FEATURES OF INTRAUTERINE MICROBIOTA IN PATIENTS WITH ENDOMETRIAL POLYPS

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Endometrial polyps (EPs) represent the most common form of benign intrauterine disorder. Microbial factor is one of the possible etiological factors of EPs. Investigation of endometrial microbiota can provide new opportunities for improvement of the EP diagnosis and treatment. The study is aimed to assess intrauterine microbiota composition in patients with endometrial polyps. A total of 84 patients with endometrial polyps based on histology assessment data were enrolled. The comparison group included 44 patients having no endometrial abnormality. Endometrial microbiota composition was assessed by the culturomics method using the extended set of selective and nonselective growth media. The endometrium sample was obtained before performing hysteroresectoscopy. In patients with EP, growth of bacterial microflora in the uterine cavity was observed 2.4 times more often compared to patients having no endometrial abnormality (OR — 2.4, 95% CI — 1.1; 5.5). In cases of EP, intrauterine microbiota composition was characterized by larger species and taxonomic diversity. Microorganisms of the genera *Staphylococcus* and *Lactobacillus prevailed*. Further research focused on endometrial microecology can provide new opportunities for further improvement of the EP diagnosis and treatment strategies.

Keywords: intrauterine microbiota, cervical canal microbiota, endometrial polyps

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ОСОБЕННОСТИ МИКРОБИОТЫ ПОЛОСТИ МАТКИ У ПАЦИЕНТОК С ПОЛИПАМИ ЭНДОМЕТРИЯ

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Полипы эндометрия (ПЭ) — наиболее распространенная форма доброкачественной внутриматочной патологии. Одним из возможных этиологических факторов ПЭ является микробный фактор. Изучение микробиоты эндометрия может предоставить новые возможности для совершенствования диагностики и лечения ПЭ. Целью исследования было изучить состав микробиоты полости матки у пациенток с полипами эндометрия. В исследование включены 84 пациентки с полипами эндометрия по данным гистологического исследования. В группу сравнения вошли 44 пациентки без патологии эндометрия. Состав микробиоты эндометрия исследовали методом культуромики с использованием расширенного набора селективных и неселективных питательных сред. Эндометрий получали перед проведением гистерорезектоскопии. У пациенток с ПЭ рост бактериальной микрофлоры в полости матки наблюдался в 2,4 раза чаще по сравнению с пациентками без патологии эндометрия (ОШ — 2,4, 95%-й ДИ — 1,1; 5,5). Состав микробиоты полости матки при наличии ПЭ отличался большим видовым и таксономическим разнообразием, преобладали микроорганизмы родов *Staphylococcus* и *Lactobacillus*. Дальнейшее изучение микроэкологии эндометрия может предоставить новые возможности для дальнейшего совершенствования диагностики и стратегий лечения ПЭ.

Ключевые слова: микробиота полости матки, микробиота цервикального канала, полипы эндометрия

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Endometrial polyps (EPs) represent the most common form of benign intrauterine disorder [1]. According to hysteroscopy data, the prevalence of EP is 6–27%, depending on the fact of having complaints [2]. The rate of EP recurrence after surgical treatment varies between 13% and 43% [3–5]. The EP emergence can be associated with many factors, such as imbalance in expression of sex hormone receptors, long-term sustained stimulation with high estrogen levels, abnormal apoptosis and cell proliferation, gene mutation, inflammation, endometrial cell oxidative stress, etc. [6].

One possible etiological factor of EPs is microbial factor, both associated [7] and not associated [8] with chronic endometritis (CE). The research conclusions about the composition of uterine cavity microbiota associated with EP are different, which is largely associated with the complexity of sample collection without contamination from the lower reproductive tract. It has been found that alteration of intrauterine micrbiota composition relative to healthy women results mainly from the increase in the rate of detecting vaginal bacteria (such as *Lactobacillus*, *Bifidobacterium*) [9, 10]. This can contribute to migration

and proliferation of cells, thereby causing local endometrial hyperplasia and the emergence of EPs [11].

Endometrial polyps play an important role in disturbance of female reproductive function [12] and deterioration of women's quality of life [13]. High risk of EP recurrence leads to repeated surgical interventions increasing the risk of intrauterine adhesions and infertility [14]. In this regard, the studies focused on identification of the causes of EP development and recurrence, as well as on the efficacy of the associated etiologically targeted therapy and EP prevention are of high relevance. For this purpose, the study to assess microbiota of the uterine cavity in patients with endometrial polyps was conducted.

METHODS

A prospective study conducted in 2022–2024 at the Kulakov National Medical Research Center for Obstetrics, Gynecology and Perinatology involved 84 patients with the histologically confirmed endometrial polyps and 44 patients of the comparison group having no endometrial abnormality. Inclusion criteria: age from 18 years to the onset of menopause; informed consent to enrollment; presence of the histologically confirmed endometrial polyp for inclusion in the index group and no endometrial abnormality for inclusion in the comparison group. Exclusion criteria: cancer; stage 3–4 endometriosis/adenomyosis; submucosal uterine fibroid or intramural fibroid showing centripetal growth; acute or chronic inflammatory disorder; infectious disease; antibacterial or hormone drug intake within 3 months before inclusion in the study. The comparison group included patients with suspected endometrial abnormalities based on the pelvic ultrasound data, but having no endometrial pathology following the histology assessment data (proliferation stage according to histology report).

All the patients were assessed in accordance with the Endometrial Polyps clinical guidelines before admission to the hospital. Since there is a correlation between the menstrual cycle phase and microbial composition of the endometrium [15–18], biomaterial was collected in phase 1 of menstrual cycle.

To assess microbiota of the cervical canal before hysteroscopy, we collected the cervical canal content with a sterile Dacron swab to the test tube with the Amies transport medium (Copan, Italy). To reduce contamination of the uterine cavity contents with microflora of lower genitalia, various loci were sequentially treated with antiseptic: first, a sterile swab was used to remove mucus from the cervix, and the cervix was cleansed with a topical antiseptic containing octenidine 0.1% and phenoxyethanol 2%; after collecting the cervical discharge for further testing, the cervical canal was twice inundated using a bacteriological swab soaked with antiseptic with an interval of 5 min. The hysteroscope operating sheath was inserted transcervically through the internal orifice into the uterine cavity without prior cervical canal dilation. Surgical forceps were inserted into the vagina/cervix, biomaterial was collected at the first attempt. Then biospecimens were taken out of forceps, put in a sterile disposable container, and delivered to the laboratory.

To isolate facultative anaerobic microorganisms, a set of universal and selective media was used: Columbia agar, chocolate agar, mannitol salt agar (Conda, Spain), Endo's medium and Sabouraud agar (State Research Center for Applied Microbiology and Biotechnology; Obolensk, Russia). Lactobacilli were cultured in the Lactobacagar growth medium (State Research Center for Applied Microbiology and Biotechnology; Obolensk, Russia), obligate anaerobes in the pre-reduced Schaedler agar (Conda, Spain) with essential supplementation and the Anaerob Basal Agar (Oxoid, UK). Obligate anaerobes were grown in the anaerobic box (Whitley DG 250 Anaerobic Workstation, UK) in the atmosphere representing a 3-component gas mixture (80% N2; 10% CO_2; 10% H_2) for 48 h. Species were identified by time-of-flight mass spectrometry (MALDI-TOF MS) in the MicroFlex mass spectrometer with the MALDI BioTyper v. 5.0 software (Bruker Daltonics, Germany).

The Originlab Pro 2021 (version 9.8.0.200, OriginLab Corporation, USA) and Statistica 10 (USA) software packages were used for statistical analysis of the data obtained and for visualization. We also used the Kolmogorov–Smirnov test to assess the normality of distribution. The normally distributed data were presented as mean ± standard deviation (SD), and comparison was performed using the Student's *t*-test. In other cases, the median with interquartile range (Me (Q25–Q75)) and the Mann–Whitney *U* test were used. Proportions (%) were calculated when assessing qualitative data. The χ^2 test helped us to compare categorical data and estimate significance of differences. Spearman's rank correlation coefficient was calculated to estimate correlations between the variables. OR with the 95% confidence interval (95% CI) was determined to compare binary data. The Margalef and Menhinick indices were applied to calculate species richness, and taxonomic diversity was calculated using the Simpson and Shannon indices (Table 1). The differences between statistical values were considered significant at $p < 0.05$.

RESULTS

The median age of patients in two groups was 37 years, i.e. half of patients were of late fertile age. The average body mass index (BMI) was 21.7 kg/m2, 19% of patients were overweight or obese. The analysis of clinical and medical history data showed that there were no significant differences in basic clinical and medical history data between patients of two groups (Table 2). Patients with EPs three times more often used intrauterine contraceptive devices (IUCD) ($p = 0.25$). A total of 39% of patients with EPs already had the history of polypectomia against the lack of such surgical history in the comparison group ($p < 0.001$).

Patients with EPs were more commonly presented with meno-/merorrhagia and infertility than the patients in the comparison group (Table 3). The fact of having menorrhagia was directly related to the polyp size ($r = 0.22$; $p = 0.04$). Other complaints were not correlated to the polyp size, number or location inside the uterine cavity. Infertility was correlated to the history of polypectomia: among 42 infertile patients polypectomia was performed in 17 individuals (40.5%), while among patients having no infertility only 16 (18.6%) underwent polypectomia ($p = 0.007$).

Investigation of the cervical canal microbiota revealed microflora growth in all the patients included in the study. A total of 49 species of microorganisms were identified: 41 species in the EP group, 28 species in the group without EPs. There were no significant differences in the species and taxonomic diversity in two groups, but it was higher in the EP group: the median Margalef index with interquartile range was 0.39 (0.19–0.39) in the EP group, 0.22 (0.22–0.45) in the group without EP, while that of Menhinick index were 0.31 (0.15–0.79) and 0.19 (0.19–0.21), of Simpson index 0.56 (0.5–0.66) and 0.5 (0.48–0.66), of Shannon index 0.95 (0.69–1.58) and 0.69 (0.66–1.39), respectively. Microorganisms of the genus *Lactobacillus* were most often identified (in 82.8% of patients), microorganisms of the genera *Streptococcus* (in 18.7% of patients) and

Table 1. Formulae for the species richness and diversity indices

Richness or diversity index	Formula
Margalef index	$d = (s - 1) / \ln N$
Menhinick index	$d_M = (s - 1) / (N)^{1/2}$
Simpson index	$\sum_{i=1}^{S} p_i^2$
Shannon index	$-\sum_{i=1}^{S} p_i \times \ln p_i$

Note: *S* — species richness (number of species); *N* — sample size (community size); n_i — number of species i bacteria; *c* — number of species common for two communities; a — number of species in the first community; *b* — number of species in the second community.

Gardnerella (in 14.8% of patients) ranked second (Fig. 1). When comparing colonization of individual microorganisms, no significant intergroup differences were revealed ($p > 0.05$). Each vertical line represents microbiota of one woman, each cell represents bacterial content of the cervical canal in lg CFU/mL.

When assessing composition of intrauterine microbiota, microflora growth was reported in 52 patients out of 128: in 40 patients of the group with EPs (47.6%) and 12 patients of the comparison group (27.3%) ($p = 0.026$). OR of detecting uterine microbial colonization in cases of EP relative to women without endometrial abnormality was 2.4 (95% CI — 1.1; 5.5). A total of 23 microbial species were isolated, which suggests more scarce species diversity of intrauterine microbiota compared to that of the cervical canal: 20 species of 9 genera in the group with EPs, 10 species of 8 genera in the group without EPs.

When comparing microbial colonization of the cervical canal and the uterine cavity, significant weak correlations ($r = 0.2–0.4$) were revealed for 10 microorganisms out of 53 (18.8%) in 24 patients. In more than a half of observations, no match between microbiota of the cervical canal and the uterine cavity was revealed.

The species and taxonomic diversity of intrauterine microbiota showed no significant differences in two groups, despite the fact that it was higher in the EP group: the median Shannon index with interquartile range was 1.98 (1.98–1.98) and 0.69 (0.67–0.69) in the groups, respectively (Fig. 2).

In the EP group, the genus *Staphylococcus* were the most frequently observed microorganisms (in 50% of patients), with the genus *Lactobacillus* in the second place (in 37.5% of patients). In the group without EPs, in contrast, microorganisms of the genus *Lactobacillus prevailed* (in 41.7% of patients), microorganisms of the genus *Staphylococcus* ranked second (in 25% of patients) (Fig. 3).

Comparison of the uterine cavity colonization with distinct microorganisms revealed differences in the form of more prominent colonization with *Lactobacillus* crispatus and

Table 2. Clinical and medical history characteristics of patients

Parameter	Group 1, *n* = 84	Group 2, *n* = 44	*P*-value
Age, years *	38.5 (32–42)	35.5 (31.5–40.5)	0.43
BMI, kg/m² *	21.7 (19.5–24.2)	21.8 (19.8–23.7)	0.98
BMI ≥ 25 kg/m² **	18 (21.4%)	6 (13.6%)	0.28
Smoking **	14 (16.7%)	10 (22.7%)	0.28
Menstrual cycle length, days *	28 (28–30)	28 (27–29)	0.23
Menstruation duration, days *	5 (5–7)	5 (5–6)	0.13
Gravidity ***	1 (0–6)	1 (0–6)	0.21
Parity ***	0 (0–3)	1 (0–3)	0.89
History of taking COCs **	26 (31%)	11 (25%)	0.48
History of using IUCD **	6 (7.1%)	1 (2.3%)	0.25
Endometriosis **	15 (17.8%)	9 (20.4%)	0.72
Adenomyosis **	15 (17.8%)	5 (11.4%)	0.33
Fibroid**	28 (33.3%)	14 (31.8%)	0.86
History of polypectomia **	33 (39.3%)	0	< 0.001

Note: * — Me (Q25–Q75); *** — Me (min–max), Mann–Whitney *U* test; ** — abs (%), χ^2 test; COCs — combined oral contraceptoves; GIT — gastrointestinal tract.

Table 3. Patient complaints

Parameter	Group 1, *n* = 84	Group 2, *n* = 44	*P*-value
Menorrhagia	23 (27.4%)	6 (13.6%)	0.07
Metrorrhagia	37 (44%)	8 (18.2%)	0.003
Intermenstrual bleeding	8 (9.5%)	1 (2.3%)	0.12
Algomenorrhea	2 (2.4%)	6 (13.6%)	0.01
Chronic pelvic pain	16 (19%)	8 (18.2%)	0.9
Infertility	31 (36.9%)	11 (25%)	0.17
Miscarriage	17 (20.2%)	6 (13.6%)	0.35

Note: abs (%),χ^2 test.

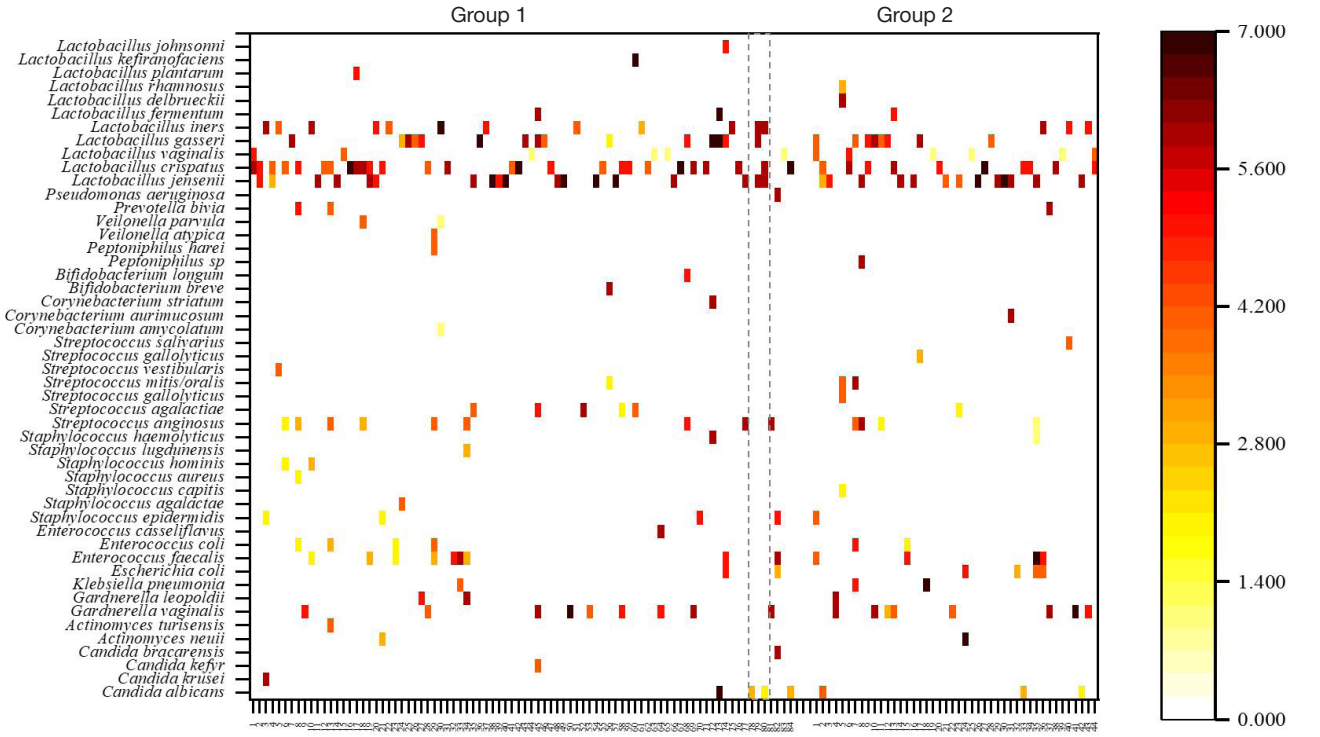

Fig. 1. Cervical canal microbiota in patients with endometrial polyps (group 1) and the comparison group (group 2) (each cell represents bacterial content of the cervical canal in lg CFU/mL)

Staphylococcus hominis, as well as with all *Staphylococcus spp*. in total in the group with EPs ($p < 0.05$).

DISCUSSION

Meno-/metrorrhagia and infertility were the main clinical manifestations in patients with EPs included in the study, which is in line with the available data on the complaints that are most common in this cohort of patients. According to the literature data, abnormal menstrual bleeding is reported in more than a half of patients with EPs [13]. The second most common complaint was infertility, with endometrial polyps represented in 1/3 of cases. Polypectomy increases the probability of getting pregnant [12]. Furthermore, large proportion of patients with recurrent EPs is also notable (39.3% in the studied group).

When studying microbial composition in the uterine cavity, colonization of the uterine cavity with microorganisms was revealed in 40.6% of patients. The literature has already accumulated a sufficient amount of data confirming non-sterility of the uterine cavity both in pathology and in the norm [15, 19–26]. The earlier studies have also shown that the number of bacteria in the endometrial microbiota is reduced 2–4-fold relative to vaginal and cervical microbiota, while bacterial diversity is increased [9, 27–29]. According to our data, the number of bacteria was actually less in the uterine cavity, but its species and taxonomic diversity was also reduced. The analysis of the association of intrauterine and cervical canal microbiota revealed no correlation in more than a half of cases. Thus, it has been confirmed again that endometrial microbiota is not identical to vaginal and cervical microbiota and has its own unique microbial composition. When comparing predominance of *Lactobacillus* in the uterine cavity and cervical canal, the 3 times lower relative abundance of *Lactobacillus* in the endometrium with regard to the cervix was reported, which is in line with the literature data [30, 31].

In our study, comparative analysis of intrauterine microbiota in patients with EPs and no endometrial abnormality was of major scientific interest. A number of studies have shown the importance of uterine microbiota for the development of disorders of female reproductive system, specifically endometrial hyperplasia and adenomyosis [23, 32]. There are sporadic studies of EP. Thus, compared to healthy women, the changes in intrauterine microbiota composition in women with EPs result largely from the increase in the detection rate of vaginal bacteria, such as *Lactobacillus* [9, 10]. In terms of pathogenesis, *Lactobacillus* and *Bifidobacterium* can contribute

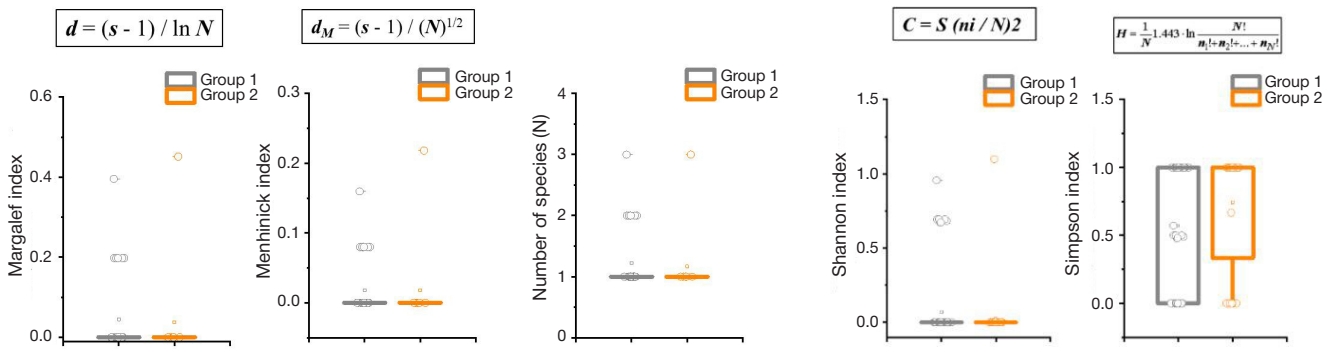

Fig. 2. Species richness and taxonomic diversity indices of intrauterine microbiota in patients of the studied groups

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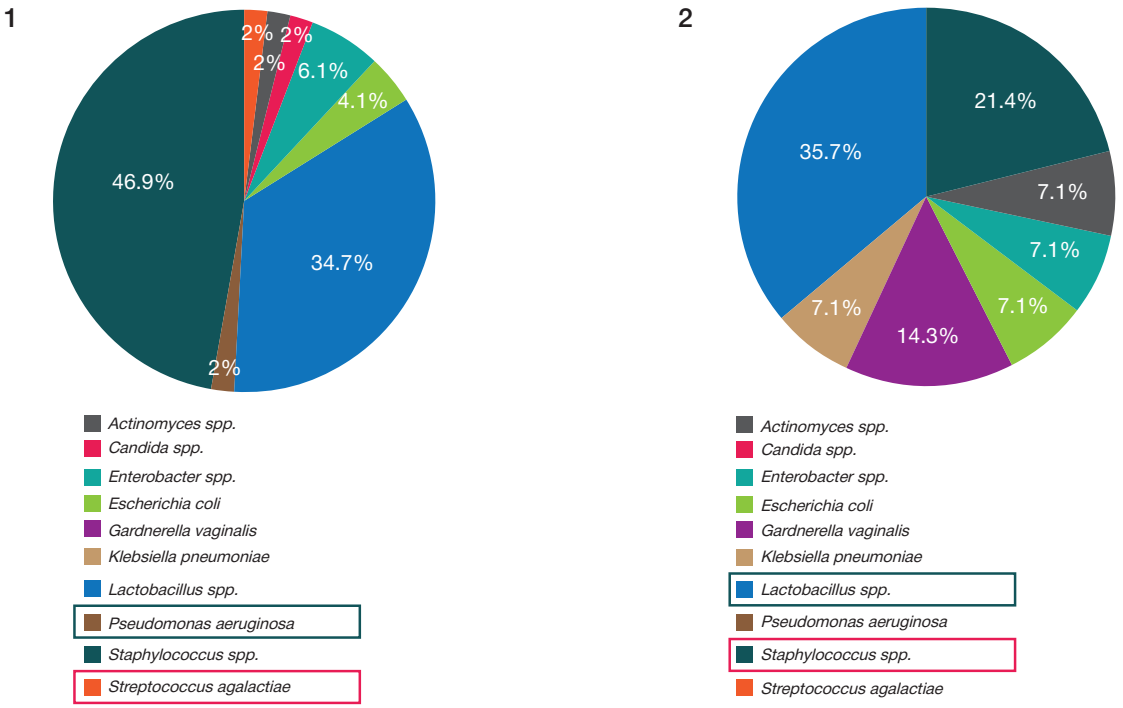

Fig. 3. Species diversity of intrauterine microbiota in patients of the studied groups: 1 — group with EPs, 2 — group without EPs

to cell migration and proliferation, which lead to local endometrial hyperplasia and the emergence of EPs [11]. We have found that microbial growth in the uterine cavity was reported 2.4 times more often in cases of having EPs compared to normal (OR — 2.4; 95% CI — 1.1; 5.5). Species diversity was higher in patients with EPs relative to the comparison group in both cervical canal (24 and 14 species, respectively) and the uterine cavity (10 and 4 species, respectively). In cases of EPs, genus *Staphylococcus* (50%) were found to be predominant species in the uterine cavity, while microorganisms of the genus *Lactobacillus* ranked second (37.5%). In contrast, in the group without EPs, microorganisms of the genus *Lactobacillus prevailed* (41.7%), and microorganisms of the genus *Staphylococcus* were found in the second place (25%).

CONCLUSIONS

In patients with EPs, growth of bacterial microflora in the uterine cavity was observed 2.4 times more often, than in patients without endometrial abnormality. The species spectrum of the uterine cavity in cases of EPs was characterized by higher taxonomic diversity, microorganisms of the genera *Staphylococcus* and *Lactobacillus prevailed*. Since chronic endometritis is one of the causes of the EP development and recurrence, prescription of antibiotic therapy when performing polypectomia in routine clinical practice can reduce the rate of EP recurrence. Thus, further investigation of endometrial micro-ecology can provide new opportunities for improvement of the EP diagnosis and treatment strategies.

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