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SEXUALLY TRANSMITTED DISEASES IN WOMEN AND SIGNIFICANCE OF COMBINED INFECTIONS

SEKSUALNO PRENOSIVE INFEKCIJE KOD ŽENA I ZNAČAJ UDRUŽENIH INFEKCIJA

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Ključne reči
Seksualno prenosive infekcije, C. trachomatis, Humani papilomavirusi (HPV), Herpes simplex virus 1, Herpes simplex virus 2, udružene infekcije.

Abstract

Frequency of sexually transmitted diseases caused by Chlamydia trachomatis, human papillomavirus (HPV) genotypes 6, 11, 16, 18, 31 and 33, as well as herpes simplex virus type 1 and 2 (HSV-1 and HSV-2), was presented in a sample of 200 women of various ages from Novi Sad and surroundings. Special attention was given to the analysis of incidence of combined infections caused by the mentioned pathogens, as well as the finding of group III of the Papanicolaou smear test in women with various infections.
The aim of the study was to examine the significance of the comprehensive diagnostic methods geared toward the application of timely preventive and therapeutic interventions, especially in view of the oncogenic potential of some of the pathogens.

INTRODUCTION

Sexually Transmitted Diseases are increasingly frequent nowadays. Scientific papers are reporting on this issue at an ever-growing rate. A significant number of these papers report Chlamydia trachomatis as the most common cause of sexually transmitted diseases in England [1]. USA [2], Scandinavian countries [3], France [4] as well as in Serbia [5, 6, 7, 8, 9]. Chlamydias are classified as bacteria (the Chlamydiaceae family, genus Chlamydia) due to having both nucleic acids (RNA and DNA, unlike viruses), characteristic coccobacillus morphology, unique reproduction cycle with the formation of typical cytoplasmic inclusions (important in diagnostics), with a specific antigenic structure, metabolic activity and sensitivity to antibiotics (unlike viruses). Their adaptation to obligate intracellular parasitism makes them similar to viruses regarding this characteristic. Therefore, the diagnostic process of infections caused by Chlamydia is similar to that of virus infections. They can be replicated for the purpose of isolation and identification only in cell cultures, with the McCoy cell culture still being the reference method for diagnosis of C. trachomatis. In addition, Chlamydia antigens can be identified in patient samples using the immunofluorescence and/or ELISA tests. Patient material can also be diagnostically tested using molecular methods. As an additional (complementary) diagnostic method, specific antibodies can be identified in patient sera using the indirect immunofluorescence assay, or ELISA test, and even the complement fixation test which determines total antibodies against the group Chlamydia antigen [1, 10, 11, 12].

Chlamydia trachomatis as a cause of sexually transmitted disease causes urogenital infections in men and women, as well as infant pneumonia and inclusion conjunctivitis of the newborn if the infection is transmitted to the eye [1, 13, 14, 15]. Chlamydia trachomatis may play a significant role in the development of infertility in women, ectopic pregnancy and complications in childbirth and puerperium (the risk of premature birth, miscarriage, postpartum endometritis, as well as premature rupture of membranes) [7, 13,16, 17, 18] .

There are no certain clinical signs that would confirm a Chlamydia trachomatis infection. Most of these infections are located on mucous membranes, which is often the reason for a lack of stronger antigenic stimulation. Therefore, the humoral immune response is usually weak, so the specific antibodies can only be confirmed by very sensitive serological tests [1, 11]. Chlamydia tends to remain long in the body intracellularly after the primary infection, which can result in a long-term latent infection even in the presence of significant antibody titers in the blood. Recent studies show that the infection can be activated, expanded, and even lead to the high-risk group III of the Papanicolaou smear test if the affected person has a combined sexually transmitted infection (usually an additional HPV or herpes simplex virus infection) [12, 18]. Therefore, an aggressive long-term therapy of these infections is necessary, and since the etiologic diagnosis of C. trachomatis infections cannot be made with confidence on clinical grounds alone (because the clinical signs are diverse, uncertain, and sometimes missing), it is necessary to regularly perform modern laboratory diagnostics [1,12,18].

Human papillomaviruses belong to the Papillomaviridae family, genus Papillomavirus, and are viruses of icosahedral (cubic) symmetry, without the outer layer, medium size (about 55 nm), whose genome is a circular double-stranded DNA, and viral proteins (E_3, E_4, E_5, E_6, E_7) also participate in the processes of the host cell transformation (oncogenic potential of the virus). These viruses infect squamous epithelial cells of the skin and mucous membranes, initially causing persistent latent infections and, after the conditions followed by a decline of immune resistance, causing a variety of benign and malignant growths. These changes in the urogenital area can be sexually transmitted. Thus, types 6 and 11 can cause benign genital warts (condylomas) in the urogenital area, and genotypes 16, 18, 31, 33, 35, 39, 45, 49, 52, 56, 57, 58, 59 and 61 have been demonstrated in malignant neoplasms of the urogenital tract (oncogenic potential typical for certain genotypes of human papillomavirus - HPV). In these changes, both benign and malignant, it is not easy to prove the virus, especially if it is in the cell in the latent phase, and if its DNA is incorporated into the cell genome or in the form of an episomal DNA (when the virus does not replicate in the cell). Virus isolation in special cell cultures is not a part of the routine diagnostics of HPV. Serological tests are not performed due to the large number of virus types. Immunoelectron microscopy is rarely used. Therefore, molecular tests for identification of viral genome are indispensable in the diagnostics of HPV, even if the virus is present in minute amounts („Southern blot" test, in situ hybridization test and PCR test) [19,20,21,22,23,24].

Herpes simplex virus type 1 (the most common cause of labial herpes, but possibly also herpes in other locations, including the genital area) and herpes simplex virus type 2 (the cause of genital herpes) belong to the family Herpesviridae, subfamily Alphaherpesvirinae, genus Simplexvirus. These viruses are of icosahedral (cubic) symmetry, the size of 100-150 nm, with two layers and a double-stranded DNA genome. They also have a property to cause persistent latent infections after the primary infection in the host organism, as well as to have the infection activated after conditions which lead to a decline in immune resistance. Herpes simplex virus type 2 is also associated with oncogenic potential (cervical cancer in women). Combined infections with one of the sexually transmitted pathogens in particular contribute to this risk [19, 25, 26, 27, 28, 29].

The aim of this study was to determine the frequency and significance of Chlamydia trachomatis infections, infections with certain genotypes of human papillomavirus (types 6 and 11, 16 and 18, 31 and 33), as well as type 1 and 2 herpes simplex virus in women of various ages in our community.

The hypothesis is that the combined infections are often accompanied by changes which are marked as group III of Papanicolaou, and which require further examination, control, and appropriate treatment.

MATERIAL AND METHODS

The sample of 200 women of various ages (19 years and upwards) was tested at the Center for Virology of the Institute for Public Health of Vojvodina. With detailed anamnesis and clinical data, swabs were collected from all patients (as directed) for the fluorescent microscopy test for Chlamydia trachomatis (by the indirect immunofluorescence test), for herpes simplex virus type 1 and 2 testing (by the direct immunofluorescence test with monoclonal antibodies), as well as for the human papillomavirus genotypes 6, 11, 16, 18, 31, and 33 testing by the molecular hybridization technique *in situ*. Results obtained were compared and statistically analyzed by X^2 test. Special emphasis was placed on the analysis of patients with a confirmed Papanicolaou group III result. Confirmation of Chlamydia trachomatis and herpes simplex virus type 1 and 2 infections was also conducted by the detection of antibodies in the serum using the ELISA tests (according to manufacturer's instructions).

RESULTS

Out of 200 examined women, 60 were aged 19-29, 57 were 30-39, 50 were 40-49, and 33 were aged 50 years and upwards. Chlamydia trachomatis infection was confirmed in 74 women (out of 200 examined), i.e. in 37.0%. The greatest number of infected was found in the age group from 30-39 (40.3%) and 40-49 (38.0%). In patients aged from 19-29, C. trachomatis infection was found in 35.0%, and in women older than 50 it was diagnosed in 33.3%. A statistically significant difference in frequency of these infections in different age groups of tested women was not discovered (Table 1).

Table 1 *- Chlamydia trachomatis infections*

AGE				TOTAL
19 - 29	30 - 39	40 – 49	> 50	
21/60	23/57	19/50	11/33	74/200
(35,0%)	(40,3%)	(38,0%)	(33,3%)	(37,0%)

ACUTE/TESTED
(% ACUTE)

Out of 200 women tested by the hybridization technique *in situ*, some of HPV genotypes (6 and 11, or 16 and 18, as well as 31 and 33) were confirmed in 23 patients (11.5%). The greatest number of infected was in the oldest age group. In patients aged 40-49, an HPV infection was detected in 16.0%, and in patients older than 50 in 15.1 % of the cases. An HPV infection was diagnosed in 6.6% of patients aged 19-29 and in 10.5% of women aged 30-39 (Table 2).

Table 2 - *HPV infections*

HPV GENOTYPES	AGE				TOTAL
	19 - 29	30 - 39	40 – 49	> 50	
6, 11	3/60 (5,0%)	4/57 (7,2%)	5/50 (10,0%)	3/33 (9,1%)	15/200 (7,5%)
16, 18	1/60 (1,7%)	2/57 (3,5%)	2/50 (4,0%)	1/33 (3,0%)	6/200 (3,0%)
31, 33	0/60 (0)	0/57 (0)	1/50 (2,0%)	1/33 (3,0%)	2/200 (1,0%)
TOTAL	4/60 (6,6%)	6/57 (10,5%)	8/50 (16,0%)	5/33 (15,1%)	23/200 (11,5%)

ACUTE/TESTED
(% ACUTE)

HPV genotypes 6 and 11 were more often found in women older than 30 (8.6% of the tested) compared to women aged 19-29, where the infection was confirmed in 5.0% of the tested. Statistically significantly highest number of these infections was confirmed in subjects aged 40-49 (10.0%) and older than 50 (9.1%) p = 0.05.

Genotypes 16 and 18 were somewhat less frequent than genotypes 6 and 11. They were more commonly found in women older than 30 (in 3.6% of the cases) compared to women younger than 30 (in 1.7% of the cases). The highest number of infected was in the age group from 40-49 (4.0%). Differences were not statistically significant. Genotypes 31 and 33 were the rarest, and only identified in subjects older than 40 (in 2.4% of the cases). All these results are presented in Table 2.

As shown in Table 3, an infection with one of the herpes simplex virus types (HSV) was confirmed in 12.0% of the tested women. Out of this number, an infection with type 1 was found in 4.0%, and type 2 in 8.0% of the tested women.

Table 3 *- HSV infections (type 1 and 2)*

HPV GENOTYPES	AGE				TOTAL
	19 - 29	30 - 39	40 – 49	> 50	
6, 11	3/60 (5,0%)	4/57 (7,2%)	5/50 (10,0%)	3/33 (9,1%)	15/200 (7,5%)
16, 18	1/60 (1,7%)	2/57 (3,5%)	2/50 (4,0%)	1/33 (3,0%)	6/200 (3,0%)
31, 33	0/60 (0)	0/57 (0)	1/50 (2,0%)	1/33 (3,0%)	2/200 (1,0%)
TOTAL	4/60 (6,6%)	6/57 (10,5%)	8/50 (16,0%)	5/33 (15,1%)	23/200 (11,5%)

ACUTE/TESTED
(% ACUTE)

While the percentage of HSV type 1 infections was greater in the age group under 30 (6.6%), the percentage of HSV type 2 infections was greater in patients older than 30 (10.0%), especially in those older than 40 (12.04%).

A combined infection (with two of the causes which were the subject of this study) was confirmed in 11.0% of the cases, and mostly in patients older than 50 (in 15.1%). In subjects aged 40-49, combined infections were diagnosed in 12.0% of the cases. In patients younger than 30 (19-29) combined infections were found in 10.0%, and in subjects aged 30-39 in 8.8% of the cases (Table 4).

Table 4 - *Combined infection*

COMBINED INFECTION	AGE				TOTAL
	19 - 29	30 - 39	40 – 49	> 50	
Chlamydia + HSV1	3/60 (5,0%)	1/57 (1,75%)	0/50 (0)	0/33 (0)	4/200 (2,0%)
Chlamydia + HSV2	0/60 (0)	0/57 (0)	1/50 (2,0%)	0/33 (0)	1/200 (0,5%)
Chlamydia + HPV	0/60 (0)	2/57 (3,5%)	2/50 (4,0%)	0/33 (0)	4/200 (2,0%)
HPV + HSV1	1/60 (1,7%)	0/57 (0)	0/50 (0)	0/33 (0)	1/200 (0,5%)
HPV + HSV2	2/60 (3,3%)	2/57 (3,5%)	3/50 (6,0%)	5/33 (15,1%)	12/200 (6,0%)
TOTAL	6/60 (10,0%)	5/57 (8,8%)	6/50 (12,0%)	5/33 (15,1%)	22/200 (11,0%)

ACUTE/TESTED
(% ACUTE)

The most common combined infections were with HPV and genital herpes virus, which was confirmed in 6.0% of the cases, most commonly in patients older than 40, and particularly in those older than 50 (15.1%), which is a statistically significant difference (p = 0.05).

A combined infection with HPV and herpes simplex virus type 1 was detected only in the youngest patients (aged 19-29), while an infection with HPV and C. trachomatis was confirmed only in women aged 30-49 (in 3.7%).

Simultaneous infections with C. trachomatis and herpes simplex virus type 1 were confirmed in the youngest patient group (under 40 years of age), while the highest number of combined infections was diagnosed in women aged 19-29 (5.0%). A combined infection with herpes simplex virus type 2 and C. trachomatis was found only in women aged 40-49 (in 2.0%).

As presented in Table 5 (5A and 5B), group III of the Papanicolaou test was present in 13 patients with only one infection confirmed (6.5% of the tested). Except for one patient, these were all women older than 30. They had an HPV infection (genotypes 16 and 18), genital herpes simplex virus and/or Chlamydia trachomatis.

Among the women with two simultaneous infections confirmed, 20 (10.0%) had group III Papanicolaou result. Most of them had a combined infection with HPV and HSV type 2 (6.0%). These women belonged to all age groups, although most were older than 40 (9.6%), and especially

Table 5A *- Papanicolaou group III*

INFECTION	AGE				TOTAL
	19 - 29	30 - 39	40 – 49	> 50	
CHLAMYDIA	1/60 (1,7%)	3/57 (5,3%)	3/50 (6,0%)	1/33 (3,0%)	8/200 (4,0%)
HPV	/	1/57 (1,75%)	1/50 (2,0%)	/	2/200 (1,0%)
HSV1	/	/	/	/	0/200 (0)
HSV2	/	2/57 (3,5%)	1/50 (2,0%)	/	3/200 (1,5%)
TOTAL	1/60 (1,7%)	6/57 (10,5%)	5/50 (10,0%)	1/33 (3,0%)	13/200 (6,5%)

ACUTE/TESTED
(% ACUTE)

Table 5B *– Papanicolaou group III*

COMBINED INFECTION	AGE				TOTAL
	19 - 29	30 - 39	40 – 49	> 50	
Chlamydia + HSV1	1/60 (1,7%)	1/57 (1,75%)	/	/	2/200 (1,0%)
Chlamydia + HSV2	/	/	1/50 (2,0%)	/	1/200 (0,5%)
Chlamydia + HPV	/	2/57 (3,5%)	2/50 (4,0%)	/	4/200 (2,0%)
HPV + HSV1	1/60 (1,7%)	/	/	/	1/200 (0,5%)
HPV + HSV2	2/60 (3,3%)	2/57 (3,5%)	3/50 (6,0%)	5/33 (15,1%)	12/200 (6,0%)
TOTAL	4/60 (6,6%)	5/57 (8,8%)	6/50 (12,0%)	5/33 (15,1%)	20/200 (10,0%)

ACUTE/TESTED
(% ACUTE)

older than 50 (15.1%). The second most common combined infections were with HPV and C. trachomatis (3.7%) in patients aged 30-49. It must be emphasized that, out of the total number of 22 patients with a combined infection caused by two pathogens, 20 (90.9%) were diagnosed with the Papanicolaou group III – the result which clearly speaks for itself.

DISCUSSION AND CONCLUSION

The determined percentage of women positive to C. trachomatis (37.0%) and the share of these infections in all age groups of women (with no statistically significant differences in the incidence of these infections) indicate the necessity of diagnostic procedures as a part of the regular routine check-up. It is important to note that 4.0% of the tested women with a confirmed C. trachomatis infection also had the group III Papanicolaou result. In addition, another 3.5% of the tested subjects with a confirmed combined infection with Chlamydia (most commonly HPV, but also HSV type 1 and 2) also had the group III Papanicolaou result. These data are indicative and require not only regular diagnostics and follow-up, but also permanent control and appropriate and timely treatment of such patients. Presented data are in accordance with conclusions of many authors who had examined this issue [1, 3, 4, 9].

The study showed that the investigated HPV genotypes (6 and 11, 16 and 18, as well as 31 and 33) analyzed using the molecular hybridization method in situ, were confirmed in 11.5% of the tested women and were more frequently identified in patients older than 30, and in particular those older than 40 and 50. This especially applies to genotypes 16 and 18, and 31 and 30, which are associated with oncogenesis according to scientific literature. Besides, types 31 and 33 were the rarest (and only found in patients older than 40). The Papanicolaou smear test confirmed the group III result in 1.0% of these women, all of whom had confirmed HPV genotypes 16 and 18. In case of a combined infection with HPV and HSV type 2, the total of 6.0% of women had the Papanicolaou group III result. All except one woman had confirmed HPV 16 and 18, or 31 and 33 genotypes. The same result of the Papanicolaou test was found in another 2.5% of women with a combined infection with HPV and HSV type 1, or HPV and C. trachomatis. Thus, regarding the combined infections with HPV and other analyzed pathogens, 8.5% of the tested women had a confirmed Papanicolaou group III result. These findings, which agree with the data from scientific literature, are significant because they draw attention to this important issue [21, 23, 24,30].

In the sample of examined women, an infection with HSV type 1 was detected in 4.0 %, and an infection with HSV type 2 in 8.0% of the tested subjects. However, the Papanicolaou group III was not found in any patients with isolated HSV type 1 infection, but was confirmed in 1.5% of the patients diagnosed only with an HSV type 2 infection. In contrast, in women with a combined infection, i.e. a simultaneous infection with HPV and HSV type 2, the Papanicolaou group III was proved in 6.0% of the tested subjects. In case of the combined infections with HSV type 1 and C. trachomatis or HPV, the Papanicolaou group III was confirmed only in 1.5% of patients. In all other combined infections (except HPV and HSV type 2), the Papanicolaou group III result was confirmed in 4.0% of the tested women. These results are in accordance with the findings of some other authors [25, 26, 27, 28, 29].

The final and obvious conclusion, which speaks for itself, is the observation that out of the total of 200 examined women, 121 had a confirmed infection (60.5%). Out of this number, 99 (49.5%) had a confirmed infection with one of the analyzed pathogens, and 22 (11.0%) had two confirmed infections. Out of 99 patients with one diagnosed infection, 13 had a finding of Papanicolaou group III (13.1%), while out of 22 patients with a confirmed combined infection (with two causing pathogens), 20 had a result of Papanicolaou group III (90.9%). Only in two cases of confirmed combined infections, the Papanicolaou group III was not found. These two patients were aged 19 -29 and had a confirmed infection with C. trachomatis and herpes simplex virus type 1.

This result in particular points to a necessity of regular diagnostics of these infections and application of prompt preventive actions and therapeutic measures in order to avoid potential adverse outcomes of the infections caused by the microorganisms analyzed in this study, some of which are known to exhibit oncogenic potential.

Sažetak

Na uzorku 200 žena različite starosti iz Novog Sada i okoline, prikazana je učestalost infekcija koje se prenose polnim putem, izazvanih sa C. Trachomatis (Chlamydia trachomatis), Humanim papillomavirusom (HPV) i to genotipovima 6 i 11, 16 i 18 i 31 i 33, kao i Herpes simplex virusom tipom 1 i tipom 2 (HSV 1 i 2). Posebno je analizirana učestalost udruženih infekcija, izazvanih pomenutim uzročnicima i prisustvo grupe III dobijene Papanicolau pregledom kod žena sa različitim infekcijama.

Cilj rada je bio da se sagleda značaj ovakve sveobuhvatne dijagnostike, radi blagovremenog preduzimanja preventivnih i terapijskih postupaka, pošto se radi o nekim od uzročnika sa onkogenim potencijalom.

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