ISSN: 2692-5206
AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

BACTERIAL VAGINOSIS

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ANNOTATION: Bacterial vaginosis (BV) is one of the most common infectious pathologies of women of childbearing age. Bacterial vaginosis is a condition in which the normal vaginal microflora, represented mainly by lactobacilli, is replaced by numerous anaerobic and other opportunistic flora. Dysbiosis has been linked to complications such as rupture of the membranes, premature birth, infections of the chorion, amnion, and amniotic fluid., intrauterine fetal death. This suggests the need for screening for bacterial vaginosis and its treatment before pregnancy.

Key words: Bacterial vaginosis; vaginal microbiocenosis; immune defense mechanisms; cytokines.

Bacterial vaginosis (BV) is a polymicrobial disease in which the normal vaginal microbiota (protective lactobacilli) is replaced by microaerophilic (Gardnerella vaginalis) and obligate anaerobic (*Bacteroides spp., Prevotella spp., Mobiluncus spp., Veillonella spp., Medasphaega spp., Leptotrichia spp., Atopobium vaginae* and others) by microorganisms [1]. There is a generally accepted opinion that there is no inflammatory leukocyte reaction in BV.

According to world statistics, BV occupies one of the first places among diseases of the vagina. Its prevalence in the population ranges from 12% to 80% and depends on the number of women surveyed [1]. BV is detected in 80-87% of women with abnormal vaginal discharge, in 37-40% of pregnant women, and in 25% of adolescent girls. However, it is not possible to determine the true incidence of BV due to the fact that approximately 50% of women have an asymptomatic condition. At the same time, BV is found in 15-19% of patients in outpatient gynecological practice, in 10-40% of pregnant women, in 24-40% of women with STIs, and in 35% of women with PID (pelvic inflammatory disease).

BV is not an STI and does not pose a danger to life, however, it becomes a risk factor for pregnancy complications, as well as a cause of the development of PID [2].

Important components of the vaginal indigenous (resident, obligate, predominant in the biotope) microflora are lactobacilli, bifidobacteria and propionic acid bacteria, which must be at least 95% in this biotope in order for the protection of the vagina to be effective. The evolution of the vaginal biotope has led to the development of adaptive mechanisms that allow these indigenous microorganisms to actively develop in the vaginal environment, adhere to the epithelium, forming strong symbiotic bonds with it, and successfully compete with facultative and transient opportunistic and pathogenic microflora.

ISSN: 2692-5206
AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

The first place among the indigenous flora is occupied by lactobacilli. *Lactobacillus crispatus*, *L. iners*, *L. jensenii* and *L. gasseri* are most often isolated. The dominant species is *L. crispatus* — they are found in 72% of women with normocenosis.

Lactobacilli are capable of:

• actively reproduce in the vaginal environment;

• adhere to the surface of epitheliocytes, leaving no room for infectious agents;

• Ferment glycogen with accumulation of organic acids;

• synthesize hydrogen peroxide, which is practically the only bactericidal factor that can be produced in the human body;

• produce lysozyme, bacteriocins;

• Stimulate local immunity.

Lactobacilli are the most adapted to colonize the vagina and protect it from colonization by opportunistic and pathogenic microorganisms [3].

Bifidobacteria are the second main component of the native flora. Five species are most common: *Bifidobacterium bifidum*, *B. longum*, *B. infantis*, *B. breve* and *B. adolescentis*. They are able to ferment glycogen to form organic acids, thus creating an optimal pH environment for themselves; adhere to the surface of the epithelium, synthesize antimicrobial metabolites, and stimulate local immunity. Effectively inhibit the growth of Gardnerella, Staphylococcus, Escherichia, Klebsiella and other opportunistic microorganisms. In healthy non-pregnant women, bifidobacteria are contained in lower concentrations than lactobacilli (up to 107 CFU/ml). During pregnancy (especially in the prenatal period), their titer increases sharply, which is a powerful factor in protecting the newborn's body from colonization by pathogenic microorganisms during passage through the birth canal [4].

The third type of indigenous flora is propionic acid bacteria. These are gram-positive asporogenic polymorphic small rods that compete well for nutrients with anaerobes. They are characterized by strict anaerobism, actively ferment glycogen to form propionic and acetic acids, and inhibit the growth of opportunistic bacteria. They have antioxidant, antimutagenic, anticarcinogenic and immunostimulating properties.

In general, the normocenosis in the vagina is characterized by a dynamic relationship between *Lactobacillus acidophilus* (produces hydrogen peroxide, which has a toxic effect on pathogenic microorganisms and maintains the pH of the vagina) and other endogenous flora. It depends on the levels of estrogens in the blood plasma; the amount of glycogen in the epithelium, because acidic environment is produced from it; pH; products of metabolism of endogenous flora and pathogenic microorganisms.

ISSN: 2692-5206
AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

Summing up, we can say that two main factors of protection are decisive — an acidic environment (pH of the vagina in the range from 3.8 to 4.5) and colonization resistance.

Colonization resistance is understood as a set of mechanisms that ensure the ability of a microbiota and a macroorganism to cooperatively protect an ecosystem from pathogenic microflora. Microorganisms within communities come into contact with each other in different planes and have a minimal free surface for contact with the matrix. Many microcolonies and similar isolated communities are combined into a common structure — a biofilm [5].

The colonization properties of native flora depend on its adhesive properties. By attaching to the surface of epitheliocytes, a biofilm is formed on the vaginal mucosa, consisting of vaginal mucus, colonies of indigenous microflora and its metabolites. This is one of the most powerful protective factors, as it prevents adhesion and excessive development of opportunistic microorganisms.

The causes of disruption of normal microflora can be endogenous and exogenous factors. Endogenous factors include various hormonal changes during puberty, pregnancy, childbirth, and abortion; neuroendocrine diseases, hypothyroidism, and diabetes; and disorders in the local immune system.

Exogenous factors: use of tampons, spermicides; frequent excessive vaginal showering and douching; change of sexual partner; use of broad-spectrum vaginal pills; therapy with antibiotics, cytostatic, glucocorticoid, antiviral drugs.

There are five main nosological forms of pathological vaginal discharge: BV, aerobic vaginitis (AV), vulvovaginal candidiasis (VVC), trichomoniasis vaginitis (TV) and mixed vaginitis [6].

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BV is understood as the dysbiotic state of the vaginal flora caused by a sharp increase in the number of opportunistic pathogens and a sharp decrease in the concentration of lactobacilli, mainly producing hydrogen peroxide. It affects all areas of a woman's activity and reduces her quality of life.

The most common complications of BV [7]:

• development of chorionamnionitis;

• premature birth, premature discharge of amniotic fluid (increases by 2.6–3.8 times);

ISSN: 2692-5206
AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

• endometritis;

• postpartum sepsis;

• recultivitis after hysterectomy;

• persistence of a latent viral infection;

• creating conditions for colonization of genitourinary organs by STI pathogens;

• tubal infertility (32%), PID (35%).

BV may become a cofactor for the development of papillomavirus infection.

Further studies have shown that, taking into account the similar cytokine gene expression profile in BV and vaginitis, the traditional view of BV as a non-inflammatory disease is not entirely correct. Vaginitis and BV are accompanied by a significant increase in the level of mRNA expression of the IL-6, IL-8, IL-10 genes and a decrease in the content of IL-12a and IL-18 compared with the control group. Vaginitis also significantly increases the level of mRNA expression of the IL-1b, TNF, IFN-γ, and CD45 genes.

BV significantly reduces the number of lactobacilli producing hydrogen peroxide, and polymicrobial, mainly anaerobic, microflora prevails. The primary causative agents of BV are anaerobic bacteria: *G. vaginalis*, *Mobiluncus* spp., *Bacteroides* spp., *Atopobium vaginae*.

Currently, progressive researchers identify 2 groups of BV markers [8-10]. Low-specific ones (defined in both healthy women and BV patients) include *G. vaginalis*, *Mobiluncus* spp., *Megasphaera* spp., *Leptotrichia* spp., to the highly specific (detectable only in women with BV) — *A. vaginae*, vaginosis-associated bacteria *Clostridium phylum*, *Mucinase*, *Sialidase*.

Pathogenesis. The number of lactobacilli producing hydrogen peroxide decreases in the vagina, while the pH of the vagina increases (pH ≥ 4.5), the growth of anaerobic bacteria and the release of amines (the smell of rotting fish).

The so—called "key cells" (glue cells) are formed - epithelial cells of the vagina, densely covered with gram-variable rods (in 70-80% of women with BV).

The clinical picture. In 50% of patients, the disease is asymptomatic in the presence of laboratory signs. Patients with BV complain of copious white or gray discharge, often with an unpleasant odor (rotting fish), especially after unprotected sexual intercourse or during menstruation. Seminal fluid has a pH of 7.0, so after ejaculation, the pH of the vagina increases, the amines become free, and being volatile, they cause this odor. Its intensification in connection with sexual intercourse is a pathognomonic ghost of BV.

As the process progresses, the discharge foams, becomes yellowish-green, thick, slightly stringy, sticky; 25-30% of women feel burning and itching. Dyspareunia and dysuria occur [13]. The duration of these symptoms can last for years.

ISSN: 2692-5206
AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

Diagnostics. BV is diagnosed on the basis of the "golden diagnostic standard" — the clinical and laboratory criteria proposed by R. Amsel [5]:

• homogeneous vaginal discharge;

• pH of vaginal discharge > 4.5;

• positive aminotest result;

• the presence of "key cells" in Gram-stained vaginal discharge smears or in a native preparation.

The diagnosis is considered confirmed if there are any 3 criteria out of the 4 suggested.

In addition to screening tests, microscopy of a Gram-stained vaginal smear is used to diagnose BV. The sensitivity and specificity of the method are close to 100%. In addition to the "key cells", additional signs of BV include the predominance of epithelial cells over leukocytes and the detection of less than 5 lactobacilli in the visual field when magnified with immersion.

Treatment. The requirements for the drug of choice for the treatment of BV are etiotropicity, a minimum percentage of relapses, convenience of forms and patient compliance, safety, optimal pharmacoeconomic indicators. The drug of choice should not inhibit the growth of lactoflora, but contribute to the normalization of microbiocenosis. It is necessary to note such advantages of local therapy as the absence of systemic action, minimal risk of adverse reactions, simplicity and convenience of use, absence of contraindications (except for individual intolerance to the drug), the possibility of use in women with extragenital pathology (especially in localized forms of the infectious process: acute vulvitis, vaginitis, cervicitis or exacerbations of chronic processes of the vagina and cervix), rapid entry into the focus of infection and rapid exposure.

Approaches to the treatment of BV have recently synchronized in the USA (MMVR — STD treatment Guidelines), Europe (European STD Guidelines) and Russia.

• Clindamycin cream 2% — 5 g in an applicator (single dose) intravaginally once a day (at night) for 7 days;

• metronidazole gel 0.75% — 5 g (single dose) intravaginally once a day (overnight) for 5 days;

• Metronidazole 500 mg orally 2 times a day for 7 days.

1 g of Metrogil vaginal gel contains 10 mg of the active ingredient metronidazole. It is an antimicrobial and antiprotozoal agent, a derivative of 5-nitromidazole. The drug is active against *Trichomonas vaginalis*, *Entamoeba histolytica*, *G. vaginalis*, *Giardia intestinalis*, *Lamblia* spp., obligate anaerobes *Bacteroides* spp., *Fusobacterium* spp., *Veillonella* spp., *Prevotella*. Indications for use are BV and urogenital trichomoniasis.

ISSN: 2692-5206
AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

Alcohol and alcohol-containing products should be avoided both during metronidazole therapy and for 24 hours after its end. If oral metronidazole is intolerant, its intravaginal administration is also contraindicated.

Metronidazole intravaginal in therapeutic concentration does not inhibit the growth of vaginal lactobacillus colonies and has a high penetrating ability into the vaginal fluid. The relative bioavailability of the vaginal gel is 2 times higher than the bioavailability of a single dose (500 mg) of metronidazole vaginal tablets. It quickly (within 5 days) eliminates clinical manifestations and provides clinical efficacy reaching 90%. Due to the low concentration in the blood serum, the risk of side effects is reduced. Finally, and most importantly, the acidic environment of the Metrogil vaginal gel contributes to the rapid normalization of the vaginal ecosystem.

When bacteria switch to the growth mode in the biofilm, significant changes occur in the expression of dozens of bacterial genes in accordance with the stage of colony development [28]. Potent antibiotics do not affect *G. vaginalis* films, which contribute to the survival of most of the pathogenic microflora after the end of antibiotic treatment [27, 29], which leads to the development of chronic and recurrent forms of the disease.

The first biofilm bacteria synthesize special adhesion proteins to build a matrix. When they are fixed, they emit signaling molecules that "recruit" new bacteria, in addition, the division of bacteria already fixed in the biofilm is stimulated.

CONCLUSION

Vaginal metronidazole preparations promote the eradication of pathogenic planktonic microorganisms, do not have a systemic effect, and the applicator ensures its rapid entry into the infection site. The use of metronidazole is accompanied by a minimal number of adverse reactions.

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