RESEARCH ARTICLE

Number of External Anogenital Warts is Associated with the Occurrence of Abnormal Cervical Cytology

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Abstract

Background: Anogenital warts (AGWs) are common results of sexually transmitted infection (STI). Human papillomavirus (HPV) types 6 and 11, which are non-oncogenic types, account for 90% of the clinical manifestations. Although the quadrivalent HPV vaccine has been launched, AGW remains prevalent in some countries and shows association with abnormal cervical cytology. Objectives: To study the prevalence of abnormal cervical cytology (low grade squamous intraepithelial lesions or worse; LSIL+) in immunocompetent Thai women newly presenting with external AGWs. Materials and Methods: Medical charts of all women attending Siriraj STI clinic during 2007-2011 were reviewed. Only women presenting with external AGWs who were not immunocompromised (pregnant, human immunodeficiency virus positive or being on immunosuppressant drugs) and had not been diagnosed with cervical cancer were included into the study. Multivariate analysis was used to determine the association between the characteristics of the patients and those of AGWs and LSIL+. Results: A total of 191 women were eligible, with a mean age of 27.0±8.9 years; and a mean body mass index of 20.6±8.9 kg/m^2. Half of them finished university. The most common type of AGWs was exophytic (80.1%). The posterior fourchette appeared to be the most common affected site of the warts (31.9%), followed by labia minora (26.6%) and mons pubis (19.9%). The median number of lesions was 3 (range 1-20). Around 40% of them had recurrent warts within 6 months after completing the treatment. The prevalence of LSIL+ at the first visit was 16.3% (LSIL 12.6%, ASC-H 1.1%, HSIL 2.6%). After adjusting for age, parity and miscarriage, number of warts ≥ 5 was the only factor associated with LSIL+(aOR 2.65, 95%CI 1.11-6.29, p 0.027). Conclusions: LSIL+ is prevalent among immunocompetent Thai women presenting with external AGWs, especially those with multiple lesions.

Keywords: Anogenital warts - number of lesions - LSIL+ - Thai females

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Introduction

Anogenital wart (AGW) has been a common sexually transmitted infection (STI) because it is a persistent infection and has a subclinical nature. The annual incidence of AGWs is 160-289 per 100,000 and the overall prevalence ranges from 0.13-0.56% (Patel et al., 2013). Human papillomavirus (HPV) infection type 6 and 11, which are non-oncogenic types, account for more than 90% of the clinical manifestations as being confirmed by a deoxyribonucleic acid (DNA) analysis of wart specimens (Ball et al., 2011). The virus may persist at the affected sites for up to 12 months without any signs of inflammation (Mariani and Venuti, 2010) resulting in the long transmissible period. However, most of the infection can be eradicated by host's immune system (Schiller et al., 2010). Although AGWs are not ubiquitous, the peak incidence in young reproductive aged people (Pirotta et al., 2010; Milojkovic et al., 2011) results in substantial reduction in quality of life (Mortensen and Larsen, 2010; Pirotta et al., 2010; Wang et al., 2011).

Recently, Ball SL et al has demonstrated that 48% of external AGWs had both oncogenic and non-oncogenic HPV infections (Ball et al., 2011). The oncogenic HPVs such as HPV 16 and 18 are related to malignancies of cervix, vagina, vulva and anus. This suggests that multiple infections of HPVs are common as being supported by previous studies that 11.7-32.1% of women with AGWs had abnormal cervical cytology or histology (Handley et al., 1992; Li et al., 2003; Sadan et al., 2005; Milojkovic et al., 2011). However, since the quadrivalent HPV vaccine has been launched, the incidence of AGWs declines dramatically (Korostil et al., 2013). Despite that, in some countries where HPV vaccination is not included in the national policy such as Thailand, AGWs remain a burdensome issue.

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Low grade squamous intraepithelial lesion (LSIL), a category of cervical cytology being classified by the Bethesda system 2001 (Solomon et al., 2002), is of paramount concern because it has high correlation with abnormal histology (Laiwejpithaya et al., 2009). The present study aims to study the abnormal cervical cytology in the immunocompetent Thai women presenting with AGWs. Its purpose is also to show the association of the characteristics of the participants and those of the warts with the abnormal cervical cytology at LSIL+.

Materials and Methods

The cross-sectional study was conducted by reviewing medical charts of patients who attended the Siriraj female STI clinic, Faculty of Medicine Siriraj Hospital, Mahidol University between 2007 and 2011. It was ethically approved by Siriraj Institutional Review Board (SIRB), Mahidol University.

The study population included women who were newly diagnosed with external AGWs. They were not currently pregnant, infected with human immunodeficiency virus (HIV) or being on any immunosuppressant medications. In addition, only women without history of cervical precancerous lesion/ cervical cancer, hysterectomy and cervical wart were eligible for the study. The warts were treated according to the CDC 2010 guideline (CDC, 2010). All women received initial Pap smears using the validated in-house liquid-based Pap smear technique (Laiwejpithaya et al., 2008).

The patients' general characteristics of interest included age, age at first coitus, number of sex partners, number of parity and miscarriages, body mass index (BMI), occupation, education level, contraception and condom use. The following characteristics of warts were collected, namely number of lesions (number of lesions between which the shortest distance is ≥1 millimeter apart), types of lesion, sites of lesions, number of treatment visits (weekly) and recurrence within six months following the completion of treatment.

The cervical cytology was classified according to the Bethesda system 2001 (Solomon et al., 2002). The index outcome, called LSIL+, included LSIL, atypical squamous cell cannot exclude HSIL (ASC-H), high grade squamous intraepithelial lesion (HSIL), atypical glandular cell (AGC) and cancer. In the present study, all women with LSIL+would be sent for the colposcopic examination according the guideline by the American Society for Colposcopy and Cervical Pathology (ASCCP). Loop electrical excisional procedure (LEEP) was provided for those with histology-confirmed moderate to severe cervical intraepithelial neoplasia (CIN II/III).

Stata version 12.0 was used in the statistical analysis. The descriptive data were presented with mean±SD, median (range) or n (%), as appropriate. Logistic regression was used to demonstrate the association of the participants' characteristics and those of the warts with LSIL+. A p value of <0.05 was considered statistically significant.

Table 1. Characteristics of the Eligible Participants (n=191)

Characteristics	Categories	N (%) or median (range)
Patients'characteristics		
Age (years)	13-19	33 (17.3)
	20-29	97 (50.8)
	30-39	44 (23.0)
	≥40	17 (8.9)
Body mass index (kg/m^2)	<18.5	41 (21.5)
	18.5-23.0	121 (63.4)
	> 23	29 (15.2)
Education	Primary school	19 (9.9)
	High school	81 (42.4)
	University	91 (47.6)
Sexual health history		
Age at first coitus (years)		19 (13-42)
	Parity	0 (0-4)
	Miscarriage	0 (0-3)
Contraception	No	95 (49.7)
	Condom use	29 (15.2)
	Hormonal contraception	67 (35.1)
No. of sex partners		2 (1-10)
History of other STIs		15 (7.9)

*STIs=sexually transmitted infections

Results

During 2007-2011, there were 259 women who were newly diagnosed with external AGWs at Siriraj STI clinic; however, 68 of them were HIV-infected or being pregnant. Thus, a total of 191 women were eligible for the study. Their characteristics were showed in Table 1. The mean age was 27.0±8.9 years; and their mean BMI was 20.6±3.2 kg/m^2. Half of them started sexual activities at the age of 19 and had two life-time sex partners. Only 15.2% reported condom use and 8% had history of STIs, which were herpes genitalis (8 cases), gonococcal infection (3 cases), trichomoniasis (2 cases), pelvic inflammatory disease (1 case) and multiple infections (1 case).

Table 2 showed the characteristics of the AGWs. The median number of lesions is 3 (range 1-20). Types of the warts are listed as followed: exophytic (80.1%), papular (11.0%), keratotic (6.3%) and flat (2.6%). The most common affected site was posterior fourchette (31.9%), followed by labia minora (26.7%) and mons pubis (19.9%). The number of treatment visits was 2 (1-10) times. After the treatment was completed, 36.7% had the recurrence of AGWs within six months.

The prevalence of LSIL+was 16.3% (LSIL 12.6%, ASC-H 1.1%, HSIL 2.6%). Of 191 specimens, there were 130 normal findings and 30 ASCUS. The colposcopic results were 20 negative findings (20/31, 64.5%), 4 CIN I (4/31, 12.9) and 5 CIN II/III (5/31, 16.1%). Cervical biopsy was performed in 9 cases and showed 6 CIN II/III, 1 CIN I, 1 HPV infection and 1 negative result. Six women with CIN II/III were advised to undergo LEEP. Only one case underwent the procedure at Siriraj hospital; and the LEEP result was compatible with that of cervical biopsy. She was 31 year-old with 7 life-time sex partners. She had started sexual activity at the age of 21 and had 3 miscarriages with the history of induced abortion. Physical examination showed 3 lesions on mons pubis and clitoris.

Table 3 showed the associations between LSIL+and the characteristics of patients and those of the warts. After

Table 2. Characteristics of the Anogenital Warts (N= 191)

Characteristics	Categories	N (%) or median (range)
Number of lesions		3 (1-20)
Type of warts	Exophytic	153 (80.1)
	Keratotic	12 (6.3)
	Flat	5 (2.6)
	Papular	21 (11.0)
Sites of lesions	Posterior fourchette	61 (31.9)
	Labia minora	51 (26.7)
	Mons pubis	38 (19.9)
	Labia majora	34 (17.8)
	Lower vagina	31 (16.2)
	Clitoris	18 (9.4)
	Anus	15 (7.9)
	Perineum	12 (6.3)
	Urethra	7 (3.7)
No. of treatment visits		2 (1-10)
Recurrence of anogenital wart at the sixth month post-treatment		70 (36.7)

Table 3. Logistic Regression When the Outcome is LSIL+

	cOR	P value	aOR[a]	p value
Sex partners≥3	1.26 (0.50-3.21)	0.622	0.90 (0.34-2.41)	0.84
Age at first coitus<16	1.52 (0.52-4.45)	0.947	0.96 (0.28-3.21)	0.213
No. of warts≥5	2.29 (0.99-5.27)	0.052	2.65 (1.11-6.29)	0.027

*LSIL+=low grade squamous intraepithelial lesion or worse, BMI=body mass index, cOR crude odd ratio, aOR=adjusted odd ratio; [a]Adjust for age, parity, miscarriage

adjusting for age, parity and miscarriage, number of wart lesions≥5 significantly associated with the prevalence of LSIL+(aOR 2.65, 95%CI 1.11-6.29, p 0.027). No association was found between LSIL+and the following characteristics: number of life-time sex partners ≥3 and age at first coitus <16 years (p>0.05 for all).

Discussion

Abnormal cervical cytology is common among immunocompetent Thai women presenting with AGWs. Compared with female patients who attended the general Gynaecologic clinic at Siriraj Hospital using the same Pap smear technique, our participants had approximately 16 times higher the prevalence of LSIL+ (16.3% *vs* 1.1%) (Laiwejpithaya et al., 2009). In contrast, the prevalence appears to be compatible with that in an urban STD clinic in the United States (Shlay et al., 1998). In addition, a study in an STD clinic in Canada showed that, compared with women with other STIs, women who had history of having AGWs had 5.3 times higher chance of having abnormal cervical cytology (Robertson et al., 1991). This supports that AGWs is an important risk factor of having abnormal Pap smear. This can be explained by two widely accepted hypotheses: the co-infection of different HPV types and the common behavioural risk factors of AGWs and cervical cancer.

The synchronous infection of oncogenic and non-oncogenic HPV has been supported by a HPV DNA analysis study on formalin-fixed paraffin-embedded cervical tissue blocks of 410 Thai women with LSIL+which showed that the most common triple HPV infection included HPV 11/16/18 (54.9%) (Suthipintawong et al., 2011), while another study in the United Kingdom using linear array assay on specimens of AGWs demonstrated that, of these, 35.5% also contained HPV 16 or 18 (Ball et al., 2011). Although no HPV DNA analysis was performed in the present study, a previous study using the polymerase chain reaction (PCR) in liquid-based cytology (LBC) of 1,662 Thai women showed that 30% of LSIL+contained oncogenic HPV types (Chansaenroj et al., 2010).

The second explanation is that STIs, including AGW, is considered to be one of the risk factors for cervical cancer development (Habel et al., 1998) due to the fact that it implies the higher exposure to HPV. The behavioral risk factors of getting STIs and HPV are similar as the prevalence of abnormal cervical cytology among these women has been reported up to 25.5% (Shlay et al., 1998). Number of sex partners was related to the occurrence of AGWs (Munk et al., 1997; Habel et al., 1998) and a study in Thai women showed that number of sex partners more than 1 was associated with increased high-risk HPV infection (Ishida et al., 2004). In the present study, the participants reported 2 (1-10) life-time partners. However, no association between number of sex partners ≥ 3 and LSIL+has been demonstrated. Moreover, unlike the study by Li et al. (2003), we found no association between age at first coitus <16 and LSIL+.

Besides women with AGWs tend to have higher prevalence of LSIL+, those who have normal cervical cytology are also at risk of developing cervical cancer in the future. Petersen CS reported that 9/55 (16.4%) of pap smear-negative women with external AGWs are harbouring HPV 16/18 (Petersen et al., 1991) which are the most common cervical cancer-related HPV types in Thailand (Lurchachaiwong et al., 2011). This may imply that, among 130 women with normal cervical cytology in the present study, around 21 may develop precancerous lesion or cervical cancer later. This is supported by a study by Milojkovic M that, after following women with AGWs for 10-14 years, there were three time increase in the prevalence of cervical cancer, from 0.9%-2.7% (Milojkovic et al., 2011).

The present study pioneers to explore the association of LSIL+with the characteristics of AGWs. The number of lesions is the only significant associating factor. HPV normally becomes infective only if there is a microtrauma on the skin surface down to the basal layer of epithelium (Schiller et al., 2010). The infected basal cells would later proliferate in an uncontrollable pattern leading to the overgrowth, which can be seen as warts. The higher number of lesions implies the more traumatic sites on the surface of the genital tract, including cervix, allowing oncogenic HPV to gain access to the cervical basal layer. Thus, women with higher number of warts should be more health-conscious and undergo Pap smears regularly.

The Pap smear technique plays an important role in the measurement of the index outcome (LSIL+). Comparing to the conventional Pap smear, Siriraj liquid-based cytology gives the higher detection rate of abnormal Pap smear (Laiwejpithaya et al., 2008). The high detection rate of this new technique is beneficial since 2.4% of normal

conventional Pap smear (1/42) in the Canadian women with AGWs revealed CIN II/III by biopsy under colposcopy (Howard et al., 2002). Another study in Thailand which extracted DNA from the pathologically prepared slides demonstrated that 40.5% (15/37) of normal cervical histology revealed HPV infection (Tungsinmunkong et al., 2006). Colposcopic examination was 3.1 times more sensitive than single Pap smear in detecting CIN (Handley et al., 1992); nonetheless, colposcopy is not recommended as a routine examination for this population (Howard et al., 2002; Li et al., 2003).

The limitation of the study is that this is a cross-sectional study by reviewing the medical charts which might contain incomplete data. In addition, colposcopy was not performed in all cases; and abnormal Pap smear was not histologically confirmed.

In conclusion, the present study has showed that women with AGWs at risk of having abnormal cervical cytology. As a result, they should be encouraged to undergo the cervical cancer screening, especially those with multiple wart lesions.

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