities [1, 18].

Chorionic villus necrosis and fields of fibrinoid necrosis in the intervillous space are attributed by some authors to the history of inflammation associated with sexually transmitted diseases [19, 20], others attribute them to thrombotic complications [17], and others believe that dystrophic and inflammatory transformation of chorionic villi, as well as massive deposition of fibrinoid in the intervillous space, are indirect signs of immune rejection of pregnancy [1].

The absence of a significant relationship between the degree of the described inflammatory changes in the abortion material and reproductive losses in the anamnesis additionally confirms that the revealed morphological aspects depend only on the chorion karyotype.

An immunohistochemical study showed a sharply decreased level of CD56 and an increased HLA-DR class II in the endometrium and decidual tissue with repeated reproductive losses, in contrast to primigravida patients. Concurrently, no dependence of the expression of the studied markers was found on the chorion karyotype. Thus, in primigravidas with an uncomplicated anamnesis in a missed miscarriage, it makes sense to only establish the chorion karyotype; and immunohistochemical examination of abortuses with the determination of CD56 and HLA-DR class II markers is advisable in repeated missed miscarriage, regardless of the chorion karyotype. Further study of the aspects of NK cell expression and major histocompatibility complex indicators in the first trimester of pregnancy is required to understand the immune genesis of recurrent miscarriage mechanisms.

CONCLUSIONS

1. In missed miscarriage in cases with chorionic chromosomal abnormalities, abortuses are characterized by significant edema in combination with sclerosis of the chorion villi, more severe inflammatory changes in the form of the chorion villi necrosis, moderate and severe lymphocytic-macrophage infiltration of the decidual tissue (67.46% and 30.18% respectively), and endometrium (60.95% and 27.81%), with the presence of microabscess-type clusters of leukocytes in them. If a genetic study cannot be performed, these histological characteristics can be used by pathologists as indirect signs of chorionic chromosomal abnormalities.
2. The degree of inflammatory severity changes in the abortion material based only on the chorion karyotype and not on the term of pregnancy, the duration of the presence of a non-viable ovum in the uterine cavity, or the patient's history of reproductive losses.
3. Determining the chorion karyotype is advisable only to identify the cause of a missed miscarriage in patients with an uncomplicated obstetric and gynecological history during the first missed miscarriage.
4. Immunohistochemical study of abortion material with the determination of CD56 and HLA-DR class II markers is indicated for repeated missed miscarriage, regardless of the chorion karyotype.

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