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FEATURES OF THE ENDOMETRIAL MICROBIOME OF INFERTILE WOMEN AND ITS EFFECT ON THE VIABILITY OF THE "IMPLANTATION WINDOW" PHASE

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Changes in the endometrial microbiome (dysbiotic type) were more often combined with dyschronism phenomena (inconsistency in the rate of the gland maturation with the secretory phase of the menstrual cycle) in women than with secretory changes. The data obtained allow us to state the dysbiotic type of microbiota appears to be a marker of violation of the morphological characteristics of the endometrium during the "implantation window" phase, mainly against the background of a chronic inflammatory process. The dysbiotic profile of the endometrium in infertile women is the cause of a violation of molecular mechanisms necessary for adequate blastocyst implantation. The studying endometrial microbiota increases the likelihood of predicting reproductive outcomes before embryo transfer and choosing an effective treatment strategy when changing quantitative and qualitative species characteristics.

Keywords: endometrium, endometrial microbiota, "implantation window" phase, lactobacillar (eubiotic) and dysbiotic microbiota types.

Introduction. The existing facts about the complexity and multifactorial conditionality of the implantation process have been supplemented by a new microbiological measurement of the human reproductive potential [5].

The idea of the complexity of microbial communities of various niches of the human body became possible with the introduction of the method of sequencing the ribosomal ribonucleic acid (rRNA) 16S gene, which is present in almost all bacteria [21].

The refutation of the dogma about the sterility of the uterus, separated from the lower infected part of the reproductive tract by the cervix, became possible with the isolation of bacterial deoxyribonucleic acid (DNA) taxa in 95% of endometrial samples after hysterectomy in non-pregnant women without signs of inflammation or vaginosis in conditions minimizing the risk of contamination [10].

Putting sequencing methods into practice made it possible to identify the relationship of microbiota disorders with various manifestations of reproductive dysfunction (from the formation of gametes in the gonads to implantation failures and/or pregnancy complications) and gynecological diseases [19,24].

However, a consensus on the microbial composition of the uterine nucleus of infertile and fertile women has not yet been formed, despite evidence of differences in the microbiota of the lower and upper parts of the reproductive system [1,28,34].

A vivid example of the abnormal endometrial microbiota with qualitative and quantitative transformations is chronic endometritis (CE) in 45% of infertile women with implantation failures and recurrent pregnancy losses [8,9,12,25,30].

Molecular detection of bacterial pathogens in endometrial samples showed an agreement between results using either polymerase chain reaction or sequencing in 77.0% [31].

The mechanism of the effect of the endometrial microbiota on the possibility of recurrent reproductive losses in CE remains unclear. The 16S ribosomal RNA sequencing method showed a large number of Phyllobacterium and Sphingomonas in the endometrium and a positive correlation of their content with immune B cells, a negative correlation with macrophages [22].

The features of the microbiome of women with endometrial polyp (EP) are believed to be associated with the possibility of their development on the CE background due to the continuous production of pro-inflammatory biological factors [3,6].

Data on the influence of the microbial community of the uterus on the effectiveness of the realization of the reproductive potential are contradictory due to small samples of patients, differences in assessment methods (a variety of Lactobacillus types, their relationship with opportunistic microorganisms, the presence of obligate pathogens).

Publications on the relationship between the predominance of Lactobacillus spp. in the endometrium (≥ 90% or ≥ 80%) by sequencing 16S ribosomal RNA with a significant increase in the frequency of implantation, clinical pregnancy, its prolongation and live birth [23] confirm the prospects of predicting the outcomes of infertility treatment/IVF programs based on the analysis of the uterine microbiome.

Controversial issues of the expediency and effectiveness of antibacterial therapy in infertile women are associated with the lack of clear ideas about the endometrial microbiota in each case. A recent meta-analysis of five studies (796 women) showed no differences in the reproductive performance of women with CE who received antibiotic therapy compared with the control group without treatment [13].

On the contrary, an increase in the frequency of implantation and pregnancy in IVF protocols of women with unexplained infertility, the restoration of fertility in case of recurrent implantation failures is associated with the CE antibiotic therapy [8,13,14].

The objective of the research: to study the microbiota and morphological characteristics of the endometrium in the phase of the "implantation window" of women with infertility of various genesis.

Materials and methods of the research: A prospective examination of 127 women of reproductive age who applied for infertility, including after ineffective attempts of in vitro fertilization (IVF), was performed.

The selection and examination of mar-

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ried couples were carried out on the basis of the Department of Assisted Reproductive Technologies of the Federal State Budgetary Institution "National Research Center of Endocrinology" of the Ministry of Health of the Russian Federation in Moscow, as well as the center for the emergency medical care of the Republican Hospital No. 2 in Yakutsk.

Criteria for inclusion in the study: age from 25 to 40; infertile women with verified CE, including in combination with endometrial polyp (EP); with tubal and idiopathic infertility; absence of male infertility factor; absence of infertility or fertility disorders of any other genesis; voluntary informed consent to 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, antibiotic therapy at least a month before inclusion in the study.

The first group consisted of women with unexplained infertility (idiopathic) (n=32), the second – with tubal infertility (n=38), the third – with infertility on the CE background in combination with EP (n=21), the fourth – with infertility on the CE background in general (n=36).

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 scope of the examination included assessment of complaints, anamnesis, general and gynecological examination, laboratory (clinical blood test, general urinalysis, biochemical method, hemostasiogram) and instrumental (hysteroscopy) studies.

Hysteroscopy was performed on days 7-9 of m.c. (when diagnosing the signs of PE and PE by ultrasound of the pelvic organs) with subsequent collection of material for morphological examination. The morphological signs of CE were presented by inflammatory infiltrates from lymphoid elements around glands and blood vessels, rarely diffusely; focal infiltrates in the form of "lymphoid follicles" in the basal and in all parts of the functional layer, consisting of leukocytes and histiocytes; the presence of plasma cells; focal stroma fibrosis; sclerotic changes in the walls of the spiral arteries of the endometrium.

CE was also verified immunohistochemically (markers CD 138+). In other cases, endometrial aspiration pipel-biopsy was performed during the "implantation window" phase (on days 20-24 of the menstrual cycle (ppm)).

Pathomorphological and immunohistochemical studies were performed according to the standard method.

Microbiological examination of the endometrium by real-time polymerase chain reaction (PCR) (Femoflor 16 tests, from Scientific and Production Association "50 DNA Technology" LLC (Russia)) was conducted to assess the presence and 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 from BIO-RAD (USA).

The protocol for patients' monitoring and the examination program were approved by the local ethics committee, 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 involving humans".

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

Qualitative variables were analyzed by constructing conjugacy tables using Pearson's chi-squared ($\chi 2$) test, with a small number of observations (less than 5) – Fisher's exact test.

Statistically significant differences were considered at $p < 0.05$.

Results and research methods. According to the histological study of endometrial biopsies in the "implantation window" phase, their compliance with the secretion phase was statistically sig-

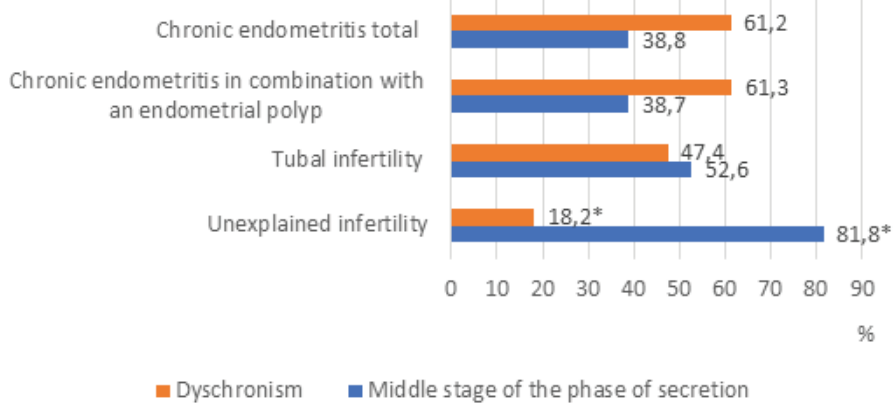

Fig. 1. Conclusions of morphological studies of endometrial biopsies of infertile women in the "implantation window" phase. *Differences in indicators are statistically significant from all groups ($p<0.05$)

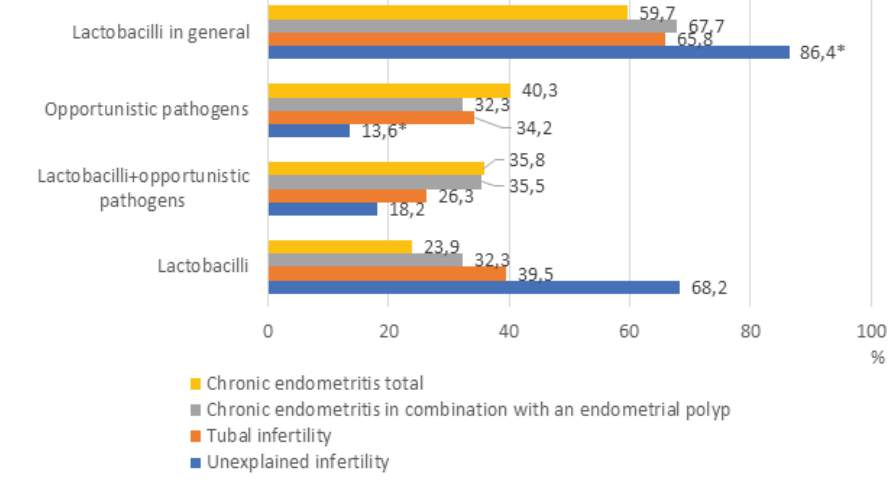

Fig. 2. Features of the endometrial microbiota of infertile women in the "implantation window" phase. *Differences in indicators are statistically significant between groups of women with unexplained infertility and CE ($p<0.05$)

nificantly more common in women with unexplained infertility – one and a half times than with TI (p=0.03, χ2=5.1), twice – with CE (p=0.00, χ2 =12.3), including in combination with EP (p= 0.002, χ2 =9.7) (Figure 1).

Figure 1 – Conclusions of morphological studies of endometrial biopsies of infertile women in the "implantation window" phase

Morphological signs of inconsistency between the architectonics of the endometrium and the "implantation window" phase, dyschronism in the maturation of the glandular epithelium and stroma, and uneven distribution of glands with accumulations in the perivascular zones in women with unexplained infertility were statistically significantly less common than in other groups: 2.6 times than with TI (p=0.03; χ2=5.1), 3.4 times – with CE (p=0.00; χ2=12.3) and its combination with EP (p=0.002; χ2=9.7).

In endometrial biopsies of almost half of women with TI, a picture of the middle stage of the phase of secretion was revealed, in the rest – dyschronism.

The features of the uterine microbiome of infertile women (Figure 2) were determined by the dominant type of bacteria detected: lactobacillar (more than 90%), mixed (less than 90% in combination with opportunistic microorganisms) and dysbiotic (absence of lactobacilli, predominance of opportunistic microorganisms).

The predominance of the lactobacillar type of microbiota in the endometrium of women with unexplained infertility was more common than in the other groups, but without statistically significant differences.

The frequency of a mixed microbiota profile (lactobacilli less than 90% of the total bacterial mass in combination with opportunistic microorganisms) in the endometrium of infertile women of different groups did not significantly differ. Bacterial communities with a high proportion of potential pathogens (isolated or mixed) in the endometrium of women with unexplained infertility were detected three times less often than with CE (p=0.03; χ2=5.3), twice as often as TI, however, no statistically significant intergroup differences were found.

The lactobacillar profile in the endometrium of women with unexplained infertility was detected more often than in the other groups, one and a half times than with CE (p=0.03; χ2=5.3).

Data on the occurrence of a variant of a reduced level of lactobacilli in combination with opportunistic microorganisms in groups of infertile women are presented in Figure 3

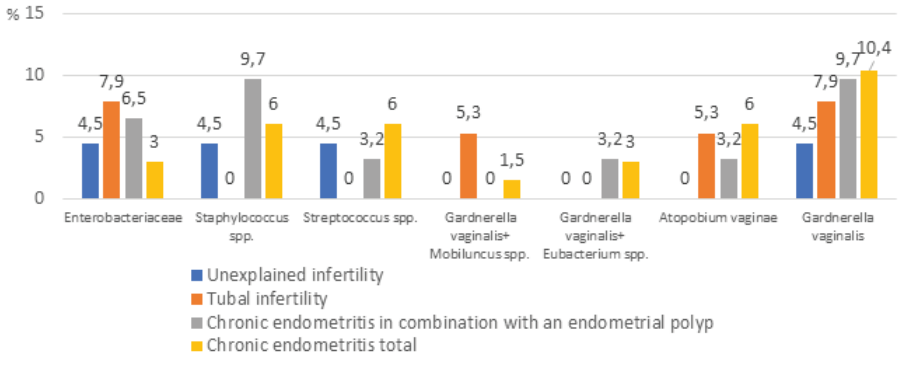

Fig. 3. Characteristics of the non-lactobacillar biotope of the endometrium of infertile women. There were no statistically significant differences between the groups

The spectrum of microorganisms with a mixed type of microbiota was represented mainly by monocultures with the highest proportion of Gardnerella vaginalis, Enterobacteriaceae and Staphylococcus spp. compared with other infections. Gardnerella vaginalis mixed with Mobiluncus spp. and Eubacterium spp. were found in separate groups of women with infertility (in a small number).

The characteristics of the endometrial biotope of infertile women with the dominant opportunistic microorganisms (dysbiotic) are shown in Figure 4.

The basis of the dysbiotic microbiome of the uterus of infertile women consisted mainly of monocultures (Gardnerella vaginalis, Mycoplasma hominis, Ureaplasma spp., Streptococcus spp. and Enterobacteriaceae), mixed facultative and obligate anaerobic bacteria were found in insignificant quantities. Obligate pathogens were not detected in the uterine cavity of infertile women.

The results of the analysis of the endometrial biotope of infertile women with different morphological characteristics of the endometrium in the "implantation window" phase are presented in Table 1.

The eubiotic profile of the endometrial microbiota was more common in women with its structure corresponding to the middle stage of the phase of secretion with the highest index in unexplained infertility: twice (p=0.03; χ2=5.8) than with TPI, three times – than with CE (p=0.00; χ2=14.0) and its combination with EP (p=0.04; χ2=9.1). The endometrial microbiome with a high proportion of lactobacilli in the presence of morphological signs of dyschronism was determined only in 6.3% of women.

In women with a mixed endometrial biotope (lactobacilli content less than 90% with the variability of opportunistic microorganisms), samples with morphological signs of the middle stage of the phase of secretion were detected in

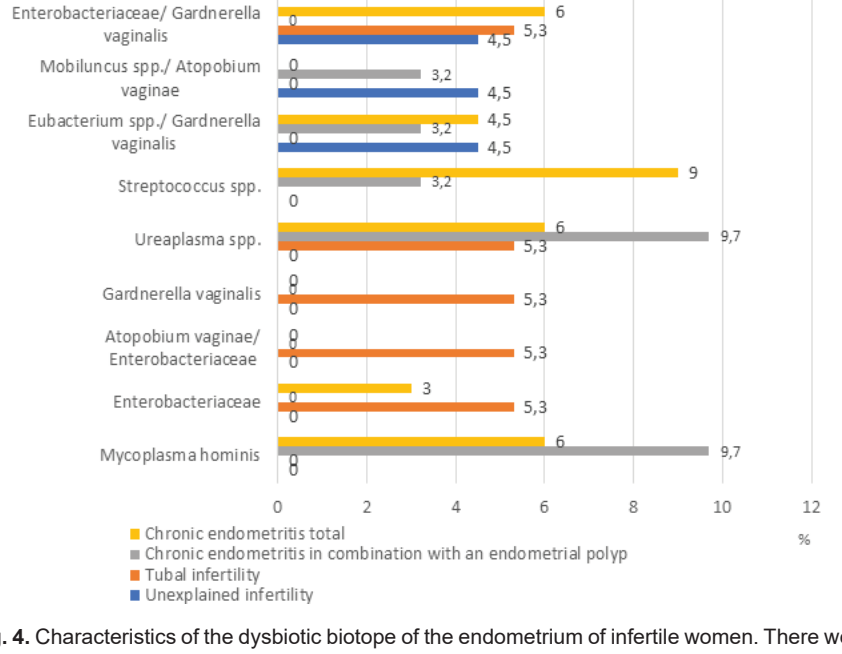

Fig. 4. Characteristics of the dysbiotic biotope of the endometrium of infertile women. There were no statistically significant differences between the groups

Morphological features of the endometrium in the "implantation window" phase in various variants of the uterine microbiome of infertile women

Groups		N	Lactobacilli		Lactobacilli+ opportunistic pathogens		Opportunistic pathogens	
			middle stage of the phase of secretion	dyschronism	middle stage of the phase of secretion	dyschronism	middle stage of the phase of secretion	dyschronism
Unexplained infertility	abs.	22	14*	1	3	1	1	2
	%		63.6	4.5	13.6	4.5	4.5	9.1
Tubal infertility	abs.	38	12	3	5	5	3	10
	%		31.6	7.9	13.2	13.2	7.9	26.3
Chronic endometritis in combination with an endometrial polyp	abs.	31	7	3	4	7	1	9
	%		22.6	9.7	12.9	22.6	3.2	29.0
Chronic endometritis total	abs.	67	14	2	9	15	3	24
	%		20.9	3.0	13.4	22.4	4.5	35.8

Note – * differences in indicators are statistically significant from other groups (p<0.05)

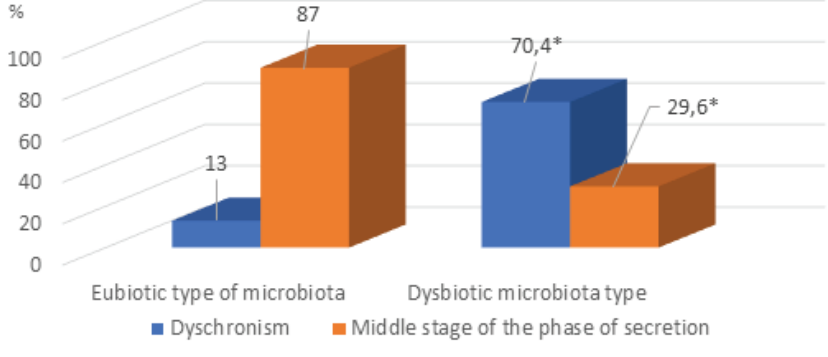

Fig. 5. Characteristics of the endometrial microbiome with various morphological characteristics in the "implantation window" phase. * Differences in indicators between groups are statistically significant (p<0.05)

13.3%, dyschronism – twice as high with CE as with TPI and unexplained infertility (22.5% vs. 8.8% on average). In the presence of potential bacterial pathogens in the endometrium, a discrepancy between its architectonics and the secretory phase of the menstrual cycle was more often noted. The morphological consistency of the endometrium during the "implantation window" phase was determined only in 5.0% of infertile women with a dysbiotic type of microbiota.

Data on the nature of the endometrial microbiota (eubiotic and dysbiotic types) depending on the morphological characteristics in the "implantation window" phase are presented in Figure 5.

The eubiotic type of microbiota in a sample of infertile women with a picture of the middle stage of the phase of secretion in endometrial samples was significantly more often than with incomplete secretory transformation of the stroma (p = 0.00; $\chi 2$=38.6). In case of endometrial glands and stroma dyschronism in the "implantation window" phase, most women had a dysbiotic microbiota type, almost five times more likely than with secretory changes (p = 0.00; $\chi 2$=38.6).

Our results suggest that the dominant Lactobacillus spp. biotope, modulating the function of endometrial cells and the local immunity system, is involved in the regulation of the fertile potential. It is probably the lactobacillar microbial profile that defines the endometrium as an immunologically favorable niche for blastocyst implantation [2,4]. The dominance of Lactobacillus (relative abundance> 90% relative to MBP) in the endometrial microbiota of infertile women is associated not only with the success of implantation, but also with the live birth rate in IVF protocols [15,18]. We believe that microbial homeostasis in the endometrium determines resistance to colonization by opportunistic flora, the ability to express genes that affect receptivity in the "implantation window" phase [27]. The data obtained allow us to state the concept of a complete remodelling necessary for a susceptible endometrium, mainly in the presence of a lactobacillar type of microbiota. The causes of infertility in these women may be associated with an imbalance of pro- and anti-inflammatory reactions in the endometrium.

Microbial diversity in the endometrium of infertile women with CE with a high proportion of Gardnerella vaginalis and Atopobium vaginae should be considered as a violation of protective physiological barriers and/or functional inferiority of cellular immunity components. Data on a lower frequency of Gardnerella vaginalis in women without CE allowed the authors to suggest their adverse effect on the possibility of pregnancy in natural cycles and IVF protocols [26].

The dysbiotic profile of the endometrium in 40.3% of infertile women with CE, a third – with TPI and 13.6% – with unexplained infertility seems, similar to the opinion of other authors [7,16,20], to be the cause of unfavorable molecular mechanisms for implantation. The presence of type IV CST (community state types) microbiota in the endometrium, especially Gardnerella and Streptococcus genra, is associated with a significant decrease in the frequency of implanta-

tion, pregnancy and miscarriage [18]. Changes in the endometrial microbiome of women with EP on the CE background (reduction of the lactobacillar profile by less than 90% in 22.6%; dysbiotic type – 29.0%) were associated with the phenomena of dyschronism (inconsistency of changes in the architectonics of the mucosa with the secretory phase of the menstrual cycle). Such correlations confirm the concept of a decrease in women's reproductive potential with a change in the molecular functions of endometrial microbes involved in the regulation of cellular metabolism, the immune system, and signaling cascades [11,29,32,33].

The pathological effects of bacteria on the endometrium at the dysbiotic profile are associated with a change in the functional activity of the local immune system and the development of an unfavorable environment for blastocyst implantation [3]. Obviously, the decision in favor of antibiotic therapy should be made after the confirmation of the inflammatory process modulated by the presence of non-lactobacillar microbiota in the endometrium.

Conclusion. Thus, the dysbiotic microbiota type appears to be a marker of a violation of the morphological characteristics of the endometrium during the "implantation window" phase, mainly on the background of a chronic inflammatory process of the endometrium. The effect of the non-lactobacillar biotope on the transformation of the endometrium in the "implantation window" phase and the possibility of inflammation depend on the balance of local immunoregulatory resources, which is the subject of further research.

The analysis of the composition of the endometrial microbiota is informative for predicting reproductive outcomes before embryo transfer, improving diagnosis and choosing a treatment strategy. The detection of lactobacillar type microbiota in the endometrium in infertile women with CE proves to be a reasoned rejection of antibiotic therapy.

Conflict of interests. The authors state no possible conflicts of interests.

Contribution of the authors

Polina M.L. conceived and developed the study. Polina M.L., Vitiazeva I.I., Douglas N.I., Zakharova P.N. participated in the collection, analysis and interpretation of data.

Polina M.L., Vitiazeva I.I., Zakharova P.N. wrote a draft report. All authors reviewed the report and approved of the final version before submission. All authors have read and agreed with the published version of the manuscript.

Reference

1. Wee B.A., Thomas M., Sweeney E.L. [et al.] A retrospective pilot study to determine whether the reproductive tract microbiota differs between women with a history of infertility and fertile women. Aust. N. Z. J. Obstet. Gynaecol. 2018; 58: 341–348. doi: 10.1111/ajo.12754.
2. Baker J.M., Chase D.M., Herbst-Kralovetz M.M. Uterine Microbiota: Residents, Tourists, or Invaders? Front. Immunol. 2018; 9: 208.
3. Fang R.L., Chen L.X., Shu W.S. [et al.] Barcoded sequencing reveals diverse intrauterine microbiomes in patients suffering with endometrial polyps. Am. J. Transl. Res. 2016; 8: 1581–1592.
4. Benner M., Ferwerda G., Joosten I., van der Molen R.G. How uterine microbiota might be responsible for a receptive, fertile endometrium. Hum. Reprod. Update. 2018; 24: 393–415.
5. Cariati F., D'Argenio V., Tomaiuolo R. The evolving role of genetic tests in reproductive medicine. J. Transl. Med. 2019; 17: 267.
6. El-Hamarneh T., Hey-Cunningham A.J., Berbic M. [et al.] Cellular immune environment in endometrial polyps. Fertil. Steril. 2013; 100: 1364–1372.
7. Verstraelen H., Vilchez-Vargas R., Desimpel F. [et al.] Characterisation of the human uterine microbiome in non-pregnant women through deep sequencing of the V1-2 region of the 16S rRNA gene. Peer J 4. 2016; e1602. 10.7717/peerj.1602
8. Cicinelli E., Matteo M., Trojano G. [et al.] Chronic endometritis in patients with unexplained infertility: Prevalence and effects of antibiotic treatment on spontaneous conception. Am. J. Reprod. Immunol. 2018; 79(1). doi: 10.1111/aji.12782.
9. Puente E., Alonso L., Laganà A.S. [et al.] Chronic endometritis: old problem, novel insights and future challenges. J. Int. J. Fertil. Steril. 2020; 13(4): 250-6.
10. Mitchell C.M., Haick A., Nkwopara E. [et al.] Colonization of the upper genital tract by vaginal bacterial species in nonpregnant women. Am J Obstet Gynecol. 2015; 212: 611. e1–9. 10.1016/j.ajog.2014.11.043
11. Song S.D., Acharya K.D., Zhu J.E. [et al.]. Daily Vaginal Microbiota Fluctuations Associated with Natural Hormonal Cycle, Contraceptives, Diet, and Exercise mSphere. 2020; 5 (4): e00593–20. 10.1128/mSphere.00593-20
12. Cicinelli E., Resta L., Nicoletti R. [et al.] Detection of chronic endometritis at fluid hysteroscopy. J Minim Invasive Gynecol. 2005; 12 (6): 514–8.
13. Vitagliano A., Saccardi C., Noventa M. [et al.]Effects of chronic endometritis therapy on in vitro fertilization outcome in women with repeated implantation failure: a systematic review and meta-analysis. Fertil Steril. 2018; 110: 103–112. e1.
14. Sfakianoudis K., Simopoulou M., Nikas Y. [et al.] Efficient treatment of chronic endometritis through a novel approach of intrauterine antibiotic infusion: a case series. BMC Womens Health. 2018; 18(1): 197.
15. Franasiak J.M., Werner M.D., Juneau C.R. [et al.]Endometrial microbiome at the time of embryo transfer: Next-generation sequencing of the 16S ribosomal subunit. J. Assist. Reprod. Genet. 2016; 33: 129–136.
16. Moreno I., Garcia-Grau I., Perez-Villaroya D. [et al.] Endometrial microbiota composition is associated with reproductive outcome in infertile patients. Microbiome. 2022; 10(1): 1.
17. Espinoza J., Erez O., Romero R. Preconceptional antibiotic treatment to prevent preterm birth in women with a previous preterm delivery. Am J Obstet Gynecol. 2006; 194 (3): 630–7.
18. Evidence that the endometrial microbiota has an effect on implantation success or failure / I. Moreno, F.M. Codoñer, F. Vilella [et al.] // Am. J. Obstet. Gynecol. – 2016. – Vol.215. – P.684–703.
19. Franasiak J.M., Scott R.T. Jr. Introduction: microbiome in human reproduction. Fertil Steril. 2015; 104:1341–3.
20. Giudice L.C. Challenging dogma: the endometrium has a microbiome with functional consequences! Am J Obstet Gynecol. 2016; 215(6): 682-683.
21. 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: 693267.
22. Chen P., Guo Y. [et al.] Interaction Between Chronic Endometritis Caused Endometrial Microbiota Disorder and Endometrial Immune Environment Change in Recurrent Implantation Failure. Front Immunol. 2021; 12: 748447.
23. Kyono K., Hashimoto T., Nagai Y., Sakuraba Y. Analysis of endometrial microbiota by 16S ribosomal RNA gene sequencing among infertile patients: A single-center pilot study. Reprod. Med. Biol. 2018; 17: 297–306.
24. Miles S.M., Hardy B.L., Merrell D.S. Investigation of the microbiota of the reproductive tract in women undergoing a total hysterectomy and bilateral salpingo-oopherectomy. Fertil Steril. 2017; 107: 813–20.
25. Moreno I., Simon C. Relevance of assessing the uterine microbiota in infertility. Fertil. Steril. 2018; 110: 337–343.
26. Onderdonk A.B., Delaney M.L., Fichorova R.N. The Human Microbiome during Bacterial Vaginosis. Clin Microbiol Rev. 2016; 29(2): 223-38.
27. Power M.L., Quaglieri C., Schulkin J. Reproductive Microbiomes: A New Thread in the Microbial Network. Reprod. Sci. 2017; 24: 1482–1492.
28. Campisciano G., Florian F., D'Eustacchio A. [et al.] Subclinical alteration of the cervical-vaginal microbiome in women with idiopathic infertility. J. Cell Physiol. 2017; 232: 1681–1688.
29. Garcia-Grau I., Perez-Villaroya D., Bau D. [et al.] Taxonomical and Functional Assessment of the Endometrial Microbiota in A Context of Recurrent Reproductive Failure: A Case Report. Pathogens. 2019; 8: 205.
30. Takebayashi A., Kimura F., Kishi Y. [et al.] The association between endometriosis and chronic endometritis. PLoS ONE. 2014; 9: e88354.
31. Moreno I., Cicinelli E., Garcia-Grau I. [et al.] The diagnosis of chronic endometritis in infertile asymptomatic women: a comparative study of histology, microbial cultures, hysteroscopy, and molecular microbiology. Am J Obstet Gynecol. 2018; 218: 602.e1–16.
32. Chen C., Song X., Wei W. [et al.] The microbiota continuum along the female reproductive tract and its relation to uterine-related diseases. Nat. Commun. 2017; 8: 875.
33. Crha I., Ventruba P., Žáková J. [et al.] Uterine microbiome and endometrial receptivity. Ceska Gynekol. 2019; 84(1): 49-54. English. PMID: 31213058.
34. Younes J.A., Lievens E., Hummelen R. [et al.] Women and Their Microbes: The Unexpected Friendship. Trends Microbiol. 2018; 26: 16–32. doi: 10.1016/j.tim.2017.07.008.