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VAGINAL CANDIDIASIS – GYNECOLOGICAL ASPECT OF THE PROBLEM

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Vaginal candidiasis (VC) is one of the most common reasons for consultations with a gynecologist, with an increasing trend in occurrence in female patients. It is estimated that 75% of all women experience an episode of vulvovaginal candidiasis in their lifetime, 50% of them experience at least a second episode, and 5% have recurrent candidiasis. Cervical and vaginal secretions act as the last line of defense from ascendant infection pathway spreading. Factors that may disturb vaginal ecosystem are: endogenous factors, way of life, infectious factors and iatrogenic factors. The most common cause of VC in 85-90% of cases is C. albicans, but other Candida species tend to be more likely to cause VVC (Candida tropicalis , Candida glabrata , C particulary, C crusei and so on). These non-albicans species have been found to be fluconazole and antimycotics resistant in more than 70% of cases. This is especially true for C. glabrata. There are several predisposing factors that have been associated with VC recurrence and resistance, such as Candida genotypes, resistance and virulence, immunodeficiency, unregulated hyperglycemia, use of oral contraceptives, long-term use of antibiotics. Therapy approach should be individual, including local and oral antimycotics until the symptoms disappear. The maintenance dose can be continuous or intermittent. Due to hormone concentration increase, increase in local glycogen, alternations of vaginal flora, VC incidence in pregnancy is two times higher in comparison to other female population. The problem of vaginal candidiasis requires individual approach, taking into account all the risk factors and accompanying physiological conditions or diseases in female patients. Acta Medica Medianae 2014;53(4):46-53.

Key words: *vaginal candidiasis, vaginal discharge, recurrence, resistance, pregnancy*

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Introduction

Vaginal candidiasis (VC) is one of the most common reasons for consultations with a gynecologist, with an increasing trend in occurrence in female patients. The number of patients with recurrent and resistant vaginal candidiasis to standard local antimycotic therapy is constantly growing. A special aspect of this type of candidiasis is its treatment in pregnant women, and interpretation of cytological findings (PAP test) as well.

The incidence of vaginal candidiasis

It is estimated that 75% of all women experience an episode of vulvovaginal candidiasis in their lifetime, 50% of them experience at least a second episode, and 5% have recurrent candidiasis (more than 4 episodes per year). In the USA there is an annual occurrence of 13 million cases of VC and 10 million visits to gynecology surgeries for this problem alone. The incidence has nearly doubled and increased in the last ten years from 118 to 200 per 100.000 women in England and in the USA. Candida albicans is the infecting agent in 90% of patients. Overall prevalence of VC is in the range between 18.5 and 23 %. VVC is presently the fourth leading cause of hospital-acquired infections (1-4).

These data impose the questions on the causes of the increase in incidence and recurrence of VC. On the one hand the causes are due to the expansion of cosmetics marketing and industry including production of antibacterial soaps, commercial scented douches, feminine sprays, perfumed toilet paper, synthetic underwear and waxing that causes tiny tears in the skin. Modern way of life – European working hours, fast food, skipping meals, too much time sitting at work, stress can also be the factors responsible for the increase of VC. The other aspect of this problem is uncontrolled overuse of oral antibiotics that are widely used in everyday clinical practice.

Additional factors responsible for high incidence of this disease could be the treatment itself by the gynecologist (shortening the treatment, local therapy without systemic effects, long-term therapy with antibiotics not followed by antimycotics). Behavior of female patients in terms of avoiding visits to doctor's surgery, ap-

pointments and waiting in front of the doctor's surgery, taking pessaries to solve the problem in one day, listening to friends' advice who experienced benefits from such pessaries, and experience from previous treatments also have a great influence on high incidence of this disease. On the other hand, there are beliefs that modern women are sensitive to increased vaginal secretion due to mysophobia, neurotic personality, sexual frustrations, etc.

Normal vaginal ecosystem functioning

It is well known that vaginal discharge occurs as the result of endometrial discharge, secretion from cervical vestibular glands and plasma transudate. Cervical and vaginal secretions act as the last line of defense from the ascendant infection pathway spreading. These fluids include molecular components such as inorganic salts, urea, amino acids, and fatty acids. Vaginal discharge contains carbohydrates (bind microorganisms), defensisn, lactoferrin (binds iron), lysosomes and antibodies (IgA), cytotoxic T-lymphocytes CD3, CD4, CD8, macrophages and other antigen-presenting cells and lactobacilli as well. Cervical-vaginal secretion normally prevents the adherence and colonization of bacteria and fungi and their further invasion of the upper genital tract. This function is hormone-dependent. The function of a healthy vaginal ecosystem is enhanced by the proliferation and maturation of superficial epithelial cells, glycogen-rich cells and the physical barrier itself (5). Figure 1 presents the typical appearance of secretions with vaginal candidiasis.

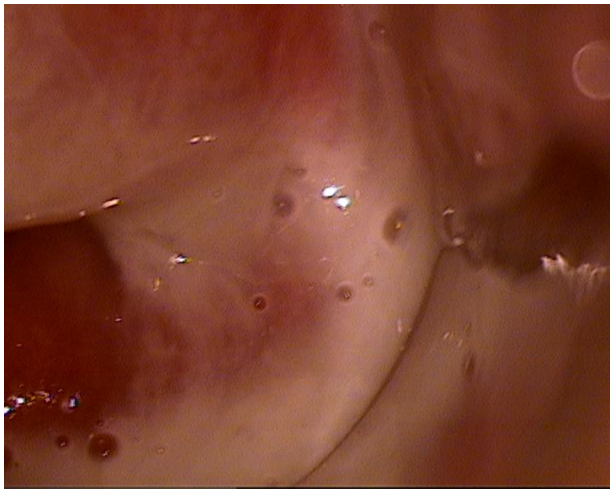

Figure 1. The appearance of secretion in vaginal candidiasis

Factors that may disturb vaginal ecosystem are: endogenous factors (hormonal changes, diabetes mellitus, immunosuppression, AIDS, oxidative stress); way of life – inadequate hygiene, synthetic underwear, use of contraceptives, overuse of antibiotics and antiseptics; infectious factors (unprotected sex); iatrogenic factors (corticosteroid, hormone, cytostatic therapy, radiotherapy).

The normal vaginal ecosystem depends on the balance of hormones and bacterial flora, maintained by estrogen levels, meaning that glycogen-rich cells provide food for Doderlein's bacilli that produce the lactic acid and maintain vaginal Ph. Normal vaginal pH is 3.8-4.5. Vaginal Ph elevated to 5-6 suggests infections such as streptococcal vaginitis, and the values of 6-7 point to atrophic vaginal epithelium. Besides Lactobacillus acidophilus that has been reported to be the predominant vaginal species, other species colonizing the vagina are L. species, L. jensenii, L. crispatus, L. casei, L. fermentum. Lactic acid production is important because it acidifies the vaginal discharge, low pH (<4.7) stimulates growth of L. Acidophilus and prevents growth of pathogenic bacteria and fungi. Also, hydrogen peroxide production has bactericidal properties, as well as bacteriocin production and bacteriocin-like protein. The very thickness of vaginal discharge enables adherence to vaginal epithelium, thus making normal flora compete with pathogenic bacteria (6).

Nowadays, a great importance has been attached to lactobacilli and their role in maintaining normal vaginal flora, leading to abundance of commercial lactobacilli-based rinsing products, pessaries of lactobacilli, pads and feminine wipes with these bacteria, there is even systemic lactobacilli therapy. On the other hand, there is lack of evidence that the use of such commercial lactobacilli- based products reduces the incidence of vaginal candidiasis (7).

Pathogenicity of harmless commensal pathogen infection conversion into a serious pathogen Candida infection

Different Candida species are part of mucocutaneous flora in 80% cases, and in 5–20% cases there is asymptomatic colonization by Candida species. It is believed that factors that alter vaginal environment of the host, along with immunodeficiency, trigger changes in switching Candida from a dimorphic agent in blastospore form into hypha form and from asymptomatic colonization into symptomatic vaginitis. Hyphal form is stimulated by pH 7, temperature of 37°C, blastospore colonization greater than 1 x 106 and the presence of N–acetyl-glucosamine in serum (8).

C. albicans can convert from harmless commensal to a serious pathogen, the transition is a fine line depending on expression of pathogen virulence factors (its genotype) and physiological status of the host. The virulence factors expressed by Candida species are numerous, but not all of them are involved in a particular infection stage and they also depend on the type of infection (mucosal or systemic) and on the nature of the host response as well. The most fre-

quently mentioned factors suggested to be virulent besides hyphal formation are extracellular hydrolytic enzyme production and phenotypic switching.

A comparative genomic analysis between benign species of Candida only (S. cerevisiae) and other species suggested that 6-7% genes had no counterpart, representing agglutinin-like sequence (ALS) and secreted aspartyl proteases (SAP) which are the most important implication in C. albicans virulence (9).

SAP proteins have numerous functions in infectious process which include the role of digestion for nutrient acquisition, distorting host cell membrane to facilitate adhesion and tissue invasion, and distorting cells and molecules of the host immune system.

The three most significant hydrolytic enzymes secreted by pathogenic Candida that are encoded by a family of 10 SAP genes are: aspartyl proteinases (SAP), phospholipase B enzymes, and lipases. Candida albicans is not the only Candida species to produce SAP genes. Candida tropicalis possess four genes, C. dubliniensis possess nine genes and so on. It is likely that proteinase production is the factor of virulence. Candida species that are less virulent or nonpathogenic do not produce significant amounts of proteinase, even though they possess SAP genes (10).

Morphological aspect and Candida infection pathogenicity

Candida is a dimorphic fungus that primarily exists as a blastospore phenotype (blastoconidia). Blastospores are characterized by their oval-shape and propagation through cellular budding. Upon perception of environmental signals it transforms into one of two filamentous forms: pseudohyphae and hyphae. Pseudohyphae are elongated ellipsoidal cells attached to one another, hyphae are cylindrical elongated forms separated by septal walls. On a native microscopic sample, hyphae are found in about 10% of positive findings, and characteristic mycelial forms in about 30% (11).

Despite the significant roles of hyphae forms in pathogenesis, it is believed that both forms are necessary for virulence of Candida mutants that are deficient in Tup 1 repressor of filamentation and are locked in filamentous form. The hypha form is stimulated by the aforementioned environmental factors of the host, but the factors that may have an impact on formation of this form from the host serum are still not well understood. Candida cells reprogrammed in such a way (able to form hyphae), phagocytosed by macrophages, initiate hyphae formation and become too large for the macrophages and macrophage lysis occur (12).

Estrogen hormones (17-β-estradiol) can also induce the formation of hyphae. Estrogen receptors identified in the vagina epithelium are responsible for hydration, elasticity, collagen concentration, and concentration of glycosa-minoglycan that form the skin barrier. As pH increases due to physiological conditions (menstrual period), protease activated receptor 2 is activated (mediator of the estrogen receptors) (13).

The course of the infection is as follows: the first step is adherence to epithelium and the receptors on its surface (N-cadherin) mediated by adhesin Als3, then endothelial cell phagocytosis, enzymatic hydrolysis (enzyme digestion) characteristic for hyphae form and aspartyl proteinase activity. Accordingly, the phases of the infection are: colonization, superficial invasion of epithelial cells, deep epithelial cells invasion, and a disseminated infection (14,15).

The presenting symptoms are secretion and itching, as well as dyspareunia and dysuria. Local finding shows redness, erythema, discharge that adheres to vaginal walls, and possible presence of multiple macular changes as well. After history taking and examination, the smear is usually taken on a dish for native examination for mycelia or Candida buds to be identified. Vaginal culture should not be requested unless a recurrence is suspected. Itching, as the most common symptom of VC, is not highly specific and in the absence of other known symptoms (white, odorless, cottage cheese type of discharge) indicates VC in only 38% of cases. Self-diagnosis has been found to be correct in only 66% of cases, while the greatest differential mistakes are related to trichomonas (30%) and the fact that no real infection is present (52%, and with other infective agents in 18% of cases) (16,17).

The most common cause of VC in 85-90% of cases is C. albicans, but other Candida species tend to be more likely to cause VC (Candida tropicalis, Candida glabrata, particulary C. crusei and so on). Considering such a distribution of different species, it seems that empirical treatment is allowed. However, the percentage of non-C. albicans increased from 9.9% in 1988 to 17.2% in 1995. These C. species are 10 times less sensitive to standard first line therapy with miconazole and clotrimazole and tend to be possible causes of resistance and recurrent candidiasis. Some recent studies (2006) have reported 24 % of non-albicans infections, a large English study also reported about 27.7%, Australian 11 % , Italian (Spinilo) 17%, and a German one reported 24 % of infections of this type (18-20).

These non-albicans species have been found to be fluconazole and antimycotics resistant in more than 70% of cases. This is especially true for C. glabrata. On the other hand, there have been only a few reports on resistant C. albicans – 3.6 %. However, the resistance could result from the changes in Candida species distribution and from inadequate use as well (self-treatment, shortened treatment, too long treatment and drug overuse). Despite the fact that definite causative factor of RVC has not been found yet, it should be pointed out that azole-resistant Candida species and non-albicans, or

their combination with other risk factors (HIV, diabetes, chemotherapy, immunosuppressive therapy) are responsible for the repeated episodes.(18,21,22).

Recurrence - resistance, associated or not?

Recurrent VC is defined as four episodes or more in a year. Approximately, it occurs in 5-8 % of cases and poses a huge medical, economic, sexual and frustrating problem. Recurrent Candida has been experienced by 15- 20% of patients after initial treatment and sterile finding. It is associated with antimycotic (fluconazole) resistance that is relatively common in aforementioned non-albicans C. species. RVC used to be a rare event in the past (only one reported case in 1990), but in the recent years it has shown the tendency to increase and is the consequence of empiric treatment (even when Candida is not the cause of the infection), long-term treatment with small doses (to prevent recurrence), over-the-counter drugs (antimycotics), and self-treatment (by phone) (19).

There are several predisposing factors that have been associated with VC recurrence and resistance, such as Candida genotypes, resistance and virulence, immunodeficiency (especially in AIDS patients) where CD4 T lymphocyte counts are less than 200 cells/ mm3 and viral load is higher than 10000 viral particles/ml. Female patients taking immunosuppressive drugs after chemotherapy-induced granulocytopenia are also at risk, and it is mandatory to apply local (topical) and systemic therapy in these patients in case of dissemination and resistance from the gastrointestinal tract (patients with liver transplant should be treated with extreme caution because of possible side effects such as increased toxicity and the Candida krusei infections - the alternative is long-term topical therapy). Both general and specific immune responses are responsible for overall poor immunological response (Th1 immune response and immune presentation). Some studies have suggested that 40-70% of women with RVC have some anergy resulting in subnormal T- lymphocyte immune response to Candida. Even blood types play an important role in immunologic local response. One study conducted by Lewis proved that A and B blood group antigens on the vaginal epithelium are protective against Candida infections (23-26).

The use of contraceptives is important, as Candida has been proved to have receptors for estrogen and progesterone and thus stimulate the proliferation. This is especially true for oral contraceptives (OC) containing high doses of estrogen (75 – 150 micrograms of estrogen). The changes that occur with such a hormone dose are similar to those in pregnancy. One study has found that women who take oral contraceptive pills have a higher rate of Candida in relation 32: 18. Progesterone may have a similar effect. Low-dose oral contraceptives do not significantly increase the incidence of VC. Therapy discontinuation is not usually required, especially in patients with low-dose OC, but it has been noted that oral azole antimycotics may stimulate hormonal effects of OC. This interaction does not affect contraception effects, but may result in spotting other side effects. On the other hand, spermicidal local contraceptive gels might alter vaginal flora and increase adherence of Candida organisms. Based on hormonal aspect, pregnancy as a physiological condition may pose a risk factor due to the aforementioned reasons (27-29).

Antibiotics are well-known risk factors causing a threefold increased risk with prolonged antibiotherapy (prior and after surgical interventions, long-term tetracycline therapy in acne treatment) and with wide spectrum antibiotics (AB) such as penicillin, cephalosporins, and tetracyclines that suppress vaginal protective flora. On the other hand, antibiotics that are relatively inactive in acid pH (sulphonamides, erythromycin, metronidazole) have no effect on VC occurrence. In case of long-term AB therapy, Candida infection occurs in about 30% of women. Due to all of these reasons, antimycotic (AM) therapy is routinely prescribed in patients with long-term history of antibiotic use without consultations with the gynecologist and without waiting for the first symptoms to occur, or longer weekly treatment if AB therapy is prolonged (30).

Predisposing factors are also uncontrolled glycaemia and diabetes. However, in the absence of other known symptoms suggestive of diabetes, pathognomonic correlation between RVC and diabetes has not been established. On the other hand, a lot of women with diabetes do not have RVC. Hyperglycemia has been identified as a risk factor for RVC since it may impair normal host defense mechanisms, including neutrophil adhesion, chemotaxis, and phagocytosis; however, it increases the ability of Candida to adhere to vaginal walls. Administration of oral AM in diabetic patients has been reserved for systemic infection or prophylaxis, but it should be noted that these drugs (azole drugs) interfere with cytochrome P450-mediated oral antidiabetic drugs metabolism (tolbutamide, glipizide, glyburide) and may result in severe hypoglycemia (31).

Mechanical factors may also be important: tightly fitted synthetic clothes, increased local temperature, mechanical irritation due to frequent sexual intercourses and so on. The role of sexual transmission and male sexual partners' treatment is controversial. One study found the presence of Candida in 48% of male sexual partners of women with RVC, while another study found no benefits that prevent recurrences of VC in women whose male sexual partners have been treated. However, Candida treatment in male sexual partners is significant for decreasing Candida prostatitis and colonization of the skin.

Gastrointestinal Candida as a risk factor has not been identified and the protective roles of dietary factors and sugar restriction in recurrence of VC have not been supported as well. On the other hand, protective role of yogurt intake or

Lactobacillus acidophilus supplements remains controversial. A study from 1992 showed a threefold reduction in RVC infection in women who consumed a yogurt-containing diet. A second study did not confirm this correlation. RVC causes discomfort, depression and other psychological problems, sexual and marital problems, financial burden, and sick leave (32,33).

No correlation has been observed between the number of sexual partners, age of first sexual intercourse, sexual intercourse frequency increase, barrier contraceptives (condoms) and the incidence of VC. It has been proved that VC was associated with receptive oral sex and masturbation with saliva. An independent risk factor is multiple sexual partners over a short period of time.

Treatment of RVC

Therapy approach should be individual, including local and oral antimycotics until the symptoms disappear (6-14 days), then continuous or intermittent maintenance therapy is administered – ketoconazole at a daily dose of 100 mg for up to 6 months, or a monthly dose of fluconazole, tioconazole weekly treatment for 6 weeks, or boric acid suppositories at a dose of 600 mg for 2 weeks (25).

An optimal protocol therapy in treatment of RVC has not been established yet, so individual approach is required based on efficacy comparison, positive response and potential effect, analysis of previous treatments and cost effectiveness. Apart from reducing these factors to the minimum, a prolonged protective treatment is recommended, based on empirical treatment indicated by reported symptoms, or a six-month protective administration of local antimycotics (treatment with a single 500mg clotrimazole applied monthly) or systemic ones (150mg fluconazole once a month after periods). Systemic administration is more efficient, but the percentage of adverse effects is higher: 12% headaches, 7% abdominal pain and nausea in 4%. On the other hand, local therapy can also have adverse effects, but they are mild and not so common: abdominal pain in 0.2% , discomfort with itching and secretion in 6% of cases (34).

A special attention in systemic AM should be paid on interaction with other drugs: antihystaminics (cause serious arrhythmias), anticoagulant drugs, and oral antidiabetics (35,36).

Due to hormone concentration increase, increase in local glycogen, alternations of vaginal flora, VC incidence in pregnancy is two times higher in comparison to other female population, and worsening effects are especially present in the third trimester of the pregnancy. On the other hand, it is significant to note that the percentage of diabetes in pregnancy (gestation diabetes) increases by 2-5%.

Incidence of vaginal candidiasis is higher in pregnant than non-pregnant patients (30:20%) according to a German study. An Italian study reported similar data (31.4:19.9%). The percentage of asymptomatic candidiasis is also higher in pregnant female patients (46.5:16%). An Australian study reports the percentage of 38% VC in pregnant women, out of whom 27% was symptomatic and 11% asymptomatic, and the percentage was higher in pregnant women with diabetes, multiple pregnancies and in the last trimester of pregnancy. On the other hand, Candida-associated clinical manifestations, such as itching and large amount of discharge, are microbiologically proven in only 50% of cases (they may results from cholestasis, allergic dermatitis) (36).

A strong link between vaginal infections and premature rupture of fetal membranes is well known. All the studies point out the first and second trimester as the most vulnerable for inflammatory response. Also, a lot of studies attempted to establish the connection between early Candida infection in pregnancy and preterm birth. A large New Zealand trial determined that preventive treatment of asymptomatic candidiasis in early pregnancy (15-19 weeks) using clotrimazole as a safe medication reduces the incidence of preterm birth. Similar data were obtained by authors from Australia where a group of pregnant women with asymptomatic candidiasis treated with a 6-day course of clotrimazole had a 40% reduction in the preterm birth rate (reduction from 5% in untreated pregnant women to 3% reduction in preterm birth rate in women treated with clotrimazole) (37).

It has been proved that Candida colonization of the upper genital tract may provoke preterm rupture of fetal membranes or may seriously compromise the health of the fetus (thrombocytopenia, lymphopenia, significant increase of inflammatory cytokines and chemokines due to chronic fetal inflammatory skin, lung and amniotic fluid disorders), and may even result in elevated maternal temperature. If left untreated in the last trimester of pregnancy, candidiasis may result in the skin and oral cavity changes in the newborns (38,39).

The cases of candida chorioamnionitis lethal to the fetus, resulting from Candida colonization of the vagina during assisted reproduction and cervical cerclage have been described, thus a cautious approach is necessary prior to these interventions, especially concerning C. glabrata. On the other hand, there are cases of successful treatment of Candida chorioamnionitis with transcervical amnioinfusion of amphotericin or (a study from 2013) with intraamniotic injections of fluconazole during amniocentesis (40).

The success rate of VC treatment in pregnancy is about 80%, and the failure and recurrences are usually due to associated diseases in pregnancy and infections with characteristic resistant species such as C. glabrata. The treatment is usually with local clotrimazole, gynazole ointment and boric acid vaginal douche. There

has been controversial evidence regarding oral antimycotic use during pregnancy, topical therapy is advised after the first trimester of pregnancy. Although some studies have described safe administration of AM in pregnancy (fluconazole), this treatment may cause possible complications – cardiac rhythm abnormalities – and is recommended in strongly indicated cases only (41).

Although not statistically significantly associated with fetus damage, the use of antimycotics, especially in the first trimester, may cause more frequent fetal cardiac anomalies (hypoplastic left heart or Tetralogy of Fallot). Fear of possible harmful effects of drug interactions to the fetus has led to a growing number of studies dealing with favourable effects of the treatment of Candida in pregnancy with phytotherapy (oil of oregano) or the mixture of bee-honey and yogurt pessaries that produce the same efficacy in treatment of Candida as the well-known antimycotics, according to Egyptian authors report (42,43).

Conclusion

The problem of vaginal candidiasis requires individual approach, taking into account all the risk factors and accompanying physiological conditions or diseases in female patients. On the other hand, multidisciplinary approach is needed (gynecologist, microbiologist, clinical pharmacologist, endocrinologist, infectologist, psychologist) due to potential specificities regarding resistance, recurrence, and systemic dissemination. Empirical treatment, self-treatment with wide-spectrum pessaries increase the rate of recurrence and resistance. It is necessary to rule out all the possible risk factors in the treatment, as well as possible concomitant infectious agents and consider the necessity of long-term and systemic treatment with antimycotics. As for clinical practice, it should be kept in mind that Candida has the role in the development of the vulvar skin disorders, and it may trigger changes to the skin of the vulvar area (atopic dermatitis, lichen, leukoplakia).

Future expectations are:

- To find the answer to the question: What agents are there in the host's blood that convert Candida from a benign commensal pathogen into an aggressive pathogen?
- To continue research studies in finding new therapeutic modalities.
- To plan therapeutic approaches using not only vaginal discharge, vaginal and cervical swabs, but at a greater extent genotyping test aiming at individualizing treatment.
- To promote prevention as the most effective treatment rather than cure Candida, with maintaining the natural balance of the vaginal ecosystem.

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VAGINALNA KANDIDIJAZA – GINEKOLOŠKI ASPEKT PROBLEMA

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Vaginalana kandidijaza (VK) je jedan od najčešćih razloga za konsultaciju sa ginekologom, sa rastućom prevalencijom u ženskoj populaciji. Barem jednom u toku života vaginalnu kandidijazu imalo je 75% žena. Od toga, 50% ima više epizoda, a 5% ima rekurentnu kandidijazu. Cervikalna i vaginalna sekrecija predstavljaju poslednju liniju odbrane od ascendentnog puta širenja infekcije kod žena. Faktori koji mogu da poremete ekositem vagine mogu biti: endogeni, stil života, prekomerna upotreba antibiotika i antiseptika, infektivni, ali i jatrogeni. Najčešći uzročnik VK u 85-90% slučajeva je C. albicans, ali ovaj procenat se iz godine u godinu smanjuje u korist drugih vrsta Candide (Candida tropicalis, Candida glabrata, C particulary, C crusei itd.). U više od 70% slučajeva ovi ne-albikans sojevi povezani su sa rezistencijom na standardne antimikotike i flukonazol. Naročitu rezistenciju su pokazali specifični sojevi C. glabrate. Na nastanak rekurencije i rezistencije utiču mnogi faktori kao što su: genotipovi candide, pad imuniteta, posebno kod bolesnica sa AIDS-om, neregulisana hiperglikemija, upotreba oralnih kontraceptiva, dugotrajna upotreba antibiotika. Terapija mora biti individualna i uključuje korišćenje lokalnih i oralnih antimikotika do prestanka simptoma, a potom se propisuju doze održavanja, koje mogu biti intermitentne ili kontinuirane. Zbog povećanja koncetracije hormona, povećanja lokalnog glikogena, promena vaginalne flore, incidencija VK tokom trudnoće je i do dva puta veća u odnosu na ostalu populaciju žena. Problem vaginalne kandidijaze zahteva individualni pristup, sa sagledavanjem svih faktora rizika i pratećih fizioloških stanja ili bolesti pacijentkinje. *Acta Medica Medianae 2014;53(4):46-53.*

Ključne reči: *vaginalna kandidijaza, vaginalni sekret, rekurencija, rezistencija, trudnoća*