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RECURRENT GENITAL CANDIDOSIS OF WOMEN: CONSEQUENCE OF REINFECTION OR RELAPSE

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Summary. *A most interesting fact for scientific investigations is that 5% of women are afflicted with recurrent genital candidosis (RGC) characterized by three or more genital, fungal infection episodes per a year. The data analysis is also interesting because it reveals that the most significant risk factors such as pregnancy, diabetes mellitus, long term use of antibiotics and citostatics, hormonal therapy and idiopathic or acquired immunodeficient conditions have not been verified.*
There are many different hypotheses about RGC pathogenesis, but two of them have set the course for further research. The first maintains that antimycotic therapy leads to eradication of Candida fungi from vaginal mucosa and that the recurrent episodes of genital candidosis are caused by re-infection. The second hypothesis has an absolutely opposite starting ground. According to this theory, the frequent RGC episodes have been caused by a failure to eradicate Candida sp. from female genital tract. According to this theory, RGC is not caused by re-infection, but by relapse.

Key words: *Recurrent genital candidosis, reinfection, relapse*

Introduction

At the beginning of the third millennium, millions of women are afflicted with persistent genital fungal infections despite various treatments that have been offered as efficacious and effective (1, 2, 3).

It is a household fact of medical literature that ¾ of female population are at least once infected with a vaginal fungus while 50% of it go through this experience twice or three times in a lifetime (4, 5).

A most interesting fact for scientific investigations is that 5% of women are afflicted with recurrent genital candidosis (RGC) characterized by three or more genital, fungal infection episodes per a year. The data analysis is also interesting because it reveals that the most significant risk factors such as pregnancy, diabetes mellitus, long term use of antibiotics and citostatics, hormonal therapy and idiopathic or acquired immunodeficient conditions have not been verified.

The reference books are filled with controversial information about the cause of chronic, episodic vaginal cadidiasis. The pathogenesis of idiopathic RGC remains enigmatic to world experts in the fields of microbiology, immunology, epidemiology, gynecology as well as to physicians who are daily faced with so-called "small cases" which yet appear to be huge unsolved problems.

The scientific efforts and interests dealing with the cause of RGC have turned into two directions.

There are many different hypotheses about RGC pathogenesis, but two of them have set the course for further research.

The first of them maintains that antimycotic therapy leads to the eradication of Candida fungi from vaginal mucosa and that the recurrent episodes of genital candidosis are caused by re-infection. Candida sp., as a colonizer and a potential pathogen, comes to vaginal mucosa either from the digestive tract (endogenic re-infection) or by sexual transmission (exogenic re-infection) (2, 6, 7, 8, 9, 10).

The second hypothesis has an absolutely opposite starting ground. According to this theory, the frequent RGC episodes have been caused by a failure to eradicate Candida sp. from the female genital tract. Antimycotics act as funigistatics not as fungicides; thus, it is most probable that a certain number of microorganisms remain on vaginal mucus in spite of the treatment. The treatment significantly reduces the number of Candida microorganisms so that there are no symptoms of infection and the patient is clinically in the phase of remission. In a changed condition, which enables fungi to reproduce, the number of microorganisms increases and the infection appears again; clinically speaking, the patient is facing another RGC episode. According to this theory, RGC is not caused by re-infection, but by relapse (2).

The RGC relapse may be caused by changed characteristics of microorganisms. The resistance to antimycotics, pathogenic increase and antigen and phenotype

variations are the most significant characteristics of Candida fungi which can be a cause of re-infection (2, 11).

The RGC relapse, as another explanation tries to prove, may be caused by a change in a nonspecific immunity of mucosa. The change of microbial flora which is a natural barrier is a predisposition for fungi multiplication on vaginal mucosa and candidosis genesis. The reproductive hormones can change the environmental conditions, increase microorganisms's virulence and weaken immunoprotection agents on vaginal mucosa.

With reference to the validity of the two hypotheses, controversial arguments have been raised. A consensus of opinion has been reached only on the matter of the above mentioned causes which all may be risk factors (3, 12).

Endogenic reinfection

A group of authors, the defenders of the first hypothesis, who see the cause of RGC in Candida re-infection, have postulated one of the most popular theories.

Miles (13) examined the presence of Candida fungi on the vaginal mucosa and the digestive tract of women who are afflicted with RGC. In all the examined patients the presence of Candida sp. in the genital tract was accompanied by its presence in the digestive tract samples. The next phase of the research showed that the isolated fungi from the women's digestive and genital tracts are in fact of the identical Candida sp. type.

The therapy principle has naturally followed: oral and local Nystatin therapy for genital candidosis.

Every new discovery sets new rules but unfortunately it never offers permanent solutions. The dual local-oral Nystantin therapy in most cases has failed to cure women's prolonged genital fungal infections and to reduce RGC prevalence.

Another group of researchers has considerably improved the observations of the problem both in its theoretical and practical aspects. The scientists who see the cause of the problem in the vaginal infection relapse due to the failure of Candida eradication from vaginal mucosa have got some contradictory results in the research.

Sobel (14), whose reactions immediately followed every publication of spectacular "discoveries" of RGC causes, together with another author, O'Conner, found that there was a higher percentage of female RGC patients in whom there had not been identified the Candida sp. colonization of digestive tract. The further investigations showed that the types of Candida fungi, present in the digestive and the genital tract, are not identical. Sobel also points out that Candida sp. colonizes the women's digestive tract mucosa in shorter or longer time intervals, but the patient, fortunately, is not afflicted with genital fungal infections.

An electron microscopy investigation has showed the intracellular localization of C. albicans blastospores and hypha in the undamaged cells of vaginal and intestinal epithelia. The intracellular fungi position can be responsible not only for the therapy procedure endurance, but also for the reappearance of the infection after the fungi have got into vaginal lumen (15).

Assuming that the Candida colonization of the digestive tract may be the cause of repeated infections, Fong (16) examined Candida presence in the vaginal and the rectal mucosa of RGC patients. Fong found that 48.2% of the patients, during the manifest infection, have a positive fungi result in the digestive tract. However, only 10.10% of the RGC women have the Candida colonization of the rectal mucosa in the remission period which is identical with the result found in the control group. Therefore, he has arrived at a conclusion that the colonization of the rectal mucosa is a consequence rather than a cause of RGC.

Following the therapeutic effects of antimicotics in the treatment of genital candidosis, Odds (17) supported the theory that episodic, genital, fungal infections are a consequence of relapse rather than re-infection. Immediately after the treatment, 90% of examined women patients had no presence of Candida sp. but only 4-6 weeks after the therapy 20-25% of the asymptomatic women were Candida sp. positive. This speedy Candida recolonization of vaginal mucosa suggests an incomplete eradication of the fungi rather than a new infection.

The karyotype of isolated Candida sp. which causes RGC helped Vasques and Sobel (18) to find in eight out of ten women the same cell type which causes genital candidosis in a three year period.

The re-infection as a possible cause of RGC has become less probable with the results of recent DNA tests and biotypes of Candida sp. kinds present in the host organism. Mercure (19) has found that patients may be afflicted with the colonization of not only similar but also very different types of Candida, which are anatomically variously distributed; the colonization may persist for an indefinite time period. The microorganisms which cause RGC are genomically and physiologically different from the Candida types present on other mucosae, but are mutually identical. Examining DNA of RGC causes, Mercure has found the identical result in 86% of the examined patients, which is certainly a proof of the infection relapse.

Spinillo (20) examined the effects of various therapeutic procedures prescribed to women depending on the Candida presence in the digestive tract. Antimycotics have been selected on the basis of the antimycogram diffusion test. The treatment effects have been looked on for one year, beginning with the second week after the end of the therapy. the relapse percentage has not been decreased although the therapy procedure for the eradication of the fungi from the digestive tract has been followed. This author's research leads us to a conclusion that the discovery mentioned at the beginning of this paper as a significant one is a wrong rather than a valid therapeutic principle in the treatment of women's episodic chronic RGC.

Exogenic reinfection

The theory of re-infection states that sexual transmission may be a cause of RGC. It is supported by the fact that Candida sp. is four times more often found in the men who are the partners of the women with genital candidosis than in others (21). Besides, the Candida types, detected in the men, are identical with the Candida sp. types isolated from the samples taken from their female partners in the phase of acute fungal infection. The "ping-pong" infections between the partners may be a cause of Candida re-infections, and in that way the cause of RGC (22).

To be honest, Candida was found in only 20% of the examined male partners. The argument which is worth mentioning is that there is a prevalence of genital fungal infections in celibate women (23).

Using the DNA tests to specify C.albicans genomes, which cause RGC in women, in order to compare them with the same fungal types detected in the samples taken from men, Lockhart proved that the types of fungi isolated from the samples taken from the women and their partners were either completely or almost identical (24).

Schaid has come to the identical results using the genetic method. Shaid found identical C.albicans kinds in 80% of the examined couples (25).

The genome examination of isolated fungi from the samples of RGC female patients as well as their partners supports the thesis that sexual transmission, i.e. exogenic re-infection, can cause the recurrent RGC.

Fong (26) examined the effect of simultaneous antimycotic therapy of the couples in order to determine the practical value of the discovery that exogenic reinfection is a possible cause of RGC. Fong has found that the simultaneous treatment of the couples decreases the number of female patients with RGC re-infection when this number is compared with the control group in which the infected couples were not treated.

Fong repeated his experiment with the couples in which the partners were not subjected to any microbiological analysis so that they were, *a priori*, treated with antimycotics; this experiment points out to an insignificant difference among the female patients with RGC, after the appearance of a new episode of RGC, no matter whether the partners have been simultaneously treated or not.

Spinillo (27), like Fong, examining the effects of therapy on the recurrence of genital candidosis in infected patients, has found that the simultaneous treatment of the couples decreases the number of female patients with RGC reinfection.

Fong's and Spinillo's results, however, are just the beginning of the investigation of simultaneous therapy efficacy.

Good points are attributed to the fact that there is a long period of serious research work which awaits us before we decidedly chose whether to treat RGC female patients's partners *a priori* or not.

The RGC Relapse as a Result of Microorganisms's Characteristics

Microorganism's resistance

Sobel (28, 29) claims that the resistance of fungi to antimycotics cannot be responsible for the appearance of recurrent genital candidosis in women. In his prospective study Sobel showed that the minimal inhibitory concentration of antymycotics against Candida types, which cause RGC, remains the same during the one year experiment.

Examining the sensitivity of Candida types (177 isolates, which cause RGC, were during the one year period) to fluconazole, itraconazole, ketoconazole, clotrimazole and miconazole, Sobel registered neither any significant difference among nor resistance in the examined types. According to this author, even if the resistance of the fungi is a cause of RGC, then, it is true for a very limited number of cases.

Fong (30) examined the sensitivity of Candida types to antimycotics *in vitro* after the antimycotic therapy (ketoconazole, clotrimazole, intraconazole). Candida fungi, which cause RGC episodes, *in vitro* conditions show high sensitivity to the used antimicotycs. Not even one of the prescribed therapies was a cause of RGC episode due to their inefficiency.

As for C.albicans, *in vitro* conditions there was registered no resistance to antimycotics. There were found only sporadic cases of resistant C.tropicalis and C.glabrata, but the stronger doses of antimycotics successfully eliminated the problem (31).

Despite the fact that there is a consensus among most of the authors on the matter of the sensitivity of Candida types *in vitro* conditions, there have been accumulated very contradictory results concerning the efficacy of different terapeuthic procedures.

Sobel, for example, got contradictory results in the two investigations concerned with this problem. In the first research the therapeutic treatment with fluconazole had the same effect as clotrimazole which had been longer in usage. His second research, which was concerned with the efficacy of the fluconazole treatment of RGC episodes, as well as the effect of this medicament on the RGC relapse, did not repeat the success of the first (32).

Desai (33) have recommend fluconazole as one of the most efficient antimycotics in the treatment of genital candidosis and as the therapy best accepted by patients.

According to the defenders of the thesis that the digestive tract is a reservoir of RGC, fluconazole is the drug of choice, because it efficiently regulates the presence of Candida on the intestinal mucosa (21).

Wooley et all. in their researches have found that fluconazole is less effective in the genital infection treatment than other commercial azol derivatives (34).

Perera claims that econazole is less effective than clotrimazole in the vaginal candidosis treatment and the prevention of its relapse (35).

The fact that there is a little researches, which been concerned with the sensitivity of Candida types to antimycotics *in vitro*, with a wide range of antimycotics in the commercial antimycogram dilution tests, as well as, with the unstandardized methods for the *in vitro* examination of fungal sensitivity to antimycotics, is probably the reason why there are many contradictory results in the *in vitro* and *in vivo* investigations of antimycoticotic efficacy in the Candida treatment.

The Virulence Factors of Microorganisms

The factors of Candida sp. pathogenicity are certainly the characteristics of microorganisms which may be risk factors in female RGC.

The most significant factors which increase the virulence of Candida types are the following: the ability of germination, phenotype variations, antigen mimicry and the production of hydrolaze.

It is a starting position that there are fewer Candida fungi on female genital tract after the infection has been clinically observed and treated by therapy. If the persisting types are more virulent, then, they are certainly one of the risk factors which makes it possible for the infection to occur again or even to cause the RGC relapse.

The morphological changes of C.albicans can also be an important factor of pathogenicity. Namely, a shift of C.albicans, from a single cell form into a multinucleic form, increases the adherence of microorganisms to the vaginal epithelium and the invasion of hydrolytic enzymes on the tissue (36).

The dimorphism is followed by the change of superficial Candida antigenes. The immunoprotection mechanisms against the existing C.albicans blastospore antigenes fail to be effective once the hypha antegenes appear. The antigene difference may disturb the existing mechanism of immuno-tolerance which used to cause the asympthomatic C.albicans colonization of the vaginal mucosa. If the antigene mimicry is a result of the changed enviromental conditions on the vaginal mucosa, rather than any nutrition conditions, then the blastospore and hypha antigenes constantly appear and disappear, which disturbs the immuno-reactions and immuno-tolerance. It is also possible to assume that the microorganism, by the shift of C.albicans from a single cell form into a multinucleic form, avoids the influence of the immunoprotection mechanisms which have reacted against the blastospore antigenes, as long as their number increases, which causes the symptomathic, fungal, vaginal infection (2).

Using the experimental animal models of vaginitis, Sobel (37) showed that the non-germinating C.albicans mutants in high concentration, intravaginally inoculated into rats, provoke the fungal infection of weak intensity, which was spontaneously cured for a short time period. The repeated experiment, this time with C.albicans types which produce filaments, showed that the pathogenic types cause vaginal candidosis in rats, inoculated with low concentration; the infection is of stronger intensity and lasts longer.

In female patients with RGC, C.albicans can be often found in the form of hypha. In asymptomathic patients, the vaginal mucosa colonization is most often verified by the detection of the Candida blastospores.

Non-immune mechanisms: the prerequisite condition or the cause of RGC

The non-immune mechanisms, which are supposed to be a cause of RGC, are the flora of vaginal mucosa and the hormone status in women.

The hormone status, the level of reproductive hormones, as a cause of RGC can be proved by the fact that the prevalence of genital candidosis is greater in pregnancy and in the patient who uses oral contraceptives or the hormone therapy in the menopause. It has been proved that estrogen increases the adherence of C.albicans to the vaginal epithelium as well as that the fungi have receptors for the reproductive hormones on the cytoplasmic membrane. The periferal lymphocytes react more slowly in pregnancy and in the patient who takes oral contraception. Estrogen weakens the reactivity of skin test sensitivity, the activity of NC cells and the phagocyte activity of neutrophiles. The cause-effect relationship among the reproductive hormones, the immunity and the vaginal infection has been examined and proved, but the model of interection among these agents during RGC pathogenesis and the influence of hormones on the immune mechanisms of the vaginal mucosa have been insufficiently investigated (2).

Some dillemas are raised by the question: how can bacterial flora cause the increased reproduction of fungi on the vaginal mucosa?

It is suspected that a smaller number of bacteria, which prevent the reproduction of fungi due to the competition for nutritional potential, or the adherence places on the vaginal epithelium, may predispose the fungal expansion. However, it is also possible that the absence of some bacteria types with fungicidal products disturbs and changes the microbial community, which stimulates the fungal reproduction and causes the fungal infection.

Doderlin's description shows that lactobacilli in vaginal mucus have a normal, physiologic, microbiologic status.

Schoder as far as in 1921 proved the cause-effect relationship between the lactobaccillus findings and the vaginal mucosa predisposition to the infection. A smaller number of or even an absence of the bacteria which generate lactic acid is a risk factor for bacterial vaginosa or vaginitis (23).

In one of the biggest studies, examining the microbial flora of vaginal mucosa in 7918 pregnant women, Hillier found out that genital candidosis is accompanied by a reduced number of lactobacilli (38, 39).

Lactobacillus sp. can prevent the fungal reproduction on the vaginal mucosa either by the increase of pH secretion, by the interference of fungi for nutritional potential or the adherance places on the vaginal epithe-

lium. It has been proved that lactobacillus sp. inhibits the germination of C.albicans *in vitro*. It is well known nowadays that the peroxidase has a toxic effect on many microorganisms due to the building up of the H_2O_2-halid antimicrobial system. The lactobacilli which produce the peroxidation may have a toxic effect on the Candida fungi H_2O_2-halid of the system. It is significant to say that the peroxidase-producing lactobacilli have been found in 98% of the healthy female population.

There has been an innumerable number of studies that have examined the bacterial flora of vaginal secretion in women with genital candidosis.

Auger and Joly (40) have made a hypothesis according to their findings that Gram negative bacteria are stronger in their effect on Candida fungi germination than Gram positive bacteria and lactobacilli.

Salvaggi (41) has found out a more frequent presence of Gram positive and negative bacteria types than lactobacilli on the vaginal mucosa in women with the genital infection.

Hiller (38, 39), in his research which included thousends of women, showed that the asymptomathic Candida sp. colonization of vaginal mucosa was accompanied by a negative peroxidase-producing lactobacilli result. According to this author H_2O_2-lactobacilli are the most important barrier against the vaginal fungal colonization.

Sobel (23) was the first who pointed out to the paradoxical character of the results in Hiller's study. Namely, Sobel agrees with Hiller *a pro po* the significance of H_2O_2 lactobacilli, but he points out to the fact that Hiller has not proved a significant relationship between the fungal genital infection and the absence of lactobacilli. The research which included thousands of pregnant women did not prove any cause-effect relationship between the absence of lactobacilli and genital candidosis or the Candida colonization.

Sobel and Chaim (42) compared the results of semiquantative bacteriological analysis of vaginal secretion in women with RGC and volunteers. The comparison has not showed any significant difference of bacteria on the vaginal microflora. The Lactobacillus type was dominant in the samples of all the examined women. There was not recorded any significant difference as far as the presence of some lactobacilli types is concerned. The presence of Gram positive and negative bacteria, as well as of aneorobic bacteria, was recorded with no significant difference in women with RGC or healthy women. The findings of some pathogenic bacterial types in women with RGC, according to Sobel's explanation, is a simultaneous infection, whereas the bacterial flora as a natural barrier does not have any effect on the RGC occurence.

The findings of lactobacilli in vaginal secretion in women with RGC causes many disputes among authors about the effect of the bacteria which generate lactic acid, on the pathogenisis of RGC.

Sobel (23) refuses a possibility that lactobacilli cause RGC. This author defends his standpoint by the fact that he has proved the presence of a greater number of Gram positive bacilli in women with RGC than in healthy ones.

Many authors reject the possibility to decrease the prevalence of RGC by the intravaginal bacilli application. It sounds almost like an anegdote that many experts do not even take into a serious consideration the effect of lactobacilli on RGC.

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REKURENTNA GENITALNA KANDIDOZA ŽENA: POSLEDICA REINFEKCIJE ILI RECIDIVA

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Kratak sadržaj. *Podaci iz referentne literature ukazuju da 5% žena boluje od rekurentne genitalne kandidoze (RGK), bolesti koju karakteriše tri ili više epizoda gljivične genitalne infekcije u toku godine. Zanimljivost ove statističke realnosti je u tome da kod ovih žena najznačajniji faktori rizika kao što su trudnoća, diaebetes mellitus, dugotrajna upotreba antibiotika, citostatika, hormonske terapije, idiopatska i stečena imunodeficijentna stanja ostaju neverifikovani.*

Postoji znatan broj raznorodnih hipoteza o patogenezi RGK, ali su dve hipoteze uslovile glavne tokove istraživanja. Jedna teorija zastupa stav da terapija antimikoticima sprovodi eradikaciju gljiva roda Candida sa vaginalne mukoze i da je ponovljena epizoda genitalne kandidoze posledica reinfekcije.

Druga hipoteza ima za osnovu dijametralno suprotnu pretpostavku. Po ovoj teoriji česte epizode RGK posledica su neeradikacije Candida sp. iz genitalnog trakta žene, odnosno posledica su recidiva.

Ključne reči: *Rekurentna genitalna kandidoza, reinfekcija, recidiv*