M.L. Polina, L.M. Mikhaleva, I.I Vityazeva, M.B. Khamoshina, I.M. Ordiyants, M.G. Lebedeva, L.A. Shelenina, P.N. Zakharova, N.I. Douglas

THE RELATIONSHIP BETWEEN THE MICROBIOTA TYPE AND IMMUNE RESOURCES OF THE ENDOMETRIUM AMONG INFERTILE WOMEN IN THE IMPLANTATION WINDOW PHASE

DOI 10.25789/YMJ.2023.82.02

УДК 618.14

The features of the microbiota and the immune profile of the endometrium of women with infertility of different genesis during the "implantation window" period have been studied. Endometrial phenotypes different in immune profile and microbiota profile within each group were identified (with infertility of unclear genesis, tube-peritoneal genesis, chronic endometritis, "thin" endometrium): "normal," dysplastic, chronic inflammation. The phenotype of chronic endometritis is revealed a significant predominance of cytokines of the pro-inflammatory Th1/Th1 profile in the presence of a dysbiotic microbiota type. The features of the dysplastic endometrial phenotype consist in a "poor" immune response (cytokines, chemokines, growth factors) against the background of pronounced fibrotic transformation. Ideas about the endometrial phenotype (normal, dysplastic, chronic inflammation) are a criterion for readiness for blastocyst implantation.

Keywords: infertility, the period of the "implantation window", chronic endometritis, immunohistochemical study, molecular phenotype, lactobacillar and dysbiotic types of microbiota.

POLINA Miroslava L. – PhD, assistant of the Department of Obstetrics and Gynaecology with a course in Perinatology of the Medical Institute of the Federal State Autonomous State Educational Institution of Higher Education People's Friendship University of Russia, Moscow, corresponding author, e-mail: polina.ml@mail.ru; **MIKHALEVA Lyudmila M.** – Corresponding Member of the Russian Academy of Sciences, Doctor of Medicine, Professor, Director of the Federal Research Institute of Human Morphology, Head of Clinical Morphology Laboratory, Moscow, Russia; **VITYAZEVA Irina I.** – MD, Head of the Department of Assisted Reproductive Technologies of the Federal State Budgetary Institution National Medical Research Center of Endocrinology of the Ministry of Health of the Russian Federation; **KHAMOSHINA Marina B.** – MD, Professor of the Department of Obstetrics and Gynaecology with the course in Perinatology of the Medical Institute FSAEI HE People's Friendship University of Russia; **ORDIYANTS I.M.** – MD, Professor of the Department of Obstetrics and Gynaecology with the course in Perinatology of the Medical Institute of the Federal State Autonomous State Educational Institution of Higher Education People's Friendship University of Russia; **LEBEDEVA Marina G.** – PhD, Associate Professor of the Department of Obstetrics and Gynaecology with the course in Perinatology of the Medical Institute, FSAEI HE People's Friendship University of Russia; **SHELENINA Lyudmila A.** – doctor of the gynecological department of F.I. Inozemtsev City Clinical Hospital, Department of Health of the city of Moscow; **DOUGLAS Natalya I.** – MD, Head of the Department of Obstetrics and Gynecology, Medical Institute of North-Eastern Federal University, Yakutsk, Russia; **ZAKHAROVA Praskovya N.** – Clinical Resident of the Department of Obstetrics and Gynecology, Medical Institute M.K. Ammosov North-Eastern Federal University, Yakutsk, Russia

From the standpoint of molecular mechanisms of embryo susceptibility formation, the endometrium, with all the scope of scientific papers, remains the most unexplored tissue of the female body. The microenvironment optimal for embryo localization, adhesion, invasion and implantation develops with differentiation of endometrial stromal cells into decidual cells and changes in the number and functional activity of immune cells [6,14]. The "subtle" mechanisms of implantation failures are associated with the difficulties of autocrine, paracrine and endocrine signaling, including sex steroids, cytokines, chemokines, growth factors and intracellular communication [16]. It is reported that more than 80% of repeated implantation losses occur on the background of an abnormal cytokine profile, however, complex molecular biological events associated with the violation of blastocyst and endometrial interactions have not been properly studied [13].

Changing ideas about the "sterility" of the endometrium to the possible presence of commensals and pathogens suggested their influence on local immune factors, but such mechanisms in the "uterine factor" of infertility require a convincing evidence base [2,5]. Shifts in bacterial balance with a decrease in the proportion of the supposedly "beneficial" microorganisms Firmicutes, Bacteroidetes, Proteobacteria and Actinobacteria are associated with impaired modulation of decidualization and implantation, activation of proinflammatory signaling pathways [2].

CE in 34-57.0% of women with repeated implantation failures is considered as a potential factor of changes in the immune environment on the background of infection with strains of gram-negative bacteria Escherichia coli and Gardnerella vaginalis, Ureaplasma urealyticum and Mycoplasma species [3,11]. The immune characteristics of the endometrium, the peculiarities of regulation of the main biological effects associated with the realization of fertility of women with CE, the influence of the composition of the microbiota on the components of the cytokine network have not been sufficiently studied. There are contradictory ideas about the molecular biological abilities of the "thin" endometrium, the effect on its "fertile resource" of the activity of immune cell populations and the microbiota during the "implantation window".

The purpose of the research: to study the features of the microbiota and the immune profile of the endometrium of women with uterine infertility in the phase of the "implantation window".

Material and methods of the research: A prospective examination of 101 infertile women of reproductive age was performed, including those after ineffective attempts of in vitro fertilization. The selection and examination of women was carried out at the bases of the Medical Center for Women's Health, the gynecological department of the 36 City Clinical Hospital of Moscow, the Department of Assisted reproductive Technologies of the Federal State Budgetary Institution "National Medical Research Center of

Endocrinology" of the Ministry of Health of the Russian Federation in Moscow, the emergency medical center of the Republican Hospital No. 2 in Yakutsk. The contingent is divided into groups: with unexplained infertility (n=11); with CE (n=22); tubal-peritoneal infertility (TPI) (n=50); with a "thin" endometrium (n=8).

The control group consisted of 10 healthy fertile women.

At the second stage, according to the results of a comprehensive examination (hysteroscopy, morphological and immunohistochemical), groups of women with different endometrial phenotypes were formed: chronic inflammation (n=32), dysplastic (n=47), norm (n=22).

Criteria for inclusion in the research: age from 25 to 40 years; infertile women with verified diseases: chronic endometritis (CE) (morphologically or immunohistochemically); TPI (obstruction of the fallopian tubes according to hysterosalpingography or chromotubation); with infertility on the EGE background; the absence of the male factor of infertility; the absence of infertility or fertility disorders of any other genesis; a voluntary informed consent to conduct the study.

Exclusion criteria: somatic diseases in the decompensation stage, acute inflammatory diseases of the pelvic organs and infectious diseases (tuberculosis, syphilis, HIV infection, viral hepatitis, acute genital herpes), autoimmune, mental diseases, the use of an intrauterine device at the time of the study, the absence of antibiotic therapy at least a month before inclusion in the study.

The examination of infertile women was carried out in accordance with the order of the Ministry of Health of the Russian Federation dated August 30, 2012 No. 107n "On the procedure for the use of assisted reproductive technologies, contraindications and restrictions to their use" (ed. dated 11.06.2015 and 01.02.2018). All patients signed an informed consent to participate in the study.

The examination of infertile women included assessment of complaints, anamnesis, general and gynecological examination, standard laboratory examination.

With sonographic CE signs on the 7-9 day of M.C., hysteroscopy was performed with biopsy sampling for morphological examination, confirmed by the detection of plasma cells labeled CD 138+.

Aspiration pipelle biopsy of the endometrium was performed in all patients during the "implantation window" (on the 20th-24th day of the menstrual cycle, 6-8 days after the peak of ovulation.

Pathomorphological and immunohistochemical examination of the endometrium was performed according to the standard methodology on the basis of the Research Institute of Human Morphology (Director of the Institute – CM of Russian Academy of Sciences, MD, Professor L.M. Mikhaleva).

The obtained biopsies were fixed with a 10% buffered formalin solution for 24 hours, followed by standard histological wiring and embedding into paraffin blocks. Histological sections 4 μm thick were made using Sacura rotary microscopes and stained with hematoxylin and eosin. The study of the preparations was carried out using a light microscope with an increase from x50 to x1000.

The interpretation of the results was carried out taking into account the stage and phase of M.C.

Immunohistochemical (IHC) examination of the endometrium was performed in the phase of the "implantation window" (luteinizing hormone LH+7) to assess the expression of cytokines, growth factors: in the glandular epithelium and stromal cells (TNF-α, IL-10, NRF2, GM-CSF and CXCL16), in the glandular epithelium – BCA1, in the stroma – TGF-β.

The analysis of the results of the IHC study was carried out taking into account the number of stained cells and the intensity of their coloring, the Histo-score (HS) was calculated according to the formula: $HS=\sum (Pi \times i)$, where Pi is the percentage of stained cells for each intensity (from 0% to 100%), i is the intensity of staining with the value 0 (absence), 1 – weak (light brown), 2 - moderate (brown) and 3 – strong (dark brown). The maximum score is 300. The analysis of the results of the IHC study with antibodies to TGF-β1 was carried out only in the endometrial stroma by a semi-quantitative method by estimating the number of positive cells regardless of the intensity of staining.

Data interpretation: 0 (the absence of positive stromal cells), 1+ (the number of cells up to 24%), 2+ (the number of cells from 25% to 49%) and 3+ (the number of cells from 50%).

The preparations were studied using a Leica DMLB light microscope with a standard set of optics. Microphotography was performed on a Leica DMLB universal biological microscope with a DFC420 color digital camera using the standard Leica Application Suite v. 3.7.0.

The reference data for the analysis of the results of immunohistochemical studies were the data of healthy fertile women (control group, n=10).

The sampling of material from the uterine cavity for microbiological examination was carried out with a double-cavity catheter for embryo transfer under aseptic conditions.

Endometrial samples were examined by real-time polymerase chain reaction (PCR) RT (Femoflor 16 tests, Scientific Production Association 50 DNA Technology LLC (Russia)) to assess the content of lactobacilli, opportunistic and pathogenic microorganisms (chlamydia, gonococci, Mycoplasma genitalium) in genome-equivalent units (GE/ml) on the IQ5 Multicolor Real-Time PCR Detection System of BIO-RAD (USA).

Samples with a bacterial titer sufficient for identification are presented (two samples from the group with a proliferative phenotype did not meet the condition, therefore 38 samples are given for analysis). The protocol for patients' monitoring and the examination program were approved by the local Ethics Committee of the Medical Institute of the Peoples' Friendship University of Russia, the study was carried out in accordance with the principles of the Helsinki Declaration of the World Association "Ethical Principles of Scientific and Medical research with human participation".

Statistical data analysis is performed in the IBM SPSS STATISTICS 22 package.

The normality of the parameter distribution was checked using the Shapiro–Wilk test. Qualitative variables were analyzed by constructing conjugacy tables using Pearson's chi-squared (χ^2) agreement criterion, with a small number of observations (less than 5), the exact Fisher test was used. The differences were considered statistically significant at $p< 0.05$. Quantitative features are presented in the form of median (Me) and upper and lower quartiles (25th and 75th percentiles).

The Mann-Whitney U-test was used for the analysis of quantitative features, and the Bonferroni correction was used for multiple comparisons (the level of statistical significance $p<0.017$).

Results and discussion. According to the results of a comprehensive study of the expression of cytokines, chemokines and growth factors in the glandular epithelium and endometrial stroma cells during the "implantation window" in groups of women with infertility of various genesis, phenotypes of normal endometrium, chronic inflammation and a dysplastic one were identified.

Molecular characteristics of the endometrium within the groups were the following: with CE – true inflammation (n=12); dysplastic (n=10); "thin" endometrium (dysplastic) (n=8); with unexplained

infertility – dysplastic (n=11); with TPI – CE (n=20), normal variant (n=12), identical in terms of indicators in the control group; dysplastic (n=18).

The conclusion about the dysplastic phenotype of the endometrium during hysteroscopy was made on the basis of pallor and thinning, pathomorphological conclusions about dystrophic-atrophic changes. Visual CE signs during hysteroscopy (focal hyperemia, stroma edema, micropolypes) were confirmed by histological (inflammatory infiltration of the stroma by lymphocytes, plasmocytes, macrophages, in most cases diffusely, around blood vessels and glands, less often – focally), expression of the CD138+ marker.

Variants of the endometrial microbiota of women with different molecular phenotypes are presented in Figure 1.

There were no significant differences in the assessment of the total bacterial mass (TBM) criterion in the groups, despite the range of values of 10^3-10^7 GE/ml. When analyzing the composition and number of microorganisms, the types of microbiota were identified: lactobacillar (the proportion of more than 90% of the total bacterial mass) and non–lactobacillar ("mixed" - with a proportion of lactobacilli less than 90.0% and a low titer of opportunistic microorganisms; dysbiotic – in the presence of only opportunistic pathogenic flora).

The lactobacillar type of microbiota was detected in women with the phenotype of the "norm" of the endometrium, half with the dysplastic one and a third with CE. The non-lactobacillar type of microbiota in the phenotype of chronic inflammation was somewhat more common than in the dysplastic one, but without significant differences. The dominance of the lactobacillar type over the non-lactobacillar type (a decrease in the titer of lactobacilli on the background of the moderate growth of opportunistic flora) took place not only with the "normal" phenotype of the endometrium, but also with the dysplastic one (ratio index – 1:0; 1.1, respectively).

In the dysplastic phenotype of the endometrium, a mixed type of microbiota prevailed – 2.5 times more often than with CE, however, no intergroup differences were found. In the group with CE, endometrial dysbiosis was detected statistically significantly more often than in the dysplastic type ($p<0.001$, $\chi^2=14.1$), due to the predominance of Gardnerella vaginalis, Ureaplasma spp. and mixtures of Atopobium vaginae/Enterobacteriaceae in high titers (10^5-10^7 GE/ml), other microorganisms in a titer of 10^3-^{4} GE/ml. A similar microbial profile in CE was noted by other authors [7].

The molecular phenotype of the "normal" endometrium is represented by a balanced production of pro-inflammatory and anti-inflammatory cytokines, chemokines and growth factors necessary for implantation (Figure 2). A moderate increase in TNF-a is necessary for the proper differentiation and development of trophoblast cells, the formation of embryo-maternal immune tolerance, extracellular trophoblast invasion and remodeling of spiral arteries [9]. We believe it is possible to assert the formation of a receptive endometrium in the presence of a eubiotic microbiota profile and the balanced expression of subtypes of Th1-proinflammatory cells and T-regulatory (Treg) cells. Our data are consistent with the statements about the favorable role of the predominance of Lactobacillus spp. on the frequency of pregnancy [12].

The leveling of the molecular biological effects of the proinflammatory cytokine "microenvironment" is associated with a favorable effect on perfusion and receptivity of the endometrium of moderate expression of cytokine IL-10 [20].

The inflammatory type of immunoregulation in CE (Figure 3) was determined by the excess expression of proinflammatory cytokines in the glandular epithelium of the endometrium in comparison with anti-inflammatory ones (an increase in TNF– α - by 1.1 times (p=0,00), GM–CSF (p=0,00), CXCL16 (p=0,00), BCA1 (p=0,00) - by 1.2 times, a decrease in IL-10 – by 2 times (p=0,00)). In endometrial stroma cells, the expression level of GM-CSF (p=0,00), TNF-α (p=0,00) and CXCL16 was significantly higher than in the control – 1.2 times (p=0,00), IL-10 – 1.8 times lower (p=0,00), *NRF2* – somewhat lower (p=0,01), TGF-α was the lowest in comparison with other groups (1 point) (p=0,01). The indicator of the TNF-α /IL-10 immunoregulatory index in glandular cells is 2.5 (with a norm of 1.1 in glandular cells) indicates molecular disturbances in the interaction of immunocompetent cells. We believe that it is the analysis of immune "networks" that will clarify the mechanisms of infertility development in the presence of a dysbiotic endometrial profile.

The formation of a microenvironment unfavorable for blastocyst implantation is due to the induction by microorganisms of a dysbiotic type of overexpression of proinflammatory cytokines of the Th1/Th17 profile, impaired tissue remodeling and trophoblast invasion.

The data obtained allow us to state that the abnormal immune microenvironment during the "implantation window" in the CE phenotype is due to an increase in the GM-CSF inflammatory response due to increased TNF-α production and impaired transmission of its signals [10]. An increase in the level of chemokine CXCL13 (BCA1) is believed to cause the recruitment of plasma cells into the endometrial stroma, the labeling of which CD138+ confirms chronic inflammation [20]. The low level of TGF-β and IL-10 expression in CE reflects the quantitative or functional deficiency of the anti-inflammatory clone of Treg cells on the background of angiogenesis disorders and fibrotic transformation of the endometrium [17]. The realization of molecular biological effects in the "inflamed" endometrium occurs on the background of a decrease in NRF2-mediated antioxidant protection in Treg cells [8].

Obviously, a change in the immune profile of the endometrium with a dysbiotic microbiota profile disrupts decidualization and architectonics, determines

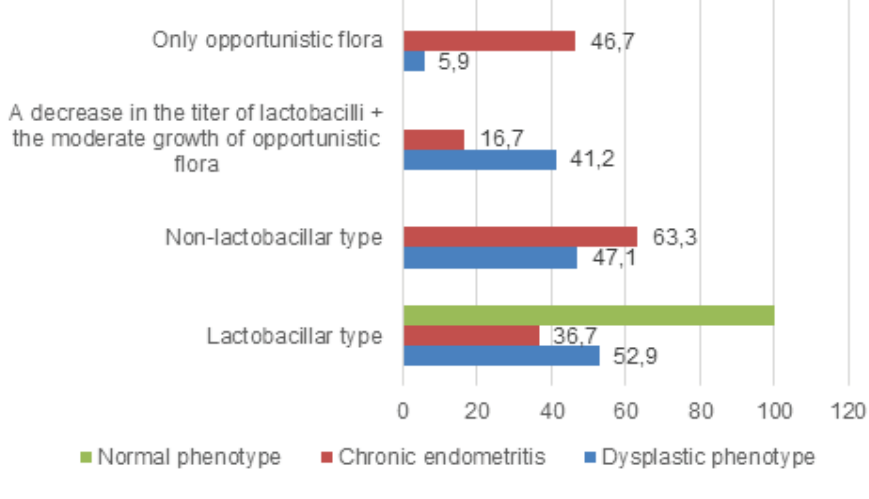
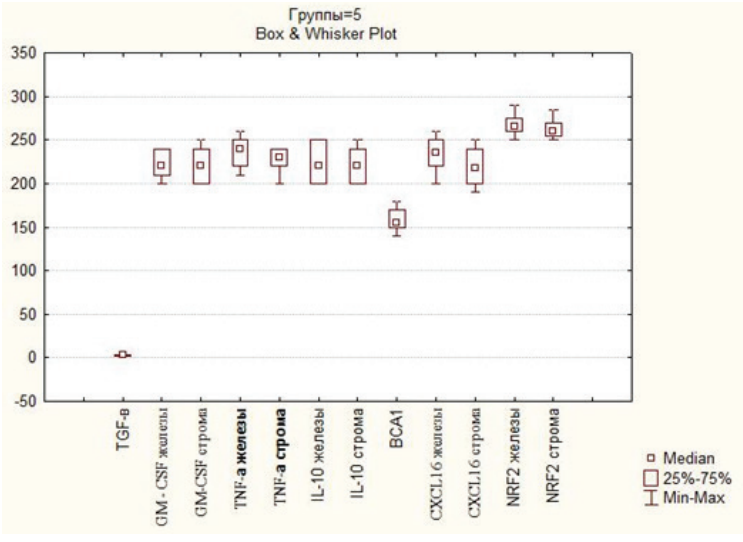
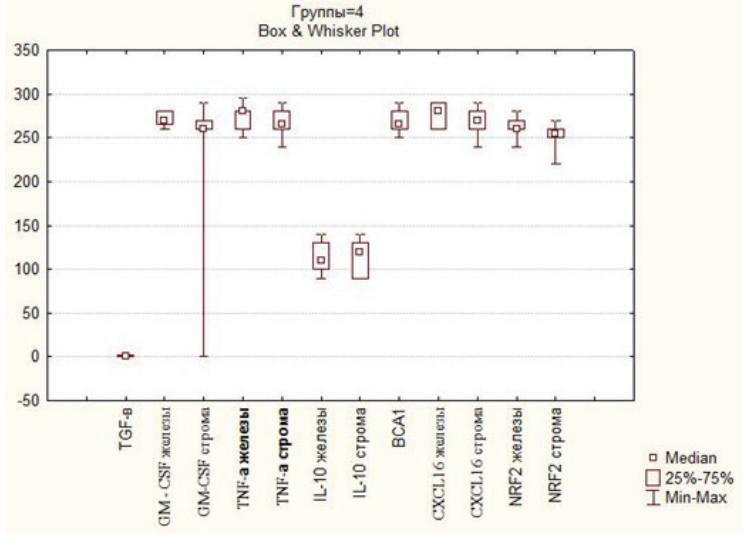


Fig. 1. Microbiota types at different phenotypes and variants at non-lactobacillary profile

a



b



c

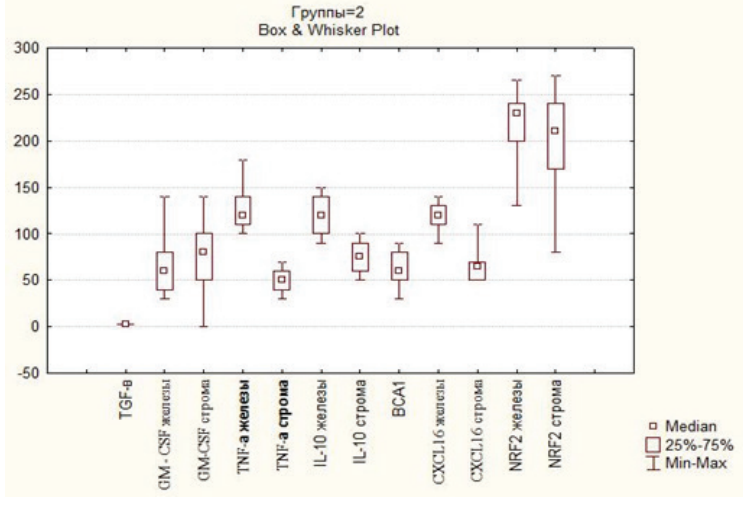


Fig. 2. Immune profile in the phenotype of normal endometrium (a), chronic endometritis (b), dysplastic phenotype (c)

abnormal expression of sex hormone receptors and an inadequate microenvironment for implantation.

We believe that in the development of molecular phenotypes of the endometrium, it is not the type of microbiota that is paramount (especially when mixed), but the immune reactions induced by microbial ligands that affect the difference in the expression of pro-inflammatory and anti-inflammatory factors, chemokines and antimicrobial metabolites.

The pathogenesis of the phenotype of chronic endometrial inflammation is based on violations of the molecular interactions of immunocompetent cells, with the predominance of the pro-inflammatory Th1 subtype. Our data suggest that the dysbiotic profile of the endometrium inevitably changes the composition of local immunocompetent cells, which, with factors recruited into the stroma, disrupt the expression of steroid hormone receptors. Overexpression of proinflammatory markers (cytokines, chemokines, and growth factors) in CE is associated with the risk of implantation failures [19].

Dystrophic-atrophic changes forming the morphological basis of the dysplastic phenotype of the endometrium were combined with a mixed type of microbiota in 41.2% (a decrease in the titer of lactobacilli <90.0% on the background of an increase in opportunistic microorganisms).

The molecular profile of the dysplastic phenotype (Figure 4) was represented by a decrease in the expression of all markers in glandular cells in comparison with the control: GM-CSF – by 3.7 times (p=0,00), TNF-α – by two times (p=0,00), IL-10 – by 1.8 times (p=0,00), CXCL16 – by 1.9 times (p=0,00), BCA1 – by 2.6 times (p=0,00), NRF2 – by 1.2 times (p=0,00). The TNF-α/IL-10 index was 1.0. In endometrial stromal cells, the expression of GM-CSF was reduced by 2.7 times (p=0,00), TNF–α by 4.6 times (p=0,00), IL-10 by 2.9 times (p=0,00), and CXCL16 by 3.4 times (p=0,00), along with the maximum TGF-β index (3 points) (p=0,01) in comparison with other phenotypes. The TNF-α/IL-10 ratio was 0.7.

The nature of the immune microenvironment of the dysplastic phenotype during the "implantation window" indicates an inhibition of the metabolic activity of the endometrium, a change in protein synthesis, and a decrease in antioxidant potential. We believe that endometrial susceptibility disorder caused by fibrotic transformation as a result of multiple intrauterine interventions is of interest from the standpoint of the "aging" of the local immune system. It is reported that

the cause of implantation failures may be premature aging of the endometrium due to local immune stresses and inflammatory damage [1]. The increase in "aging" decidual cells on the background of inability to restore proliferative activity leads to an excess of TGF-β along with suppression of the induction of differentiation of CD4 +T cells to Th17 and a decrease in the level of Treg cells [15].

The violation of local immune surveillance during the "implantation window" is likely to be connected with the activation of molecular signaling cascades associated with implantation disorders. Inhibition of NRF2 expression should be considered as the cause of a decrease in antioxidant enzymes and the development of chronic endometrial hypoxia [17]. A decrease in the expression of immune factors during the "implantation window" suggests defects in the mechanisms of stroma decidualization and secretory potential of glands, genes for controlling migration, proliferation, adhesion and cellular metabolism. Obviously, the molecular biological profiling most asynchronous to the implantation period in endometrial dysplastic phenotype was revealed in the presence of a non-lactobacillar (mixed) type of microbiota.

Heterogeneity of microbiota types in a metabolically "non-resource" endometrium probably correlates with the degree of preservation of the cellular layer and the sensitivity of receptors to steroid hormones, as well as violations of intracellular metabolism.

Conclusion. The phenotypes of the endometrium of infertile women are presented, mainly due to various immune microenvironment during the "implantation window". The heterogeneity of endometrial immune infiltration (cytokines, chemokines, growth factors) and the type of microbiota (lactobacillar, mixed and dysbiotic types) detected in various phenotypes (normal, dysplastic, chronic inflammation) determine the "consistency" of the molecular environment for embryo implantation. In the CE phenotype, defective decidualization of the endometrium is associated with a violation of the immune "landscape" during implantation and the predominance of a pro-inflammatory cytokine response. Implantation violation in CE is caused by the generation of an excessive inflammatory reaction and impaired recruitment of immune cells necessary for the formation of immune tolerance in the presence of pathogenic bacterial flora (non-lactobacillar type of microbiota). The features of the dysplastic phenotype of the endometrium, connected with plastic deficiency, are revealed in a violation of the organized interaction of immune cells (cytokines, chemokines, growth factors) on the background of severe fibrotic transformation.

Reference

1. Chen P., Yang M., Wang Y. [et al.] Aging endometrium in young women: Molecular classification of endometrial aging-based markers in women younger than 35 years with recurrent implantation failure. J Assist Reprod Genet. 2022; 39. N9. P.2143-2151. doi: 10.1007/s10815-022-02578-x

2. Chen W., Wei K., He X. [et al.] Identification of Uterine Microbiota in Infertile Women Receiving in vitro Fertilization with and Without Chronic Endometritis. Front. Cell Dev. Biol. 2021; 9. P.693267. doi: 10.3389/fcell.2021.693267

3. Cicinelli E., Matteo M., Tinelli R. [et al.] : Prevalence of chronic endometritis in repeated unexplained implantation failure and the IVF success rate after antibiotic therapy. Hum Reprod. 2015; 30. P.323–330.

4. Drizi A., Djokovic D., Laganà A.S., van Herendael B. Impaired inflammatory state of the endometrium: a multifaceted approach to endometrial inflammation. Current insights and future directions. Prz Menopauz. 2020; 19. P. 90-100.

5. Franasiak J.M., Scott R.T. Reproductive tract microbiome in assisted reproductive technologies. Fertil. Steril. 2015; 104. P. 1364–1371. doi: 10.1016/j.fertnstert.2015.10.012

6. Gellersen B., Brosens J.J. Cyclic decidualization of the human endometrium in reproductive health and failure. Endocr Rev. 2014; 35. P.851–905. doi: 10.1210/er.2014-1045

7. Haggerty C.L., Hillier S.L., Bass D.C. [et al.]: Bacterial Vaginosis and Anaerobic Bacteria Are Associated with Endometritis. Clinical Infectious Diseases. 2004; 39. P.990–995.

8. Hooper L.V., Littman D.R., Macpherson A.J. Interactions between the microbiota and the immune system. Science. 2012; 336. N 6086. P.1268–1273. doi: 10.1126/science.1223490.

9. Huang J., Qin H., Yang Y. [et al.] A Comparison of Transcriptomic Profiles in Endometrium During Window of Implantation Between Women With Unexplained Recurrent Implantation Failure and Recurrent Miscarriage. Reproduction. 2017; 153. N6. P.749–58. doi: 10.1530/REP-16-0574

10. Katz S., Zsiros V., Doczi N., Kiss A.L. Inflammation-induced epithelialto-mesenchymal transition and GM-CSF treatment stimulate mesenteric mesothelial cells to transdifferentiate into macrophages. Inflammation. 2018. P. 825. doi: 10.1007/s10753-018-0825-4

11. Kitaya K., Matsubayashi H., Takaya Y. [et al.]: Live birth rate following oral antibiotic treatment for chronic endometritis in infertile women with repeated implantation failure. Am J Reprod Immunol. 2017; 78. P.5. doi: 10.1111/aji.12719.

12. Kyono K., Hashimoto T., Kikuchi S. [et al.] A pilot study and case reports on endometrial microbiota and pregnancy outcome: An analysis using 16S rRNA gene sequencing among IVF patients, and trial therapeutic intervention for dysbiotic endometrium. Reprod. Med. Biol. 2019; 18. P.72–82. doi: 10.1002/rmb2.12250.

13. Lédée N., Petitbarat M., Chevrier L. [et al.] The Uterine Immune Profile May Help Women With Repeated Unexplained Embryo Implantation Failure After In Vitro Fertilization. Am. J. Reprod. Immunol. 2016; 75. P.388–401. 10.1111/aji.12483

14. Lessey B.A., Young SL. What exactly is endometrial receptivity? // Fertil Steril. 2019; 111. P. 611–617.

15. Li X., Cannon A.R., Hammer A.M. [et al.] IL-23 restoration of Th17 effector function is independent of IL-6 and TGF-β in a mouse model of alcohol and burn injury. J Leukoc Biol. 2017; 102. P.915–23. doi: 10.1189/jlb.3A1216-527R

16. Ohara Y., Matsubayashi H., Suzuki Y. [et al.] Clinical relevance of a newly developed endometrial receptivity test for patients with recurrent implantation failure in Japan. Reprod Med Biol. 2022; 21. P.e12444. doi: 10.1002/rmb2.12444

17. Paul M.K, Bisht B., Darmawan D.O. [et al.] Dynamic changes in intracellular ROS levels regulate airway basal stem cell homeostasis through Nrf2-dependent Notch signaling. Cell Stem Cell. 2014; 15:199–214.

18. Vannuccini S., Clifton V.L., Fraser I.S. [et al.] Infertility and reproductive disorders: impact of hormonal and inflammatory mechanisms on pregnancy outcome. Hum Reprod Update. 2016; 22, N 1. P.104–115. doi: 10.1093/humupd/dmv044.

19. von Hundelshausen P., Agten S.M., Eckardt V. [et al.] Chemokine interactome mapping enables tailored intervention in acute and chronic inflammation. Sci. Transl. Med. 2017. N 9. P.384. eaah6650. doi: 10.1126/scitranslmed.aah6650

20. Yen M., Donma O., Yildizfer F. [et al.] Association of fetuin A, adiponectin, interleukin 10 and total antioxidant capacity with IVF outcomes. Iran. J. Reprod. Med. 2014. V.12. P.747–754.