



Research Article

Comparative Analysis of Cervical Canal Microbiota Structure in Women with Various Obstetric Pathologies

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Abstract | Infection of the urogenital tract of women with various microorganisms can affect the course of pregnancy and fetal development. The aim of the study was to determine the species structure of the cervical canal microbiota and its relationship with the development of pathological processes during pregnancy. The inclusion criteria were patients with the diagnoses of: "Isthmic-cervical insufficiency requiring medical care for the mother", "Bleeding in early pregnancy", "Placental disorders", "Preterm labor", "Postpartum sepsis", "Singleton birth, spontaneous labor". Exclusion criteria were; HIV infection, diabetes mellitus, and thyroid and adrenal diseases. This study involved 2222 patients with various obstetric pathologies, where smears from the cervical canal of all patients were analyzed. Microorganism growth was detected in 1783 samples, while in 439 cases it was not. For cultivation, cultural methods of bacteriological analysis were used. For species identification, the MALDI-TOF mass spectrometry method ("Matrix-assisted laser desorption/ionization time-of-flight mass spectrometer") was used. In the group associated with complications arising during pregnancy, we found a predominant number of 263 strains of *Staphylococcus* spp. (27.6 %) and the smallest percentage was 5 strains of *Enterobacter* spp. (0.53 %). In women diagnosed with "Preterm birth", 404 *Staphylococcus* spp. (36.2 %) and 4 *Enterobacter* spp. (0.4%) were recovered. In women diagnosed with "Singleton birth, spontaneous birth", 305 *Staphylococcus* spp. (32.83 %) and 5 *Enterobacter* spp. (0.54 %) were detected. In women diagnosed with "Postpartum sepsis", 84 *Staphylococcus* spp. (32.9 %) and 3 *Enterobacter* spp. (1.2 %) were obtained. It was observed that the predominant microorganisms in all four groups were *Staphylococcus* spp., in second place - *Enterococcus* spp., in third place - *Lactobacillus* spp., in intermediate position - *Candida* spp., *Escherichia* spp., and *Streptococcus* spp., and the least amount was for - *Enterobacter* spp.

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Introduction

Currently, studying the microbiota of the female urogenital tract is one of the most pressing issues for obstetricians, gynecologists, and microbiologists. The cervicovaginal microbiota is of paramount importance in maintaining the physiological processes occurring in the genital tract, as it is a dynamic microenvironment rich in heterogeneous microorganisms, among which bacteria, fungi, viruses, and protozoa are identified (Dong *et al.*, 2023). In obstetric practice, it is especially important to timely identify clinically significant microorganisms, including *Streptococcus agalactiae* (*S. agalactiae*), *Escherichia coli* (*E. coli*), *Staphylococcus aureus* (*S. aureus*), where these microorganisms affect the course of pregnancy and its outcomes. Numerous studies have been conducted, the results of which have established that detection of these microorganisms in the mother is associated with a high percentage of neonatal infections, development of severe infectious complications, and neonatal mortality. Thus, most cases of fatal outcomes, preterm births, and rupture of fetal membranes are specifically associated with infection by the β -hemolytic streptococci (GBS) (Gonçalves *et al.*, 2022; Liu *et al.*, 2022). When this group of microorganisms is detected, as has already been proven, the risk of developing sepsis, severe neonatal meningitis, and neuronal dysfunctions significantly increases, which may subsequently lead to child disability. For these reasons, it is extremely important to conduct screening and perform biomaterial culture tests in the early stages of pregnancy (Melin *et al.*, 2013; Russell *et al.*, 2017; Viqar *et al.*, 2021).

Collection of biomaterials for studying the microbiota of vagina, cervical canal, and urethra is also an important component of a gynecological examination, as this study allowed the physician to make a more accurate diagnosis and, accordingly, prescribe effective therapy. In laboratory services, the most commonly used methods for identifying microorganisms include microscopic, microbiological culture, and molecular genetics. One of the key aspects in research is the pre-analytical stage, as it is the stage that a number of errors are differentiated, including non-compliance with the rules for preparing subjects, errors made by medical personnel during material collection, transportation of biomaterial, and its storage (Schmidt *et al.*, 2015).

By studying the biomaterials (*i.e.*, cervical canal

discharge), it is possible to determine the genus of the bacteria using microscopic examination, but it is impossible to determine its species, which leads to difficulties in treatment. In addition, it is also considered impossible to assess the sensitivity of microorganisms to antibiotics, and therefore to prescribe antibiotic therapy. For these reasons, microscopic examination is less effective compared to other methods (Tuyakova *et al.*, 2014; Andreevskaya *et al.*, 2020). Polymerase chain reaction (PCR) is a molecular genetic method that has a number of advantages such as specificity, efficiency, and sensitivity. Moreover, it allows determining the sensitivity of microorganisms to antibiotics, based on the detection of genes responsible for antibiotic resistance (Gygax *et al.*, 2007). An equally important advantage of microbiological research is the ability to assess the sensitivity of microorganisms to antibiotics, which, in turn, significantly increases the effectiveness of treatment. In studying the gynecological smears, all the aforementioned methods have high value; however, each of them has its own advantages and disadvantages (Salam *et al.*, 2023).

In the future, the information obtained will allow us to make predictions about the course of pregnancy and its outcomes, and, based on the presented data, we will be able to assess the condition and development of the fetus depending on the isolation of certain microorganisms. The objectives of this study were to examine patients with the most common obstetric pathology diagnoses, assess the structure of the cervicovaginal tract microbiota, and study its impact on the course of pregnancy.

Materials and Methods

Study design

A retrospective microbiological study was conducted between 2018 and 2022, lasting 5 years. The study was conducted at a hospital specializing in obstetrics and gynecology in collaboration with the microbiological laboratory of Samara State Medical University, Russia. It included two thousand twenty-two women, whose pregnancies were accompanied by disruptions in normal physiological processes, putting them at serious risk of developing complications. The examined patients were divided into four groups. The first group included isthmio-cervical insufficiency requiring maternal medical care, bleeding in early pregnancy, and placental disorders. The second group included preterm labor and delivery. The third group

involved singleton delivery, spontaneous delivery, which included clinically healthy women considered as the control group, while the fourth group involved postpartum sepsis patients. Subsequently, the results of the microbiological study were analyzed based on the type of group.

Samples collection

Two thousand twenty two smears of cervical canal discharge were taken from patients by an obstetrician-gynecologist using a swab probe, which was placed in a transport tube containing Ames medium and delivered to the laboratory within 2 hours.

Cultivation of microorganisms

In the microbiology laboratory, each material was inoculated individually onto nutrient agar (NA) and MacConkey agar media (Condalab, Spain), which were intended for the preliminary identification of the microorganisms most commonly detected in the urogenital tract and causing urinary tract infections. 5 % blood agar with defibrinated sheep blood (HiMedia, India) allowed for growth of microorganisms with special cultivation conditions, as well as bacteria with hemolytic activity. Sabouraud agar (HiMedia, India) was used as a selective medium that allowed for detection of growth of yeasts and mold fungi. The inoculated plates were incubated for 48 h at 37 °C. A CO₂ incubator was used to create microaerophilic conditions, preferable for cultivating *Lactobacillus* and *Enterococcus* spp. (Kim *et al.*, 2022; Chudzicka-Strugała *et al.*, 2024).

Microbial species identification

The species identification of the grown isolates was carried out using the MALDI-ToF (Matrix Assisted Laser Desorption/Ionization-Time of Flight) mass spectrometry assay with the Microflex LT device (Bruker Daltonik GmbH, Germany). Every type of colonies growing on nutrient media was applied with a tip to the target of the device and subsequently covered with a mixture in the form of α -cyano-4-hydroxycinnamic acid. Afterward, the target was placed in the device, where the bacterial cells were subjected to multiple laser pulse exposures. As a result of this process, the release of ionized ribosomal proteins of the microorganisms occurred, which entered the time of flight analyzer and moved to the detector. The time-of-flight of the particles was evaluated using the instrument's software, which converted the obtained information into a molecular

mass spectrum corresponding to the mass to charge ratio of the particles in the range from 2000 Da to 20000 Da. The mass spectra obtained during the identification process were compared to a library that represented a database with reference spectra. Based on the similarity of proteins and their mass, species identification of the microorganism was achieved. The protein profiles were analyzed using flexAnalysis 3.0 software (Bruker Daltonik GmbH, Germany). A Centroid peak detection algorithm was used to evaluate the obtained mass spectra. The reliability of the identification was determined by using MALDI Biotyper RTC software by calculating the score; if the obtained score was in the range of 0.000 to 1.699, the identification result was considered unreliable; a score from 1.700 to 1.999 indicated high reliability of identification to the genus level; a score from 2.000 to 2.999 was considered highly reliable for species identification. The signal-to-noise threshold was set at level 2. The relative intensity threshold was 0 %, the minimum threshold intensity was 600 arbitrary units, while the maximum number of analyzed peaks was 300. The TopHat method was used to calculate the baseline, and spectrum smoothing was performed using the Savitzky-Golay algorithm with a mass of 5 m/z per cycle. Visualization of the results of statistical proteomic comparison of the obtained mass spectra was carried out using MALDI Biotyper 3.0 Offline Classification software (Bruker Daltonik GmbH, Germany). During this study, the analysis of mass spectra was in accordance with the official recommendations of the manufacturer of the MALDI-ToF mass spectrometer Microflex LT (Bruker Daltonik GmbH, Germany) (Chen *et al.*, 2015, 2023).

Statistical analysis

A statistical analysis was performed using the Pearson's chi-squared test. Statistical processing of the obtained data was carried out using Microsoft Office Excel 2007. The assessment of the microbiota structure included calculation of the frequency of occurrence of the genus and species affiliation of bacteria and fungi. Numerical results were presented as derivatives and absolute numbers. The results obtained are displayed in the form of diagrams.

Results

General information

Out of the two thousand twenty two swab cultures,

microbial growth was detected in 80.2 % of samples, while no growth was observed in 19.8%. A total of 3253 microorganisms were isolated and identified, represented by the following genera: 1056 isolates of *Staphylococcus* spp. (32.5 %), 709 *Enterococcus* spp. (21.8 %), 554 *Lactobacillus* spp. (17.03 %), 400 *Candida* spp. (12.3 %), 351 *Escherichia* spp. (10.8 %), 166 *Streptococcus* spp. (5.10 %), and 17 *Enterobacter* spp. (0.52 %). The structure of microorganisms isolated during the study period is presented in Figure 1.

Next, the results of microbiological studies were analyzed independently in each group. In the group associated with complications occurring during pregnancy, 953 microorganisms of various genera

were detected in the discharge from the cervical canal, among which the predominant representatives were 263 isolates of *Staphylococcus* spp. (27.6 %). Additionally, 228 isolates of *Lactobacillus* spp. (23.93 %) were identified as the main symbionts of the cervico-vaginal microbiota. At the same time, 166 isolates of *Enterococcus* spp. (17.42 %) were isolated, with the most frequently encountered species being *E. faecalis* and *E. faecium*. Additionally, 148 isolates of *Candida* spp. (15.53 %) were obtained. A total of 96 isolates of *Escherichia* spp. (10.1 %) and 47 isolates of *Streptococcus* spp. (4.9 %) were detected, among which β -hemolytic streptococci plays a primary role. A minimal identified 5 isolates of *Enterobacter* spp. (0.53 %) were recovered.

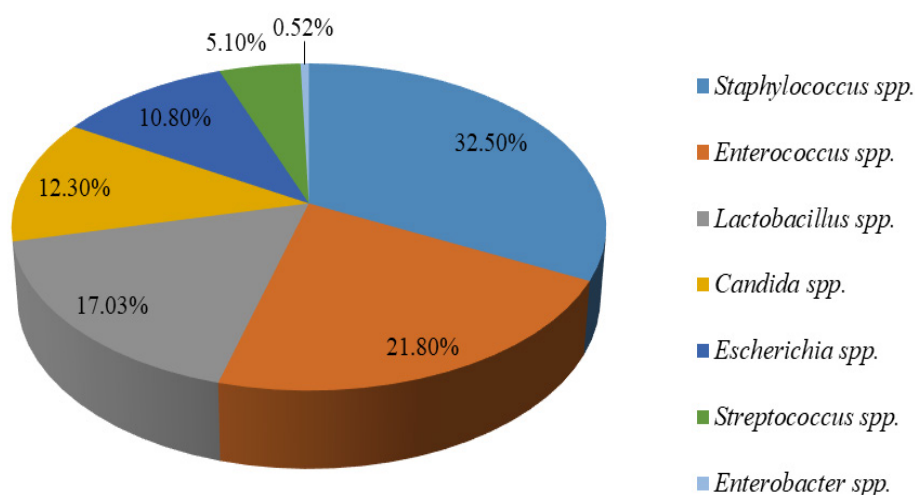


Figure 1: Structure of the cervical canal microbiota detected in women with various obstetric pathologies over a five-year study period (2018 - 2022).

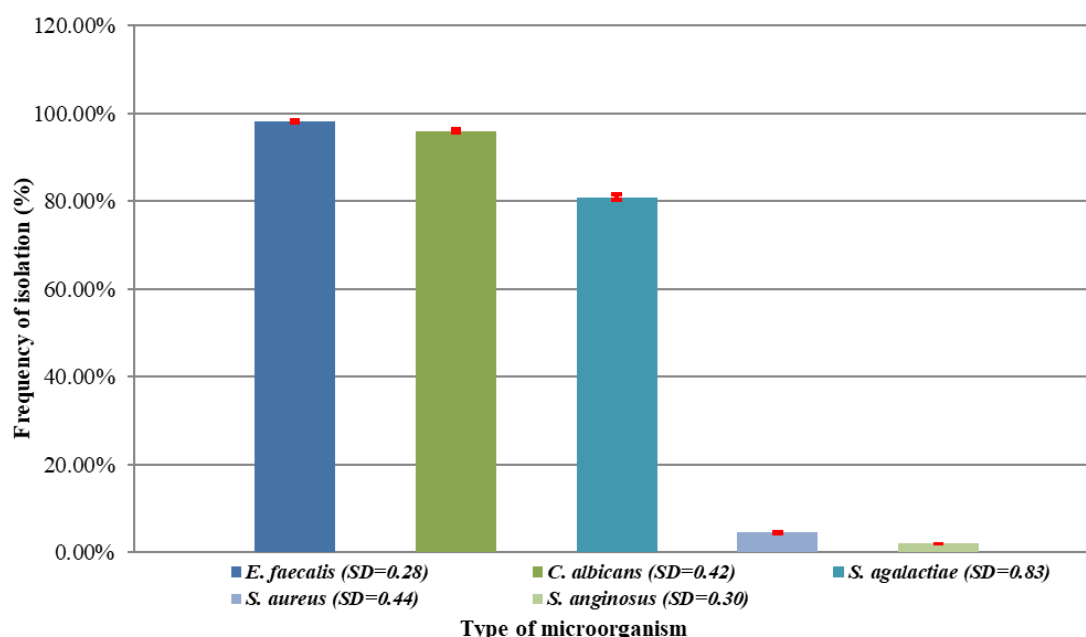


Figure 2: The species, bleeding in early pregnancy, and placental disorders. Red bars represent standard deviation ($\pm$ SD).

Bleeding in early pregnancy

In women diagnosed with “Bleeding in early pregnancy”, the percentage of *Streptococcus agalactiae* was 82.35 % of the total *Streptococcus* spp., and the share of *S. aureus* was 3.51 %. In women diagnosed with “Isthmic-cervical insufficiency”, the percentage of *Streptococcus agalactiae* was 33.33 % of the total *Streptococcus* spp., while the share of *S. aureus* was 5.88 %. In patients diagnosed with “Placental disorders”, *Streptococcus agalactiae* constituted 90 %, and the share of *S. aureus* was 7.32 %. The species structure of microorganisms identified in this category is presented in Figure 2.

Preterm labor and delivery

In the second category, we selected a cohort of women, including 553 individuals diagnosed with “Preterm labor and delivery”, in whom, 1,116 microorganisms were found on the mucous membrane of the cervical canal. 404 isolates of *Staphylococcus* spp. were identified in a prevailing amount (36.2 %), with the species diversity of *Staphylococcus* spp. in this group being more limited compared to the first cohort. The percentage of *Staphylococcus aureus* was 7.32 %, which significantly exceeds the frequency of detection of similar microorganisms in women diagnosed with “Isthmic-cervical insufficiency requiring medical care for the mother” and “Bleeding in early pregnancy”.

Among which, the largest percentage was 213 isolates of *S. haemolyticus* (39.23 %) and 156 isolates of *S. epidermidis* (28.73 %). We also identified 234 isolates of *Enterococcus* spp. (21 %), with *E. faecalis* being the predominant representative. The symbiotic flora of the cervical microbiota consisted of 170 isolates of *Lactobacillus* spp. (15.23 %), which is significantly lower in number compared to the previously mentioned genera. A total of 136 isolates of *Candida* spp. were isolated (12.2 %) and in a practically equivalent amount with a difference of only 2.16 %. 112 isolates of *Escherichia* spp. (10.04 %) were found. 56 isolates of *Streptococcus* spp. (5.02 %) were identified, with more than half of these representatives being β -hemolytic streptococci, the majority of which were *S. agalactiae* and to a significantly lesser extent *S. anginosus*. In the cohort of examined women with the diagnosis of “Placental disorders”, the percentage of *S. agalactiae* detection was 90 % out of the total *Streptococcus* spp. It is worth noting that the smallest proportion was found to be 4 isolates of *Enterobacter* spp. (0.4 %). In women diagnosed with “Preterm labor and delivery”, the percentage of *S. agalactiae* was 60.81 % of the total *Streptococcus* spp., and the share of *S. aureus* was 6.10 %. The species diversity of microorganisms isolated from women diagnosed with “Preterm labor and delivery” is presented in Figure 3.

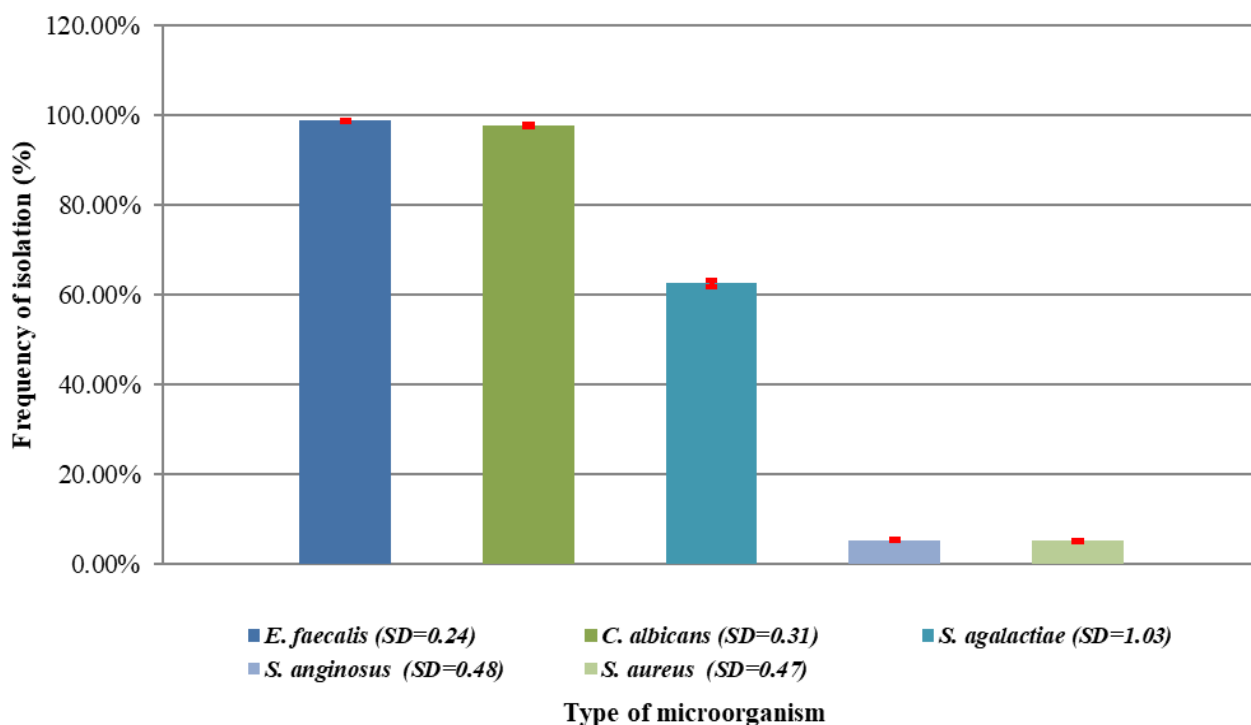


Figure 3: The species abundance of pathogenic microorganisms, prevailing in their genus and isolated from women diagnosed with preterm labor and delivery. Red bars represent standard deviation ($\pm$ SD).

Singleton and spontaneous delivery

In this retrospective study, we selected 492 women to study the nature of changes in the cervical canal microbiota in the presence of the diagnosis “Singleton delivery, spontaneous delivery”, in which, 929 microorganisms were identified, and again 305 isolates of *Staphylococcus* spp. (32.83 %) were identified in a predominant amount. Furthermore, it is noted that the activity of *Staphylococcus* spp. may be associated with the occurrence of cystitis and urethritis. A total of 232 isolates of *Enterococcus* spp. were identified (25 %). At the same time, the symbiotic flora consisted of 147 isolates of *Lactobacillus* spp. (15.82 %). In addition, 109 isolates of *Candida* spp. (11.73 %), 89 isolates of *Escherichia* spp. (9.6 %), and 42 isolates of *Streptococcus* spp. (4.52 %) were detected with significant species heterogeneity, among which the conditionally pathogenic flora was less pronounced. Less numerous species diversity was observed in *Enterobacter* spp. (0.54 %), among which only 5 isolates were isolated. In women diagnosed with “Single spontaneous delivery”, the percentage of *S. agalactiae* was 54.80 % of the total *Streptococcus* spp., and the share of *S. aureus* was 4.6 %. The species structure of microorganisms isolated from women diagnosed with “single fetus delivery, spontaneous delivery” is presented in Figure 4.

Postpartum sepsis

The greatest interest is in the fourth group diagnosed

with “Postpartum sepsis. The number of women studied with this pathology was 158, and 255 microorganisms were isolated from the mucous membranes of the cervical canal, among which the predominant representatives were 84 isolates of *Staphylococcus* spp. (32.9 %) and 77 isolates of *Enterococcus* spp. (30.2 %). However, in women diagnosed with “Postpartum sepsis”, the frequency of *S. aureus* occurrence was 27.3 %, which was 4-6 times higher compared to the other cohorts. 54 isolates of *Escherichia* spp. (21.2 %) and 21 isolates of *Streptococcus* spp. (8.24 %) were detected, of which 81 % were β -hemolytic streptococci. In this cohort, the amount of symbiotic flora was sharply reduced and amounted to only 9 isolates of *Lactobacillus* spp. (3.53 %), which indicates a high degree of colonization of the cervical canal by the pathogenic microorganisms. In the studied biomaterial, 7 isolates of *Candida* spp. (2.8 %) and 3 isolates of *Enterobacter* spp. (1.2 %) were identified. In women diagnosed with “Postpartum sepsis”, the percentage of *S. agalactiae* was 66.70 % of the total *Streptococcus* spp., and the share of *S. aureus* was 27.38 %. The species structure of the qualitative and quantitative composition of the cervical canal microbiota isolated from women diagnosed with “Postpartum sepsis” is presented in Figure 5.

The species diversity of the genus *Lactobacillus* spp. is presented in Figure 6.

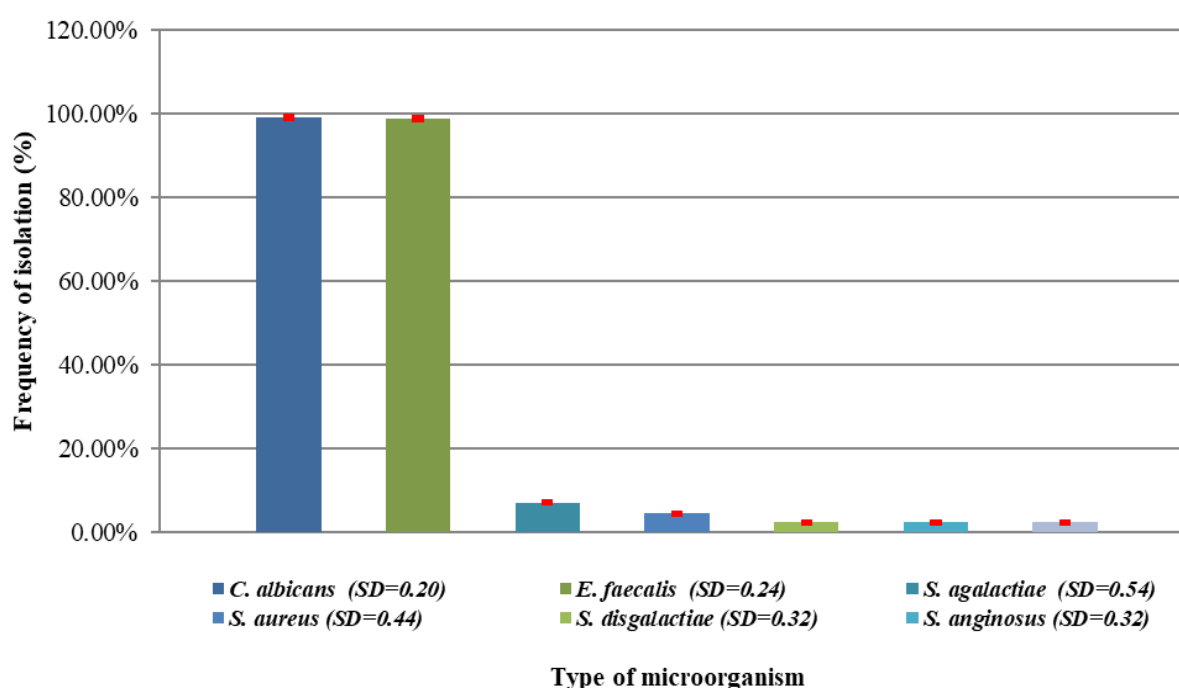


Figure 4: Species diversity of microorganisms prevailing in women diagnosed with single fetus deliver and spontaneous delivery. Red bars represent standard deviation ($\pm$ SD).

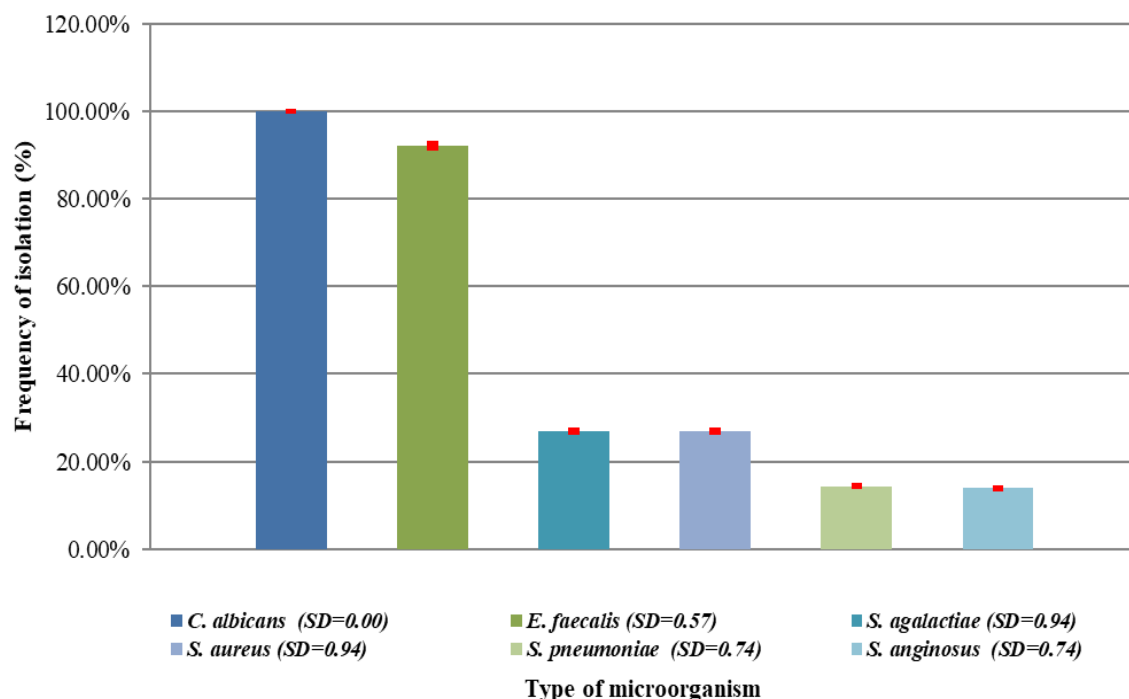


Figure 5: Species structure of the mucosal microbiota of the cervical canal in women diagnosed with postpartum sepsis. Red bars represent standard deviation ($\pm$ SD).

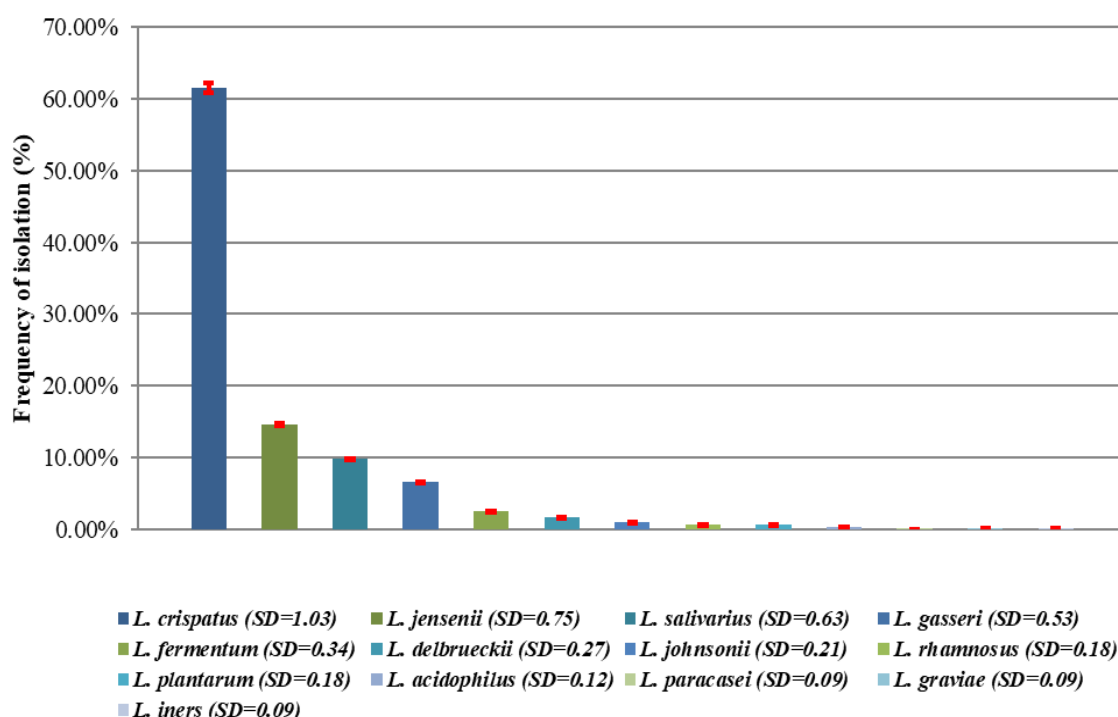


Figure 6: Species biodiversity of the symbiotic microbiota of the genus *Lactobacillus* spp. isolated from the cervical canal of women with different diagnoses. Red bars represent standard deviation ($\pm$ SD).

Discussion

In the practical part of this research work, we used a highly sensitive research method that allowed for the isolation of even a small number of microorganisms contained in the biomaterial. The specificity of this method was based on the use of selective nutrient

media to ensure the growth of microorganisms in accordance with their biological needs and metabolic activity. Identification of the bacteria and fungi was carried out using the highly informative MALDI-TOF mass spectrometry method, which is the “gold standard” that allows for the determination of the protein profile of microorganisms; ensuring reliable

identification of the species structure of bacteria and fungi in a short time. The results of this study largely depended on a pre-analytical stage of the study: collection, transportation, and storage duration of the biomaterial. Another limitation is the duration of classical cultivation, which took 48 h. The MALDI-TOF mass spectrometry method has become the “gold standard” in many countries; however, it remains inaccessible due to being expensive equipment. The obtained results allowed us to trace the relationship between the dominant microbiota of women and obstetric pathologies, which can be used in practice to predict the course of pregnancy. It is also worth noting how important it is to maintain communication between the microbiologist and the obstetrician-gynecologist, as competent interpretation of microbiological study results allows for prescription of effective therapy and significantly improves the condition of the patients.

In this study, the cohort of women was divided into four groups: patients with complications occurring during pregnancy, patients with a history of pathological preliminary period, patients with a normal course of pregnancy, and patients with sepsis. But the greatest interest is in the fourth group diagnosed with “Postpartum sepsis”, due to the fact that the number of pathogens causing severe urogenital infections significantly exceeds the number of symbiotic bacteria. In each of these groups, *Staphylococcus* spp. were predominantly isolated, among which *S. epidermidis* and *S. haemolyticus* were most frequently identified. Representatives of this genus belong to the conditionally pathogenic flora that is normally present in smears taken from the vagina and cervical canal. In the case of the development of immunodeficiency states and decreased body reactivity, the conditionally pathogenic flora becomes pathogenic. In 2018, a study was conducted at the Research Institute of Obstetrics, Gynecology, and Reproductology, which found that women with a history of early preterm births and had a high risk of pregnancy loss had a microbiota that was more associated with the order Enterobacterales, including *Staphylococcus* spp. and *Streptococcus* spp. (Sinyakova *et al.*, 2018). In this study, women diagnosed with “Preterm labor and delivery” had 404 isolates of *Staphylococcus* spp. (36.2 %) that were also isolated in a prevailing amount, among which the largest percentage was 213 isolates of *S. haemolyticus* (39.23 %) and 156 isolates of *S. epidermidis* (28.73%).

Among the order Enterobacterales, 112 isolates of *Escherichia* spp. (10.04 %) were most frequently isolated, in addition to 56 isolates of *Streptococcus* spp. (5.02 %), which correlates with a previously obtained data (Golińska *et al.*, 2023). The negative impact on the pregnancy course by conditionally pathogenic microorganisms begins to manifest actively in cases of reduced vaginal symbionts, *i.e.*, *Lactobacillus* spp., which is accompanied by a significant increase in vaginal pH and rapid colonization of the mucous membrane of the urogenital tract by the conditionally pathogenic and non-pathogenic microorganisms (Krawczyk *et al.*, 2021). Subsequently, the bacteria overcome the placental barrier and have entered the fetal membranes, infecting them and causing the development of chorioamnionitis, which later has threatened the pregnancy termination (Bianchi-Jassir *et al.*, 2017). In women diagnosed with “Singleton delivery, spontaneous delivery”, similar microorganisms were isolated in predominant quantities: 305 isolates of *Staphylococcus* spp. (32.83 %), 89 isolates of *Escherichia* spp. (9.6 %), and 42 isolates of *Streptococcus* spp. (4.52 %), but the pregnancy proceeded without the risk of associated complications, which raises a controversial question about the clinical importance and significance of the role of *Staphylococcus* spp. in obstetric and gynecological practice. According to the obtained results of the “Belgorod State National Research University”, in women whose postpartum period was complicated by the development of endometritis, *S. epidermidis* was isolated twice as often compared to the control group (Brown *et al.*, 2019). Thus, at different time intervals, the fundamental significance of *Staphylococcus* spp. has been repeatedly proven empirically both in pregnancy outcomes and postpartum period. Having analyzed the microbiota of the vagina in women with the previously mentioned diagnoses, we found that *Staphylococcus* spp. was detected somewhat more frequently compared to *Streptococcus* spp., and this genus of bacteria is of a particular clinical interest (Bodaszevska *et al.*, 2010; Rosini and Margarit, 2015). The most frequently isolated microorganism among *Streptococcus* spp. was *S. agalactiae*. This bacterial sp. is a β -hemolytic (GBS), and catalase-negative facultative anaerobe. Numerous studies have been conducted on the relationship between GBS colonization of the mucous membranes of the urogenital tract and its impact on the course of pregnancy (Armistead *et al.*, 2019; Raabe and Shane, 2019; Yuan *et al.*, 2021). Thus, according to the results of our study, 45 isolates of *S. agalactiae* were isolated

from women diagnosed with “Preterm labor and delivery”, which constituted 60.81 % of all the isolated *Streptococcus* spp. Possible pathogenetic mechanisms are closely related to changes in the microbiological landscape of the vaginal microbiota and the rapidly developing ascending infection through the cervix, which subsequently leads to the infection of the fetal and decidual membranes (Olmos-Ortiz *et al.*, 2022; Liu *et al.*, 2023). Once inside, GBS begin to actively produce proteases contained in membrane vesicles, which lead to collagen degradation, destruction of the cellular framework, and the extracellular matrix of the fetal membranes. In addition, the inflammatory process is activated with the synthesis of cytokines and prostaglandins, as a result of which the uterus begins to contract actively, which may lead to premature birth, rupture of the fetal membranes, and subsequent spread of infection through the bloodstream of the mother and child, increasing the risk of developing sepsis (Yamamoto *et al.*, 2005; Valkenburg-van den Berg *et al.*, 2009). Timely detection of *S. agalactiae* is of high value in obstetric and gynecological practice, as this pathogen, colonizing the mucous membrane of the vagina, does not cause clinical symptoms, which complicates the timely identification of this microorganism (Coggins *et al.*, 2024). *S. agalactiae* progressively modifies, leading to the development of new highly virulent adaptation mechanisms that enhance the survival of microbial strains in the human body. Thus, bacteria with the adhesin *HvgA* and laminin-binding protein (*lmb*) on their surface pose the greatest danger, as they can attach to endothelial cells of the vessels involved in the formation of the blood-brain barrier (BBB), thereby increasing the risk of *S. agalactiae* penetrating the brain's vessels, which subsequently provokes the development of meningitis (Landwehr-Kenzel *et al.*, 2014). GBS also produces a hemolytic pigment, which poses the greatest danger to the fetus, as it reduces the barrier function of the amniotic epithelium and the placental barrier (Armistead *et al.*, 2021). By penetrating the amniotic fluid and infecting it, the likelihood of bacterial invasion into the lungs as a result of aspiration increases, which may subsequently lead to the development of pneumonia (Sharma *et al.*, 2013). *Enterococcus* spp. are Gram (+) aerobic cocci that colonize the digestive tract (Daca *et al.*, 2024). The most common representatives of *Enterococcus* spp. are *E. faecalis* and *E. faecium*, which are commensal microorganisms of the intestinal microbiota (Golob *et al.*, 2019). *Enterococcus* spp. are closely associated

with several processes occurring in the intestinal microbiome, as they contribute to activation of cellular and humoral immunity, modulate the immune response, and participate in maintaining intestinal homeostasis, through stabilizing the pH environment, synthesizing vitamins, and suppressing the active reproduction of putrefactive bacteria (Madani *et al.*, 2024). However, when the barrier function of the intestinal mucosa is weakened, *E. faecalis* and *E. faecium* are capable of migrating into the bloodstream, causing the development of bacteremia, which can subsequently lead to infection of other organs and tissues, thereby increasing the risk of serious complications. Most often, *Enterococcus* spp. colonize the epithelium of the mucous membranes of the urinary tract and vagina, entering these tissues with the bloodstream, in addition to the anatomical features of the female urogenital system (Banla *et al.*, 2019). According to the obtained results of this study, the percentage of *Enterococcus* spp. was 21.80 % and *Lactobacillus* spp. was 17.03 %. The presence of *Enterococcus* spp. in the biomaterial of the subjects may often indicate existing inflammatory processes in the genitourinary tract. Among the symbionts of the internal environment, *Lactobacillus* spp. play a key role via colonizing the epithelium of the vagina through the interaction between the surface charges of the host cells and the bacteria. The adhesion process of *Lactobacillus* spp. to the epithelial cells correlates with the level of estrogen in the blood (Tachedjian *et al.*, 2017). Deviation of this indicator from the normal causes a change in the charge of the host cells and modification of the properties of the bacteria, which, in turn, affects the composition of the microflora and, consequently, the pH levels (Redondo-Lopez *et al.*, 1990). It should be noted that a significant feature of these bacteria is their ability to metabolize cellular glycogen into glucose, and then into lactic acid, thereby maintaining the optimal acidity of the vagina, which is within the pH range of 3.5-4.5 (Stojanović *et al.*, 2012; Chee *et al.*, 2020). Also, *Lactobacillus* spp. are capable of producing hydrogen peroxide and bacteriocins, which by their biochemical nature are thermostable proteins capable of exerting a destructive effect on the cytoplasmic membrane of both Gram (+) and Gram (-) bacteria, as well as breaking down the murein, which is part of their cell wall (Ocaña *et al.*, 1999; Gaspar *et al.*, 2018). *Lactobacillus* spp. play a significant role in preventing colonization of the vaginal mucosa by the pathogenic microorganisms and in maintaining the normal microbiological

landscape of the cervico-vaginal tract. At the same time, a decrease in the symbiotic flora represented by *Lactobacillus* spp. may indicate a decrease in the protective properties of the cervical microbiota and an increased likelihood of colonization of the mucous membranes by the pathogenic microorganisms (Liu *et al.*, 2023). Pathogens also suppress activity of the bacteria that produce the main protective substance, *i.e.*, lactic acid, which subsequently significantly alters the pH level and reduces the barrier function of the epithelial mucosa of the vagina (Mendling, 2016; Saraf *et al.*, 2021). The results of several previous studies revealed the ability of *E. coli* and *E. faecalis* not only to form highly structured vaginal biofilms but also to penetrate biofilms formed by *Gardnerella vaginalis* (*G. vaginalis*) (Castro *et al.*, 2016; Reuschel *et al.*, 2020). Such a pathogenicity factor allows *E. coli* and *E. faecalis* to persist in the vagina for a prolonged period and subsequently migrate to the upper sections of the urogenital tract, causing the development of urinary tract infections. In *E. coli*, this is mediated *via* the synthesis of an antigen responsible for inter bacterial interaction, while in *E. faecalis*, it is conducted through the ability to produce a protein by which co-aggregation with other bacteria of the vaginal micro-ecosystem may occur (Javed and Manzoor, 2020; Jahic, 2022). For pregnant women, episodes of significant changes in the microbiological landscape may be fatal, leading to rupture of the fetal membranes, infection of the fetus, and death of the newborn (Brokaw *et al.*, 2021). By analyzing the vaginal microbiota in women whose pregnancies were accompanied by the development of pathological processes and women with a normal gestational period, we observed a significant decrease in the concentration of *Lactobacillus* spp. with a simultaneous increase in the amount of *Enterococcus* spp. This indicates a high degree of dependence on epithelial colonization of the vagina between symbiotic bacteria and uropathogens. In women with normal pregnancy progression, the abundance of *Lactobacillus* spp. was somewhat lower compared to *Enterococcus* spp., but no serious complications were observed during pregnancy or at the postpartum period, suggesting that the pathogenic activity of these bacteria is associated with the presence of urinary tract infections and severe dysbiotic disorders (Sharon *et al.*, 2023).

Conclusions and Recommendations

Upon assessing the microbiological landscape

and comparing it with the diagnosis of patients, it was found that significant changes in the cervical canal microbiota lead to serious consequences and complications for the mother's body. In the future, it would be interesting to conduct multiple studies to compare microbiological results with other obstetric pathologies and identify the effect of cervicovaginal microbiota on the condition of newborns. *E. faecalis*, *C. albicans*, *S. agalactiae*, *S. aureus*, and *S. anginosus* are of fundamental clinical importance. That is why it is extremely important for obstetricians-gynecologists and microbiologists to assess the composition of the cervical canal microbiota in women during gestation. This study involves data that can help the physicians predict the course of pregnancy, and determine the risks and the possible adverse outcomes.

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Novelty Statement

The novelty of the study lies in the established pattern between the processes and various obstetric pathologies, which in the future will allow for the advance prediction of the course of pregnancy and possible outcomes for both the mother and the fetus.

Author's Contribution

Conceptualization: AVK, AAA, AVY and IAB
 Conducting the study: AAA and IAB
 Analysis of results: AVK and IAB
 Literature search: AVK, AAA, AVY and IAB
 Article preparation: AVK, AAA, AVY and IAB
 Review writing and editing: AVK, AAA

Ethical approval

The study design was approved by the local Ethics Committee on Bioethics of the Federal State Budgetary Educational Institution of Higher Education «Samara State Medical University» of the Ministry of Healthcare of the Russian Federation (FSBEI HE SamSMU MOH Russia), protocol No. 242 dated November 23, 2022. Written consents of the participants were provided.

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Conflict of interests

The authors have declared no conflicts of interest.

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