

# Epidemiological, clinical, and virological characteristics of women with genital warts in Greece

P. Loumpardia<sup>1</sup>, K. Bourmpos<sup>1</sup>, G.A. Loumpardias<sup>1</sup>, V. Kalampoki<sup>1</sup>, G. Valasoulis<sup>1</sup>, O. Valari<sup>1</sup>,  
D. Vythoulkas<sup>1</sup>, E. Deligeoroglou<sup>2</sup>, G. Koliopoulos<sup>1</sup>

<sup>1</sup>Department of Obstetrics and Gynaecology, Ioannina University Hospital, Ioannina

<sup>2</sup>Department of Obstetrics and Gynaecology, Areteion University Hospital, Athens (Greece)

## Summary

This is a prospective study of the epidemiological, clinical, and virological characteristics of cases of genital warts in a Greek University Hospital. The women completed a questionnaire regarding their medical and sexual history and underwent cervical cytology, HPV DNA typing, mRNA testing, colposcopy, Chlamydia testing, and proctoscopy. Univariate and multivariate analyses were performed. The most commonly detected types were type 6 (36.1%) and 16 (24.3%). E6/E7 mRNA testing was positive in 21.5%. Concurrent cervical intraepithelial neoplasia grade 2 or worse was found in 11.1% and intra-anal warts in 10.4%. For chlamydial infection the number of sexual partners was a significant predictor. Women with warts infected with types 6 and 11 constituted only 37.5% of the total. This could have a negative effect on the efficacy of vaccination in reducing the incidence of the disease. Based on the present findings the authors recommend cytology and colposcopy for all women with genital warts.

*Key words:* Genital warts; Condylomata acuminata; Human papillomavirus; DNA; Fingerprinting; Chlamydia.

## Introduction

Genital warts is caused by infection by human papillomavirus (HPV) mostly of low-risk types (6 and 11) and is a common disease, with 4% of the female population having been diagnosed with the disease in the UK [1]. In the UK 80,000 and in the USA over 300,000 diagnoses are made annually. The condition does not usually cause major morbidity or mortality, but has serious aesthetic and psychosexual sequelae. Studies have shown that women with genital warts have worse body image than women without or have high anxiety levels and more commonly have conflicts with their partners [2]. Also genital warts in pregnancy have been associated with juvenile respiratory papillomatosis through vertical viral transmission to the newborn [3] and obstruction of respiratory tract. All these issues make women seek treatment. Given that genital warts is a common disease and that recurrence following treatment is frequent, the financial burden for the healthcare system increases considerably. A single successful episode of treatment of genital warts has been estimated to cost approximately 400 USD. The high healthcare costs have created an argument for the use of the quadrivalent HPV vaccine which aims to prevent not only cervical cancer but also the acquisition of genital warts.

Given the importance of this condition and because the lack of detailed data in Greece, the authors undertook this

study in order to address the local epidemiological and molecular issues of this disease.

## Materials and Methods

All women that presented to the colposcopy department of the University Hospital of Ioannina with genital warts from February 2010 until May 2011 were asked to participate in this study which had ethical approval from the University of Ioannina. In their initial visit, each woman had a cervical smear taken which was placed in ThinPrep medium. This sample was used for the following tests:

- Liquid based cytology (LBC) which was reported according to the Bethesda system;
- HPV DNA testing with a genotyping test for detection of 35 HPV genotypes; the test was considered positive for high-risk types when at least one of the following types was detected: 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82, and 85.
- Flow cytometric evaluation of E6/E7 mRNA of high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82) with an HPV detection kit. The test was considered positive if the result was >1.5%.

In women with symptoms suggestive of possible chlamydial infection such as vaginal discharge, postcoital bleeding or pelvic pain, an endocervical swab was taken for Chlamydia testing by PCR.

Once the samples were taken, a detailed colposcopic examination of the whole lower genital tract was performed and any lesions were recorded with biopsy if necessary. Colposcopically directed biopsy was done in patients, who aside from the genital warts, colposcopy raised the suspicion of a high-grade cervical lesion. If perianal warts were evident, or if the patient requested,

Revised manuscript accepted for publication December 2, 2013

Table 1. — Demographic characteristics.

Mean age	25.7 (median 24)
Mean age at first intercourse	17.8 (median 18)
Mean number of sexual partners	6.9 (median 5)
Smokers	65/144 (45.1%)
Nulliparous	130/144 (90.3%)
Vaccinated against HPV	13/144 (9%)

Table 2. — Distribution of HPV types.

HPV type	No	%
6	52	36.11
11	2	1.38
16	35	24.31
18	2	1.39
31	12	8.33
33	5	3.47
35	2	1.39
42	14	9.72
45	0	0
51	21	14.58
52	4	2.78
53	14	9.72
54	4	2.72
56	5	3.47
58	6	4.17
59	5	3.47
61	6	4.17
62	2	1.39
66	3	2.08
70	4	2.78
73	1	0.69
84	2	1.39
Any	106	73.61

proctoscopy was also performed. The treatment choice for the warts was individualized with usual treatment options including prescription of podophyllotoxin or imiquimod or laser ablation at the same or a subsequent visit. At the end of the visit, the women were asked to complete a questionnaire regarding their medical and sexual history. The univariate statistical analysis was done with the Fisher's exact test and the multivariate by logistic regression.

## Results

A total of 144 women with genital warts were included in this study. The mean age was 25.7 years. The demographic characteristics are given in Table 1.

HPV DNA genotyping of the cervical smear revealed the following: Single type HPV infection in 43/144 (29.86%), multiple type infection in 66/144 (45.83%), negative test in 15/144 (10.41%), and in 20/144 (13.88%) women genotyping was not performed either due to lost sample or lack of reagents or because a sample was not taken. The most common detected HPV types were type 6 (36.1%) and 16 (24.3%). The distribution of the various HPV types is shown in Table 2.

Table 3. — Test results.

TEST	Outcome	Result (%)
HPV DNA typing	Single infection	29.86
	Multiple infection	45.83
	No type	10.42
	Invalid result or no test	13.89
HPV mRNA testing	Positive	21.53
	Negative	55.55
	Invalid result or no test	22.92
Pap test	WNL	15.28
	ASCUS	10.42
	LSIL	53.47
	HSIL	5.55
	Invalid result or no test	15.28
Chlamydia PCR	Positive	5.55
	Negative	29.17
	No test	65.28
Colposcopy + biopsy	CIN2+	11.11
	Intra-anal warts	10.42

HPV mRNA testing with flow cytometry results were the following: positive result in 31/144 (21.52%), negative in 80/144 (55.55%), no result due to lost sample or lack of reagents or because of failure to take a sample in 32/144 (22.22%), and invalid result in 1/144 (0.69%).

The results of the LBC Papanicolaou test were: within normal limits (WNL) in 22/144 (15.27%), atypical cells of undetermined significance (ASCUS) in 15/144 (10.41%), low-grade squamous intraepithelial lesion (LSIL) in 77/144 (53.47%), high-grade squamous intraepithelial lesion (HSIL) in 8/144 (5.55%), and no data in 22/144 (15.27%).

The histology results showed that 16/144(11.11%) had cervical intraepithelial neoplasia grade 2 or worse (CIN2+). Intra-anal warts were detected in 15/144 (10.41%).

PCR for Chlamydia was positive in 8/144 (5.55%), negative in 42/144 (29.16%), and 94/144 (65.27%) were not tested. Test results are summarized in Table 3.

### Univariate analysis

A positive flow result was significantly associated with high-risk type HPV DNA presence ( $p = 0.008$ ) but not with age or parity. Multiple type HPV infection was significantly associated with nulliparity ( $p = 0.033$ ) but not with smoking or age at first sexual intercourse, however the association with over five sexual partners marginally failed to reach significance ( $p = 0.059$ ). Chlamydial infection was not associated with smoking, number of partners, age or parity. Presence of CIN2+ was only associated with HSIL cytology ( $p < 0.001$ ).

### Multivariate analysis

Chlamydial infection and high-grade histology were studied dependent variables. Age, smoking, parity, age at first intercourse, and number of sexual partners were the independent variables. For chlamydial infection, the number of sexual partners was a significant predictor with odds

ratio 1.25 (95% CI 1.05-1.48) for every additional partner. For CIN2+ histology, no predictor was found.

## Discussion

Genital warts are not only caused by low-risk types. A proportion will have high-risk type leading to E6 and E7 expression (21%) and CIN2+ (11%). This should not be overlooked. Therefore, all women should have cervical cytology and colposcopy. If a possible high-grade lesion is seen on the cervix at colposcopy, it is recommended to not to use laser vaporization of cervical condylomas, before the biopsy of the suspicious region. As 10% of women have intra-anal warts, proctoscopy should be discussed in the women with relevant sexual history [4].

Even though positive flow cytometry result was not associated with the finding of CIN2+ in this study, it is known that E6 and E7 mRNA expression is a key step to cervical carcinogenesis [5]. It may be that these women in this study with a positive flow result but no CIN2+ on histology are at risk of high-grade lesions in the future.

Studies have shown that 90% of genital warts are caused by types 6 and 11 with up to 50% of lesions containing coinfections with other types [6-8]. In this study the frequency of women with genital warts who were infected with types 6 and 11 was 37.5%. The percentage of HPV 11 was only 1.388%. There is a recent male study in which the genotypes most commonly detected in genital warts were HPV 6 (43.8%), HPV 11 (10.7%), and HPV 16 (9.8%) [9]. The cost of care of genital warts in England exerts a considerable impact on health services which clearly demonstrates the importance of immunization using the HPV vaccine [10]. Not taking into consideration the issue of cross-reactivity with types not included in the vaccine, immunization by the quadrivalent vaccine would have prevented at most 60.5% of the cases and by the bivalent 30.5% of the cases even though the bivalent vaccine is not aimed at prevention of genital warts. The present data suggest that the vaccine may not be as effective in preventing genital warts in particular population.

Simultaneous Chlamydial infection was found in 5.6% of women with genital warts. The percentage is not high enough to warrant testing for all women with warts. As no reliable predictors were found for positive Chlamydia result, the authors cannot recommend Chlamydia testing in only a small subgroup of patients with specific epidemiological characteristics.

Given the serious effects of Chlamydia infection on fertility, the authors would encourage clinicians to have a high degree of suspicion in nulliparous women especially when they report multiple sexual partners.

## References

- [1] Fenton K.A., Korovessis C., Johnson A.M., McCadden A., McManus S., Wellings K., *et al.*: "Sexual behaviour in Britain: reported sexually transmitted infections and prevalent genital Chlamydia trachomatis infection". *Lancet*, 2001, 358, 1851.
- [2] Maw R.D., Reitano M., Roy M.: "An international survey of patients with genital warts: perceptions regarding treatment and impact on lifestyle". *Int. J. STD. AIDS*, 1998, 10, 571.
- [3] Syrjänen S.: "Human papillomaviruses in head and neck carcinomas". *N. Engl. J. Med.*, 2007, 356, 1993.
- [4] Valari O., Koliopoulos G., Karakitsos P., Valasoulis G., Founta C., Godevenos D., *et al.*: "Human papillomavirus DNA and mRNA positivity of the anal canal in women with lower genital tract HPV lesions: predictors and clinical implications". *Gynecol. Oncol.*, 122, 505.
- [5] Coquillard G., Palao B., Patterson B.K.: "Quantification of intracellular HPV E6/E7 mRNA expression increases the specificity and positive predictive value of cervical cancer screening compared to HPV DNA". *Gynecol. Oncol.*, 2011, 120, 89.
- [6] Gross G., Wagner D., Schneider A., Ikenberg H., Gissmann L.: "Sexual transmissibility of papillomaviruses". *Z. Hautkr.*, 1985, 60, 1737.
- [7] Munk C., Svare E.I., Poll P., Bock J.E., Kjaer S.K.: "History of genital warts in 10,838 women 20 to 29 years of age from the general population. Risk factors and association with Papanicolaou smear history". *Sex. Transm. Dis.*, 1997, 24, 567.
- [8] Vandepapeliere P., Barrasso R., Meijer C.J., Walboomers J.M., Wetendorf M., Stanberry L.R., Lacey C.J.: "Randomized controlled trial of an adjuvanted human papillomavirus (HPV) type 6 L2E7 vaccine: infection of external anogenital warts with multiple HPV types and failure of therapeutic vaccination". *J. Infect. Dis.*, 2005, 192, 2099.
- [9] Anic G.M., Lee J.H., Stockwell H., Rollison D.E., Wu Y., Papenfuss M.R., *et al.*: "Incidence and human papillomavirus (HPV) type distribution of genital warts in a multinational cohort of men: the HPV in men study". *J. Infect. Dis.*, 2011, 204, 1886.
- [10] Desai S., Wetten S., Woodhall S.C., Peters L., Hughes G., Soldan K.: "Genital warts and cost of care in England". *Sex. Transm. Infect.*, 2011, 87, 464.

Address reprint requests to:

P. LOUMPARDIA, M.D.

Department of Obstetrics and Gynaecology,

Ioannina University Hospital

St. Niarxou Avenue

Ioannina (Greece)

e-mail: bettyloumpardia@hotmail.com