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GENITAL WARTS IN WOMEN – 12-YEAR INCIDENCE RATE TRENDS IN NOVI SAD

*GENITALNE BRADAVICE KOD ŽENA:
DVANAESTOGODIŠNJI TREND STOPE INCIDENCIJE U NOVOM SADU*

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Summary

Introduction. Data on the incidence and age distribution of women with genital warts in Serbia are limited. The aim of this study was to determine the epidemiological characteristics of genital warts in the female population aged 15 - 69 years in Novi Sad. **Material and Methods.** A descriptive epidemiological study was conducted using the data of the Primary Health Care Center "Novi Sad". The study data refer to women examined by primary care gynecologists during a 12-year period (2010 - 2021). **Results.** During the observed period, 654 out of 240,494 examined women aged 15 - 69 years, i.e. 609 out of 164,578 women aged 15 - 49 years, had newly diagnosed genital warts. The cumulative overall incidence rate of genital warts in women aged 15 - 69 was 2.7/1,000 (95% confidence interval 2.64 - 2.77), while in women aged 15 - 49 it was 3.7/1,000 (95% confidence interval 3.61 - 3.79). The trend in genital warts incidence in both observed age groups was stable. The highest annual incidence rate of genital warts was registered among women aged 15 - 19 years, and it was statistically significantly ($p < 0.0001$) higher than in all the other age groups. The annual estimated number of women with newly diagnosed genital warts in Novi Sad was 547, of which 187 (34.2%) were women aged 15 - 19 years. **Conclusion.** Our results provide essential epidemiological data that may be used as the basis for future population studies, as well as for the evaluation of the effectiveness of the human papillomavirus vaccination campaign, after its wide implementation in the vulnerable population.

Key words: Condylomata Acuminata; Women; Incidence; Papillomavirus Vaccines; Epidemiology; Diagnosis; Serbia

Introduction

Genital warts (GWs) are the most common genital infection caused by human papillomavirus (HPV). They are one of the most common sexually transmitted viral infections worldwide, presenting as single

Sažetak

Uvod. Nema dovoljno podataka o učestalosti i uzrasnoj distribuciji genitalnih bradavica kod žena u Srbiji. Cilj ove studije bio je da se odrede epidemiološke karakteristike genitalnih bradavica u populaciji žena Novog Sada uzrasta 15–69 godina. **Materijal i metode.** Sprovedena je deskriptivna epidemiološka studija upotrebom podataka iz primarnog nivoa zdravstvene zaštite Doma zdravlja Novi Sad. Podaci studije se odnose na žene koje je pregledao ginekolog primarnog nivoa zdravstvene zaštite tokom dvanaestogodišnjeg perioda (od 2010. do 2021. godine). **Rezultati.** Tokom posmatranog perioda, 654 žene od ukupno 240.494 pregledanih, uzrasta 15–69 godina, odnosno 609 žena od pregledanih 164.578 uzrasta 15–49 je imalo novootkrivenu dijagnozu genitalnih bradavica. Kumulativna opšta stopa incidencije genitalnih bradavica za žene uzrasta 15–69 godina bila je 2,7/1000 (95% CI 2,64–2,77), dok je za žene uzrasta 15–49 godina bila 3,7/1000 (95% CI 3,61–3,79). Trend incidencije genitalnih bradavica u posmatranom periodu u obe uzrasne grupe bio je stabilan. Najviša godišnja stopa incidencije genitalnih bradavica je registrovana u uzrastu 15–19 godina i ona je bila statistički značajno ($p < 0,0001$) viša u odnosu na incidencije u svim ostalim posmatranim uzrastima. Godišnji procenjen broj novootkrivenih dijagnoza genitalnih bradavica kod žena u Novom Sadu bio je 547, a 187 (34,2%) žena je bilo uzrasta 15–19 godina. **Zaključak.** Naši rezultati daju bazične epidemiološke podatke koji se mogu koristiti kao polazište za buduća istraživanja u populaciji, kao i za procenu efikasnosti kampanje vakcinacije protiv humanog papiloma virusa, nakon njene široke primene u osetljivim grupama.

Ključne reči: genitalne bradavice; žene; incidenca; HPV vakcina; epidemiologija; dijagnoza; Srbija

or multiple papules on the vulva, perianal area, vagina, cervix, penis, anus, scrotum and urethra [1–3].

The prevalence of HPV infection has been steadily increasing, with an estimated 20 million people in the United States (US) being infected with the virus [2, 3]. The GWs affect both males and females,

Abbreviations

GW	– genital wart
HPV	– human papillomavirus
US	– United States
PHCC	– Primary Health Care Center
CI	– confidence interval
UK	– United Kingdom

with an estimated 6.2 million new cases annually among subjects aged 14 - 44 years [4]. More than 150 HPV types have been identified, of which approximately 40 cause infections in the genital area [5, 6].

Genital HPV types are categorized according to their epidemiological association with cervical cancer. High-risk types have the potential to act as carcinogens. Types 6 and 11 can cause benign or low-grade cervical cell changes, as well as GWs, and recurrent respiratory papillomatosis [7].

Approximately 90% of all cases of GWs are caused by HPV-6 and HPV-11 types that rarely progress to cancerous lesions, whereas warts associated with HPV-16 and HPV-18 may be predisposed to oncogenic transformation [8]. The GWs caused by HPV types 6 and 11, although not fatal, require diagnosis and treatment, otherwise they may lead to a significant impairment of the quality of life [9].

So far, two vaccines have been licensed against low-oncogenic HPV types (6 and 11) [10]. According to the experiences to date, in countries where vaccination has previously been implemented, the quadrivalent vaccine has shown a significant decrease in the incidence of GWs [11].

Considering the fact that diagnosis of GWs is not subject to mandatory notification in our country [12], the estimation of their incidence and distribution can be made only based on results of specific epidemiological studies. In Vojvodina, Serbia, women with GWs are usually diagnosed and treated by gynecologists or dermatovenereologists.

According to the analysis of a representative sample in the US, approximately one in 100 sexually active adults has GWs [13]. Based on the estimate that 1% of the sexually active population aged 15 - 59 years has GWs at least once in a lifetime, and given that population of this age group in Novi Sad accounts for about 220,000 people, it may be assumed that at least 2,000 – 2,200 citizens are facing with GWs in Novi Sad.

The aim of this study was to evaluate the crude and age-specific incidence of GWs, as well as to estimate the annual number of newly diagnosed GWs in the female population of Novi Sad.

Material and Methods

We conducted a retrospective observational study covering 12 consecutive years (2010 - 2021). Six gynecologists examined a population of 25,000 women aged ≥ 15 years (corresponding to 6% of the total female population of this age in Novi Sad). Gynecologists were selected based on the number of contracts/reviews they performed annually at the

Primary Health Care Center (PHCC) of Novi Sad. The data for this study were obtained from the electronic database of the PHCC, i.e. from the Gynecology Department of the PHCC in Novi Sad.

The diagnosis of GWs is based on visual inspection and no laboratory tests are required. The GWs are defined as warts in or around the genital area which include the external genitalia, perineum, and perianal region. The new case of GWs was defined as a case in a person who reported never having GWs before. The participants with recurrent episodes of GWs were excluded from the study.

The patients with the diagnosis of GWs were divided by predetermined age groups during the period from 2010 to 2021. Basic statistical indicators, general (crude) and specific incidence rates were examined. Incidence rates and 95% confidence intervals (CI) were calculated using the annual number of newly diagnosed cases of GWs in women (numerator) and the number of women visiting any of the included gynecologists annually in the study period in Novi Sad according to the Census in the Republic of Serbia (2011) (denominator) and multiplied by 100,000 women per year. The estimated number of women with GWs in Novi Sad was extrapolated from the obtained prevalence rates by age groups and the estimated population of Novi Sad according to the 2011 Census. Two tailed p-values less than 0.05 were considered statistically significant.

The personal data of the included women were not used during the analysis. Only registration forms of patients were used, and no clearance by an Ethics Committee for retrospective analysis of anonymized data is required in Serbia.

Results

During a 12-year period, 654 out of 240,494 examined women aged 15 - 69 years, i.e. 609 out of 164,578 women aged 15 - 49 years, had newly diagnosed GWs. The number of women who visited any of the six community gynecologists included in the study has significantly increased from 2010 (11,300) to 2021 (25,488) (**Table 1**).

Table 1 summarizes the crude annual incidence rate of GWs divided into two age groups during the entire study period. Namely, the cumulative crude incidence rate of GWs in the group aged 15 - 69 years was 2.7/1,000 (95% CI 2.64 - 2.77), while the age-specific incidence in the group aged 15 - 49 years was 3.7/1,000 (95% CI 3.61 - 3.79). The trend in GWs incidence during the 12-year period in both observed groups was stable.

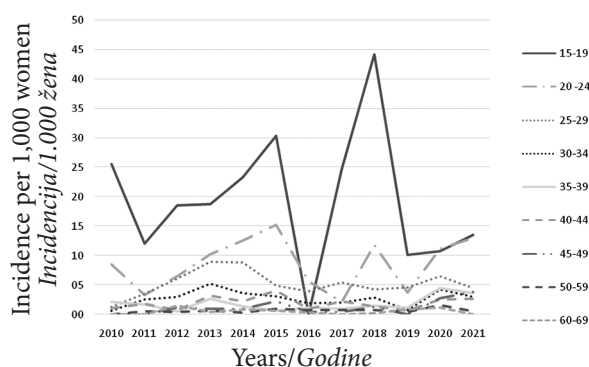
In regard to the examined age groups, the highest annual incidence rate of GWs was registered among women aged 15 - 19 years. In this age group, the incidence rates in 2015 and 2018 were 30.4/1,000 and 44.2/1,000 women, respectively, and they exceeded the incidence rates in other age groups during the study period (**Graph 1**).

The 12-year incidence rate (18.6/1,000, 95% CI 17.55 - 19.69) of GWs in women aged 15 - 19 years

Table 1. Crude incidence rates of genital warts in two observed age groups in Novi Sad, 2010 - 2021**Tabela 1.** Opšte stope incidencije genitalnih bradavica u dve posmatrane uzrasne grupe u Novom Sadu, 2010 – 2021

Years/Godine	Age group/Uzrasna grupa					
	All ages (15 - 69)/Sva godišta (15-69)			Women aged 15 - 49 years/Žene od 15 do 49 godina		
	No of observed women/ <i>Broj pregledanih žena</i>	No of diagnosed genital warts/ <i>Broj dijagnovanih genitalnih bradavica</i>	Incidence rate per 1,000 women (95% confidence interval)/ <i>Stopa incidencije /1.000 žena (95% granica poverenja)</i>	No of examined women/ <i>Broj pregledanih žena</i>	No of diagnosed genital warts/ <i>Broj dijagnovanih genitalnih bradavica</i>	Incidence rate per 1,000 women (95% confidence interval)/ <i>Stopa incidencije /1.000 žena (95% granica poverenja)</i>
2010	11,300	41	3.6 (3.26-3.96)	8,704	41	4.7 (4.26-5.17)
2011	13,471	31	2.3 (2.05-2.57)	10,039	30	3.0 (2.68-3.35)
2012	15,841	47	3.0 (2.74-3.28)	11,465	43	3.7 (3.36-4.06)
2013	19,153	78	4.1 (3.82-4.39)	13,427	75	5.6 (5.22-6.00)
2014	21,203	75	3.5 (3.26-3.76)	14,515	71	4.9 (4.55-5.26)
2015	22,374	73	3.3 (3.07-3.54)	15,009	67	4.5 (4.17-4.84)
2016	22,800	37	1.6 (1.44-1.77)	14,967	33	2.2 (1.97-2.45)
2017	22,829	36	1.6 (1.44-1.77)	14,619	33	2.3 (2.06-2.56)
2018	22,063	44	2.0 (1.82-2.19)	13,576	40	2.9 (2.62-3.20)
2019	22,508	24	1.1 (0.97-1.24)	13,758	18	1.3 (1.12-1.50)
2020	21,464	85	4.0 (3.74-4.27)	15,897	77	4.8 (4.47-5.14)
2021	25,488	83	3.3 (3.08-3.53)	18,602	81	4.4 (4.11-4.70)
Total/Ukupno	240,494	654	2.8 (2.64-2.77)	164,578	609	3.7 (3.61-3.79)

was significantly ($p < 0.0001$) higher than in all the other age groups (range 0.5 and 9.3/1000 women). There was no statistically significant ($p = 0.4708$) difference in the incidence rate between the cohorts of women aged between 15 and 19 years (20.2 95% CI 14.84 - 26.47; 21.5 95% CI 17.85 - 25.51; 23.6 95% CI 20.84 - 26.53; 20.1 95% CI 18.13 - 22.19; 14.5 95% CI 13.01 - 16.09, respectively). The estimated number of women diagnosed with GWs in Novi Sad annually was 547 (corresponding to 6,564 new GWs cases during a 12-year period), of whom 187 (34.2%) were women aged 15 - 19 years (**Table 2**). The trend of GWs incidence decreased with the increasing age ($y = -2,1846x + 24,815$, $R^2 = 0.8714$) of women (data are not shown).

**Graph 1.** Incidence rates of genital warts in women by age groups in Novi Sad, 2010 - 2021**Grafikon 1.** Stope incidencije genitalnih bradavica po uzrastima žena u Novom Sadu, 2010-2021

Discussion

To our knowledge, this is the first study to evaluate certain epidemiological characteristics of GWs in the territory of Vojvodina. Although we are aware that cases of GWs in our study were probably under-reported (GWs are not subject to mandatory notification in our country and the majority of people did not seek treatment for GWs), our results are quite comparable to those reported in other various settings.

Regarding the available data, with the exception of the United Kingdom (UK), GWs is not a notifiable condition in most other countries. In line with this, there is limited epidemiological data of GWs in certain European countries, especially in Eastern Europe, and even less in other regions, such as Africa, Latin America and South Asia [1]. Direct assessment regarding the incidence and distribution of GWs depends on the type of data sources, case definitions, test methods, time periods and study designs of GWs in certain territories. Taking into account that sources of epidemiological data of GWs are usually obtained from notifications of various specialists (general practitioners, gynecologists, dermatovenereologists, urologists) for different territories, as well as from medical histories of clinically treated women or from other sources, this imposes the potential problem to gain insight into the real number of patients with GWs which complicates the possibility of comparison in different territories.

It is important to underline that our data were obtained from the period before the wide introduction of the HPV vaccine for specific age groups into the immunization calendar in Serbia [14].

Table 2. Twelve-year incidence rates and estimated annual number of women with genital warts by age groups in Novi Sad**Tabela 2.** Dvanaestogodišnje stope incidencije i godišnji procenjen broj genitalnih bradavica u određenim uzrasnim grupama u Novom Sadu

Age Uzrast	Women with a diagnosis of genital warts <i>Žene sa dijagnozom genitalnih bradavica</i>		Women exam- ined by a gynecologist <i>Žene koje su bile na pregledu kod ginekologa</i>		Incidence/1,000 women (95% confidence interval) <i>Incidencija/1.000 žena (95% grani- ca poverenja)</i>	p value <i>p vrednost</i>	p value <i>p vrednost</i>	Estimated annual number of women with genital warts <i>Procenjen broj žena sa dijagno- zom genitalnih bra- davica (godišnje)^a</i>
	No/Br.	%	No/Br.	%				
15	4	0.6	198	0.1	20.2 (14.84-26.47)			ND
16	10	1.5	466	0.2	21.5 (17.85-25.51)			ND
17	21	3.2	888	0.4	23.6 (20.84-26.53)	p=0.4708*		ND
18	31	4.7	1,543	0.6	20.1 (18.13-22.19)			ND
19	30	4.6	2,066	0.9	14.5 (13.01-16.09)			ND
Subtotal (15 - 19) <i>Podzbir (15-19)</i>	96	14.7	5,161	2.1	18.6 (17.55-19.69)	NA		187
20-24	125	19.1	13,495	5.6	9.3 (8.82-9.80)			120
25-29	142	21.7	25,966	10.8	5.5 (5.23-5.78)	p< 0.0001**		91
30-34	103	15.7	36,600	15.2	2.8 (2.63-2.97)		p< 0.0001****	46
35-39	63	9.6	34,077	14.2	1.8 (1.66-1.95)			28
40-44	48	7.3	24,396	10.1	2.0 (1.83-2.18)			27
45-49	32	4.9	24,883	10.3	1.3 (1.16-1.45)	p< 0.0001***		17
50-59	27	4.1	40,955	17.0	0.7 (0.62-0.79)			19
60-69	18	2.8	34,961	14.5	0.5 (0.43-0.58)			12
Total/ <i>Ukupno</i>	654	100	240,494	100	2.7 (2.64-2.77)			547

Legend/*Legenda*:*No statistically significant difference between each cohort in the age group of 15 - 19 years/**Bez statistički značajne razlike između svake pojedinačne kohorte u uzrastu 15-19 godina***Incidence rate of genital warts among women aged 20 - 24 years is statistically significantly higher than in women aged 25 - 29 and 30 - 34 years/*Stopa incidencije genitalnih bradavica kod žena uzrasta 20-24 godine je statistički značajno viša u odnosu na stope incidencije žena uzrasta 25-29 i 30-34 godine****Incidence rate of genital warts in the age group of 40 - 44 years is statistically significantly higher than in those aged 35 - 39, 45 - 49, 50 - 59 and 60 - 69 years/*Stopa incidencije genitalnih bradavica kod žena uzrasta 40-44 godine je statistički značajno viša u odnosu na stope incidencije žena uzrasta 35-39, 45-49, 50-59 i 60-69 godina*****Incidence rate of genital warts in the age group of 15 - 19 years is statistically significantly higher than in all the other groups/*Stopa incidencije genitalnih bradavica kod žena uzrasta 15-19 godina je statistički značajno viša u odnosu na stope incidencije svih ostalih posmatranih uzrasta*^aAccording to the 2011 Census/*Prema Popisu stanovništva iz 2011.*ND - not determined/*Neodređeno*; NA - not applicable/*Neprimenljivo*

During the study period, we found that the age-specific incidence of GWs in fertile women (15 - 49 years) was higher (3.7/1,000 women) than the crude incidence (2.7/1,000) in women aged 15 - 69 years) and ranged from 1.3/1,000 (2019 year) to 5.6/1,000 (2013 year). Incidence rates in women aged 15 - 69 years ranged from 1.1/1,000 (2019 year) to 4.1/1,000 (2013 year). Our results are comparable with the results of the study conducted in Italy, during 2009/2010, among women aged 15 - 64 years, where the crude incidence rate was 3.0/1,000 [15]. In addition, similar incidence rate of GWs was reported in the study conducted in England [16]. Authors from Australia analyzed the data from the nationally representative general practice cross-sectional program and from the National Hospital Morbidity Database, and determined that the annual incidence rate of GWs was 2.2/1,000 [17].

On the other hand, findings from the studies conducted in Spain [18] and Germany [19], showed lower annual incidence rates of GWs (Spain 1.6/1,000, and Germany 1.1/1,000) in comparison with our results. A possible explanation for this may lie in the fact that the study period in two listed studies was shorter than in our study.

The studies conducted in Mexico [20] and Italy [21], where the denominator was the number of women examined by physicians, reported a higher incidence rate of GWs (4.3/1,000 in both studies) than in our study. The study performed in Mexico [20] presented data from the pre-vaccination period, similar to our study, and higher GWs incidence rates compared to ours can be explained by different cultural habits and different methodological approach during the investigation. A study conducted in Italy [21] in-

volved 78 gynecologists from different regions of Italy, reported a higher incidence than in our study. It can be explained primarily by inclusion of higher number of gynecologists and participation of women from entire Italian population in comparison with women selected in our study. Bearing this in mind, our annual estimated number (547) of newly diagnosed cases of GWs during the entire study period (6,564 new GWs cases) is probably underestimated (only medically attended cases of GWs were observed), but inclusion of a larger number of community gynecologists, dermatovenereologists, as well as general practitioners in a surveillance network during the future investigation may substantially improve the recognition of GWs in a wider population.

In the US, due to younger age of first sexual intercourse among young people and the increasing trend in the total number of sexual partners, nearly half of new cases of sexually transmitted infections are found in young adults aged 15 - 24 years [22]. In terms of age, epidemiological data from the US National Health and Nutrition Examination Survey showed that the prevalence of HPV infection in a representative sample of women was the highest (45%) among those aged 20 - 24 year [23].

The authors of the study conducted in Italy, after selecting a wider range of age participants, reported the highest incidence rate and prevalence of GWs among women aged 15 - 24 in comparison with other age groups [15]. In addition, the study conducted in Germany revealed the highest incidence of GWs among women aged 14 - 25 years [19]. Interestingly, similar to our results, the results of aforementioned Italian study [15] showed that prevalence and incidence rate of GWs significantly decreased with the increasing age of women. Finally, a published systematic review also confirmed that the highest incidence of GWs worldwide is found among women under the age of 24 years [1], which is consistent with our results.

However, if we compared the incidence and age distribution of GWs widely, it is very important to take into account different study populations, cultural differences, lifestyle of participants and other reasons specific for youth behavior. For example, contrary to most abovementioned results, the highest prevalence of GWs among observed women

aged 18 - 60 years in India was in 25 - 29 year age group [24].

As we said, GWs may lead to a significant impairment of the quality of life [9]. This was confirmed by a study conducted in the UK that evaluated a measure of health-related quality of life. Authors of this study underlined that young women aged from 15 - 19 years had the highest prevalence of GWs, and therefore had the greatest loss of quality of life [25]. Considering the mentioned estimation and our findings, we can assume that girls of this age in Novi Sad had similar consequences regarding the loss of quality of life.

Recommendations of the Center for Disease Control and Prevention for reducing the risk of GWs include proper and regular use of condoms, reduction in the number of sexual partners, but the main specific measure for reduction of GWs is wide implementation of vaccination against HPV [26]. Until 2010, 50% of European countries introduced HPV vaccination within the first three years after the European Commission granted a license for human use of the first HPV vaccines. By 2019, most European Union/European Economic Area countries had introduced HPV vaccination in their national immunization programs [27]. Although HPV infection is a significant public health problem in Serbia, it is regulated, for the time being, through the recommended immunization policy [14].

Conclusion

Our results provide essential epidemiological data that may be used as the basis for future more comprehensive investigations, as well as for evaluation of the effectiveness of the human papillomavirus vaccination campaign, after its wide implementation in the vulnerable population. Although our findings should be taken with caution (we may have underestimated the incidence rates by including only medically attended cases of genital warts), it is expected that the introduction of human papillomavirus vaccination can significantly reduce the incidence of genital warts, primarily in the young population (15 - 19 years of age), similar to the experience in other developed regions.

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