Microbiological and clinical-anatomical factors of miscarriage

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Annotation: *Abortion is a serious medical and social problem. The etiology of early abortions is extremely diverse and depends on many factors. One of the important reasons for this pathology is a violation of the vaginal biocenosis. Despite active research into the etiology of abortion, many questions remain unanswered.*

Key words: *miscarriage; predictor factors; Lactobacillus iners; Lactobacillus crispatus; chronic endometritis; vaginal microbiocenosis.*

Target — to study clinical, anatomical and microbiological factors of miscarriage.

Materials and methods of research. The prospective cohort study involved 159 pregnant women who underwent a comprehensive medical examination in the first trimester of pregnancy. The history, course of pregnancy, vaginal microflora and pregnancy outcome were studied. The vaginal microflora was studied using microscopy, bacteriological methods and quantitative real-time PCR. Depending on the outcome of the current pregnancy, the patients were divided into two groups: women with a positive outcome and women with early pregnancy termination. Predictors of miscarriage in the current pregnancy were analyzed according to stage of labor.

Research results. The current miscarriage rate among women was 13%. Predictors of early miscarriage were identified: chronic endometritis (RR10.54; 95% CI 2.54-43.64), predominance of Lactobacillus inners in the vaginal flora (RR8.52; 95% CI 2.07-35.05), predominance of non-lactobacillary types of microorganisms on microscopic examination (RR4.50; 95% CI 1.02-19.69). The

predominance of Lactobacillus crispatus in the vaginal microbiota was a factor contributing to increased length of pregnancy in late pregnancy (RR0.20; 95% CI 0.04-0.99).

Conclusion. Several important anatomical and microbiological predictors of early pregnancy loss have been established, which allows prenatal preparation and treatment planning for pregnant women with different risks of miscarriage.

Introduction: Miscarriage is a serious medical problem due to the unfavorable demographic situation in Japan. A significant proportion of pregnancies do not occur at different stages due to socio-economic and environmental factors, the spread of sexually transmitted infections, hereditary and acquired disorders of the hemostatic system. In the modern world, the number of older pregnant women is significantly increasing, many of whom suffer from chronic diseases. This situation can lead to the development of complications during pregnancy and create conditions for its early termination. The role of genitourinary infections in the development of miscarriage is undeniable. The adverse effect on pregnancy outcome is due to the transfer of pathogenic and opportunistic bacteria from the vagina to the cervix and uterine cavity, which leads to the development of cervicitis, duodenitis and chorioamnionitis. However, it should be noted that the contribution of infectious agents to the development of miscarriage is different at different stages of pregnancy. Previous studies have shown that the role of infection in the development of spontaneous abortion and early unintended pregnancy is relatively small. At the same time, bacterial vaginosis and aerobic vaginosis are risk factors for late spontaneous abortion, intra-amniotic infection and postpartum complications. Various invasive interventions on the pelvic organs, change of sexual partners, biological disorders of the genital organs and urinary tract infections are the main risk factors for intrauterine infection. The range of infectious agents that cause diseases of the genital organs is very wide. The persistence of opportunistic infectious and pathogenic microflora in the vagina and endometrium causes morphofunctional disorders of the reproductive system, as well as the formation of chronic

inflammation. However, there is evidence to the contrary, that the microflora of the vagina, cervix and endometrium differs in numbers and species composition. The question of the contribution of Lactobacillus inner to the development of miscarriage remains open. Despite the fact that this species belongs to the lactobacillary microflora, some studies show that the predominance of L. iners is often observed in the transition period between the normal state of the vaginal microbiocenosis and the disturbed one, which can lead to the dominance of pathogenic vaginal microflora and the development of infectious diseases of the vagina. Identification of infectious risk factors for miscarriage is necessary both to understand the mechanisms of development of this pathology and to develop preventive measures. The purpose of this study was to study clinical, anamnestic and microbiological predictors of miscarriage.

Materials and methods: 159 pregnant women aged 21-40 years in the first trimester of pregnancy (up to 13 weeks) were observed. History of chronic endometritis and tubulitis, cervical erosion, menstrual irregularities, external genital endometriosis, 27 clinical and laboratory studies of pH-metry of vaginal discharge, inflammatory reaction, predominance of non-lactobacillary microorganisms during microscopic examination, presence of yeast cells/pseudomycelium, presence of key cells, the number of isolated non-lactobacillary species of microorganisms in a cultural study, the proportion of lactobacilli in a molecular biological study, the dominance of certain types of lactobacilli in vaginal discharge, namely L. crispatus, L. iners, L. jensenii, L. gasseri, total concentration of bacterial DNA - total bacterial mass (TBM) - and concentration (absolute and relative) of Lactobacillus, Enterobacteriaceae, Streptococcus, Staphylococcus, Gardnerella vaginalis/Prevotella bivia/Porphyromonas, Eubacterium, Sneathia/Leptotrichia/Fusobacterium, Megasphaera/Veillon ella/Dialister, Lachnobacterium spp./Clostridium, Mobiluncus spp./Corynebacterium, Peptostrepto coccus, Atopobium vaginae, Mycoplasma hominis, Ureaplasma and Candida. We examined vaginal discharge, which was collected from the posterolateral fornix using two sterile swabs and a

spatula. The pH value of vaginal secretions was measured using ColportestpH test strips by applying vaginal secretions to the sensor element of the test strip using a spatula. pH values in Colpotest tests range from pH3.0 to 7.0. Vaginal secretions, applied to two glass slides, were stained with 1% methylene blue and Gram stained to determine the number of leukemias and bacterial morphology. In this case, the ratio of the number of leukocytes to the number of epithelial cells was calculated (normally ≤1: 1). In addition, the presence of lactobacilli, other microorganisms, yeast-like fungi, Trichomonas, and key cells was assessed. For bacteriological examination, vaginal discharge was placed in two Petri dishes with an artificial nutrient medium containing 5% sheep blood (Oxoid, UK). To isolate yeast-like fungi of the genus Candida, Sabouraud broth was used, followed by plating on Sabouraud agar. Identification of isolated microorganisms was carried out on a Microflex mass spectrometer (Bruker, Germany) using the Maldi Bio Typer RTC database. The vaginal microflora was examined using the Femoflor-16 test (DNA-Technology, Moscow). The test is based on the quantitative real-time PCR method and allows you to determine the amount of DNA of the desired microorganism in the sample, which is expressed in genomic equivalents (GE) per sample. The amount of HE is proportional to the number of microorganism cells. Statistical analysis of the results was carried out using the NCSS 12 statistical package (NCSS, LCC). For continuous variables, data were calculated as medians with interquartile ranges; the Mann–Whitney U test was used to analyze differences; for categorical variables, data were calculated as frequencies, and differences were analyzed using the Pearson chi-square test.

Results: An analysis of the outcomes of this pregnancy showed that 138 women were delivered on time, 21 women had early termination of pregnancy, while in 53% of cases, termination of pregnancy occurred in the late stages (after 16 weeks), of which 43% were premature births and 10% late miscarriage. In 47%, spontaneous termination of pregnancy was noted in the early stages: spontaneous miscarriage - 33%, non-developing pregnancy - 14%. Taking into account the fact that etiological risk factors for adverse pregnancy outcomes, in

particular the infectious process, can occur within certain periods, the study of predictors of miscarriage was carried out for two groups: early termination of pregnancy (spontaneous early miscarriage and non-developing pregnancy (n = 10)) and spontaneous termination of pregnancy in late stages (spontaneous late miscarriage and premature birth (n = 11)). An analysis of the relationship between adverse pregnancy outcomes and gynecological history data showed that chronic endometritis is a significant predictor of miscarriage. According to the calculated odds ratio, in women with chronic endometritis, the risk of spontaneous abortion in the early stages increases by 10.5 times (95% CI 2.54–43.64; $p < 0.05$). The risk of miscarriage was slightly higher in women with chronic salpingoophoritis, menstrual dysfunction and cervical pathology, but statistical significance for these factors could not be identified. A significant predictor of early pregnancy loss was the predominance of non-lactobacillary microorganisms in vaginal discharge, which increased the risk of miscarriage by 4.5 times (95% CI 1.02–19.69). The presence of an inflammatory reaction on microscopic examination of a Gram-stained specimen also contributed to an increase in the odds of early (OR 1.68; 95% CI 0.40–6.92) and late (OR 3.27; 95% CI 0.93) miscarriage. −11.5) terms, but no statistical significance was found for this factor. The detection of elements of yeast-like fungi, a decrease in the proportion of lactobacillary flora in the MBM, the isolation of non-lactobacillary species of microorganisms during cultural studies, and changes in the pH of the vaginal environment were not associated with an increased risk of miscarriage. It should be noted that there is a slight increase in the risk of pregnancy loss in women with severe anaerobic dysbiosis, but significant differences in this factor could not be identified. In women in whose vaginal discharge key cells or pronounced aerobic dysbiosis were found, there were no cases of early termination of the current pregnancy. In this regard, it was not possible to assess the relationship of these factors with miscarriage. The most common species of lactobacilli in the studied groups of women were L. iners, L. crispatus, L. jensenii and L. gasseri. The proportion of L. iners was significantly higher in women with both early and late pregnancy

losses, and L. crispatus was significantly lower in women with late miscarriages compared with women who delivered at term. The content of L. jensenii was slightly higher in women with cases of late pregnancy loss, but no significant differences were found for this species. There were also no statistically significant differences in the content of L. gasseri in women with spontaneous termination of pregnancy, either in the early or late stages. Based on the results of the analysis of the relationship between miscarriage and the species composition of the lactobacillary microflora of the vagina, it was found that a statistically significant predictor of early pregnancy loss is the dominance of L. iners, which increases the risk of pregnancy loss by 8.5 times (95% CI 2.07–35.05). The odds ratio showed an increased risk of developing and late forms of miscarriage with dominance of L. iners (OR 3.04; 95% CI 0.87–10.69), but no statistical significance was obtained for late cases. On the contrary, L. crispatus dominance was a significant predictor of spontaneous late pregnancy loss and preterm birth (95% CI 0.04–0.99). Dominance of L. jensenii and L. gasseri species was not associated with miscarriage.

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