Review Article

A Never-Ending Story of Anogenital Warts: Review Article

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Anogenital wart (AGW) has long been one of the most common sexually transmitted infections, which has negative effects on psychological and social issues. Its slowly progressive nature and long dormant stage prevent AGW from elimination. Although diagnosis is as simple as inspection using the naked eyes or a magnifying glass and basic medical treatment is the main treatment modality, the long period of clinical response appears to be the biggest challenge. Many patients suffer from this non-fatal disease for over half a year. Onward transmission obviously continues during the occurrence of lesions. Primary prevention, particularly vaccination against human papillomavirus (HPV vaccine), is an ideal method. HPV vaccine is a promising method; however, its high cost limits wide accessibility. In addition, despite being vaccinated, some women present with AGW. Therefore, a never-ending story of AGW remains to be explored. The Siriraj Female STI Clinic, which has over 20 years of experience in treating women with AGW, would like to share some experience so that these patients will be treated with more understanding.

Keywords: Anogenital wart, Prevention, Surveillance, Siriraj experience

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Anogenital warts (AGW) is a common sexually transmitted infection (STI) caused by human papillomavirus (HPV) infection. Diagnosis of AGW is mainly performed by inspection with or without a magnifying glass. The lesions are categorized into four types, including (a) exophytic growth or condyloma acuminata, (b) keratotic wart, (c) flat wart, and (d) papular wart as being demonstrated in Figure 1[(1)]. AGW occur mostly at the vulva and introitus. It is important to keep in mind that patients with atypical lesion(s), lesion(s) of the cervix, or lesion(s) in menopausal women should receive biopsy to exclude malignancy[(2)]. Despite the fact that HPV vaccine has been developed for over a decade, its high cost limits the uptake rate in Thailand. Moreover, as direct contact, particularly sexual relation, is the main route of transmission, AGW can be seen at any levels of health care units. The low symptomatic nature but long persistent infection makes AGW a never-ending story to be explored.

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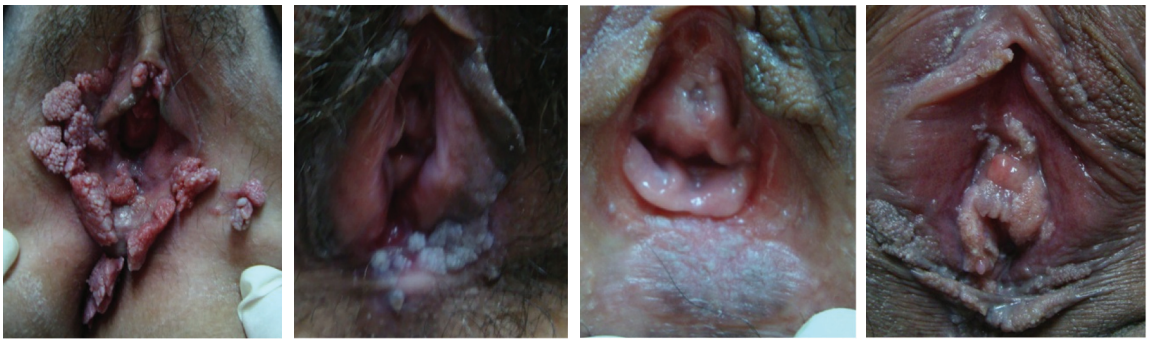
Etiologic organism and pathogenesis

HPV is a double-stranded deoxyribonucleic acid (dsDNA) in the papillomavirus family. These organisms are able to infect both mucosal and cutaneous surfaces. Of its eight functioning genes, six are able to control the transcription of non-structural or early proteins including E1 (replication), E2 (replication and transcription), E4 (viral release), E5 (immune invasion), E6 (binding to p53), and E7 (binding to pRB). Two other genes control transcription of structural or late proteins, the L1 (major capsid protein) and L2 (minor capsid protein). However, each gene usually occurs in different cell cycles and periods. As a result, HPV infection can be detected in either a latent period in which HPV DNA still exists in the absence of viral production or an active phase with active lesions in the presence of the ability for viral spreading[(3)]. Based on the authors' experience, AGW can manifest up to ten years after the last sexual relation.

HPV is classified into two types, non-oncogenic type and oncogenic type. The most common types of non-oncogenic or low-risk viruses are HPV



a. exophytic wart b. keratotic wart c. flat wart d. papular wart

Figure 1. Four types of anogenital warts.

Source: Chayachinda C, Unit of Gynaecological Infectious Diseases and Female Sexually-Transmitted Infections, Faculty of Medicine Siriraj Hospital, Mahidol University

types 6 and 11, which account for 90% of AGW. In addition, they associate with recurrent respiratory papillomatosis (RRP) and precancerous lesions of genital organs and anus, cervical intraepithelial neoplasia grade 1 (CIN I), vulvar and vaginal intra-epithelial neoplasia grade 1 (VIN I and VAIN I), anal intra-epithelial neoplasia grade 1 (AIN1), and some tumors such as the Buschke-Lowenstein tumor. Among oncogenic HPV types, HPV types 16 and 18 are the most common variants They relate to many kinds of cancer such as 70% of cervical cancer, 60% of vaginal cancer, 40% of cancers of external genital organs, 80% of anal cancer, and 60% of tonsil and pharyngeal cancers[4]. However, Ball et al reported that both non-oncogenic and oncogenic types have been identified simultaneously in 48% of AGW and 35.5% of those had HPV types 16 and 28[5].

The proposed mechanism of HPV-related diseases is that basal cells get HPV infection by microtrauma resulting in uncontrollable cells replication. Apparently, spreading of viruses mostly occurs during the presence of lesions. The observation shows that AGW patients who are obsessed with touching or cleansing the lesions tend to have new lesions nearby in the follow-up visit. Moreover, the authors have a few patients who never experience anal intercourse presenting with perianal warts. One explanation can be minor trauma on anal orifice following defecation. Although, innate immunity plays a more important role in hindering the viruses than adaptive immunity, a high-level of antibody can also stimulate the response of innate immunity during recurrent episode.

Adverse outcomes of AGW

Although AGW is not a life-threatening disease, it has plenty adverse impacts on mental health and psychological issue. From the authors' survey in the Siriraj Female STI Clinic in 2019, among 67 women with active AGW lesions, 80% of them are highly concerned about recurrent disease, sexual function, and resolution of lesions. Another study in the authors' clinic, which was done in follow-up cases of AGW, showed that only 41 out of 215 women whose AGW had resolved reported sexual activities in the prior four weeks. Among them, the prevalence of sexual dysfunction based on Thai version of Female Sexual Function Index (TFSFI) was as high as 61.7%, which is four times higher than that of general Thai women[6]. Sexual desire is the most affected domain, followed by sexual arousal, orgasm, dyspareunia, lubrication, and sexual satisfaction[7].

Among pregnant women giving birth at Siriraj hospital between 2007 and 2016 (n=90,262), there was a higher incidence of teenage pregnancy (13 to 19 years old), overt diabetes mellitus (DM), and other STIs in those who had active AGW during delivery (n=490), at 30.8% versus 8.1%, 1.2% versus 0.2%, and 8.1% versus 0.8%, respectively. The risk of having a low birth weight baby is significant higher in those with AGW during delivery (20.2% versus 13.7%, risk ratio 1.39, 95% CI 1.16 to 1.67)[8].

It should be considered that the virus causing AGW also causes abnormal results of pap smear. Low grade squamous intraepithelial lesion or worse (LSIL+) can be found in women with AGW more than in those who have no AGW (16.3% versus 1.1%), especially in those who have at least five lesions (OR 2.65, 95% CI 1.11 to 6.29)[9]. Moreover, the study by Chayachinda et al reported that LSIL+ lesions were found in 24.5% (13/53) of women with human immunodeficiency virus (HIV)-infection

together with AGW in those who were visiting the Female STI Clinic for the first time. Of them, five HIV-infected women were diagnosed with high-grade squamous intraepithelial lesions whereas none had cancer[10].

Our experience shows that around 10% of women presenting with AGW have coincident fungal vaginitis. The AGW per se can cause vulvar itching but other causes have to be excluded. This underlines the importance of speculum examination in this population. Adding to the benefits of thorough lesion detection and pap testing, other vaginal infection/infestation should be examined.

Treatment[2]

The optimal goal of treatment is to remove all visible wart(s) and to relieve any related symptoms such as itching and adverse physical and mental effects. Lopaschuk[11] reported that 40% to 60% of untreated cases resolved spontaneously but they were still able to transmit to other people. In the other cases, lesions remained unchanged or increased in number and size. There are several methods of treatments, but gynecologists usually choose the appropriate choices based on size, anatomical site and number of lesions, cost, and their preference. Nevertheless, no evidence suggests that one treatment is superior to the other. In some cases, clinicians need to use combined therapies to cure all the lesions. Modalities of AGW treatment are shown in Table 1.

The AGW treatment in the authors' clinic includes 85% trichloroacetic acid (TCA) or cryotherapy for clinic-based treatment, 5% imiquimod as the second-line treatment, and surgical removal for large lesion. In 2016, there were 217 patients with AGWs attending the authors' clinic. Of them, 28 were pregnant women, four had systemic lupus erythematosus, nine had HIV-infection, and two had diabetes mellitus. Their mean age was 28.0±10.2 years. Most of the lesions locate on the external genitalia (72.1%). The treatment modalities included local application with 85% TCA (64.3%), followed by 5% imiquimod (27.9%), cryosurgery (3.9%), and surgical removal (3.9%). The median treatment-to-cure periods were four (2 to 10), eight (4 to 16), five (3 to 7), and one week, respectively. The recurrence rates at three months after being cured were 13.0%, 8.8%, 0.0%, and 12.5%, respectively. To control the immediate pain following the application of 85% TCA, the authors used a small fan blowing on the applied area for five minutes. This clearly increases patients' satisfaction. Silver nitrate stick can also be used to locally destroy the lesions, albeit limited data.

Follow-up[2]

Our routine follow-up interval is 1 to 2 weeks. Most patients usually respond after three months of treatment. Factors that might affect the curable rate are immune status of patients and their compliance. Other treatment option(s) should be considered if there is no improvement with the current method or there are any severe adverse effects. Persistent hypopigmentation or hyperpigmentation can occur after treatment. Additionally, vulvodynia and pain during defecation can result in chronic pain syndromes.

Counseling[2]

Clinicians should keep in mind these key messages, 1) size of lesion can remain unchanged, increase, or decrease in untreated patients. 2) The patients with AGW do not need to undergo cervical cancer screening more frequently than those without AGW. 3) HPV acquisition cannot be clearly determined. HPV can exist in patient for several months or years and spread to partners even without obvious symptoms or lesions. 4) Although AGW is not severe, it has significant psychological impacts on patients, and it can affect their social and family life. 5) Treatment may not eliminate all viruses and the recurrence after complete treatment is not uncommon. 6) Patients with AGW should be recommended to check for other STIs. 7) The use of condoms should be encouraged even though it might not significantly lower the risks of infection. 8) Currently, HPV vaccine is available to prevent AGW but it is not a treatment for any active lesion or existing HPV infection.

The authors would like to underline the last message that the mentioned HPV vaccine refers to only 4-valent or 9-valent vaccine, and it may prevent incidence of AGW at up to 90%, not 100%. Moreover, if the vaccination occurs after having started sexual relations, there is some chance that the woman is already HPV-infected, and the pathogenesis is on-going. One patient in the authors' clinic who was vaccinated with 4-valent HPV vaccine in the past seven years presented with her first-time AGW. She is a 39-year-old monogamous woman without immunocompromised condition. Pap smear, which was done on the vaccination day, showed LSIL. This implies that she got HPV-infected before the vaccination despite the fact that her sexual partner never had any genital lesions. This piece of the authors' experience may help physicians give holistic counselling with broader mind.

Table 1. Recommended regimens for anogenital wart treatment[11]

	Recommendations
Patient self-applied regimens	
Imiquimod 5%	- Stimulating of local innate immunity and activating toll-like receptor (TLR)-7 for releasing cytokine to enhance cellular immunity - Apply at lesion(s) before bedtime, 3 times/week and wash with soap and water in the morning - Side effects: inflammation with edema and redness, lowering efficacy of condom - Do not recommend to use in vagina and anal canal - Do not recommend to use in pregnant and breast-feeding women
Podophyllotoxin 0.5% solution or gel	- Binding with cellular microtubules and inhibiting mitotic division - Apply twice daily, 3 days consecutively in a week (maximum 4 weeks) - Side effects: inflammation with edema and redness - Do not recommend in large lesions (>10 cm^2) or use more than 0.5 mL - Do not recommend to use in vagina and anal canal - Do not recommend to use in pregnant and breast-feeding women
Provider applied regimens	
Cryotherapy	- Apply once a week - Recommend for lesion(s) at urethral opening - Side effects: pain (delayed), inflammation, scar and vaginal perforation (rarely) - Can be used in vagina and anal canal - Can be used in pregnant and breast-feeding women
80% to 90% trichloroacetic acid	- Apply once a week - Side effects: pain (immediate), inflammation and edema (inflammation can be relieved with sodium bicarbonate solutions) - Can be used in vagina and anal canal - Can be used in pregnant and breast-feeding women
Surgical removal	- Apply local anesthesia before removal - Side effects: edema, pain, excessive bleeding and infection - Can be used in vagina and anal canal - Can be used in pregnant and breast-feeding women
Electrocauterization	- Apply local anesthesia before removal and providers need to wear a virus-filtering mask - Side effects: edema, pain, excessive bleeding and infection - Can be used in vagina and anal canal - Can be used in pregnant and breast-feeding women
Alternative options	
Podophyllin 10% to 25% in tincture of benzoin	- Apply once a week - Side effects: inflammation and itchy - Do not recommend in large lesions (>10 cm^2) or use more than 0.5 mL - Do not recommend to use in pregnant and breast-feeding women
Sinecatechins (green tea extract) 15% ointment	- Effect of epigallocatechin gallate to destroy infected cells - Apply 3 times daily (maximum in 16 weeks consecutively) - Side effects: edema, redness and scar - Do not recommend to use in vagina and anal canal - Do not recommend to use in pregnant and breast-feeding women
Fluorouracil 1% gel or 5% cream	- Recommend in wide lesions at vaginal and urethra area - Apply before bedtime, 3 times/week - Side effects: edema, redness and scar - Can be used in vagina and anal canal - Do not recommend to use in pregnant and breast-feeding women
Interferon	- Apply in vagina twice daily, 5 days/week for 4 weeks - Side effects: headache, fever and ulceration - Can be used in vagina and anal canal - Do not recommend to use in pregnant and breast-feeding women

Management of sexual partners[2]

The same types of HPV in patients can pass directly to their partners. Partners should come to hospital and receive counseling about the risk of having AGW. Visible genital lesions should be looked for or treated but HPV DNA testing is not recommended. Since the duration of existing HPV is unknown, patients may not need to inform their future partners about the AGW.

AGW in pregnancy[2]

Cesarean delivery is recommended if the birth canal is obstructed by the AGW, which may result in excessive bleeding. Pregnant women should receive counseling about the low risk of RRP and there is no evidence supporting cesarean section for preventing this complication. The prevalence of AGW during delivery in Siriraj Hospital was 490/90,262 (0.5%). Most patients were in the age group of 20 to 29 years. Cesarean section rate was 41.6%, which was not different from the rate in overall deliveries (43.7%). However, the cesarean section rate was basically high in out setting[8].

Surveillance

In general, there are two methods of surveillance, active surveillance (searching for new cases in high-risk or general population) and passive surveillance (diagnosis and treatment in symptomatic patients). AGW is a slowly progressive disease and does not cause cancer, so its surveillance mainly uses a passive method. According to epidemiological data from the Department of Disease Control, Ministry of Public Health, a report showed that the number patients with AGW were 4,004, 4,066, and 4,448 (6.03, 6.12, and 6.8 per 100,000 population) in 2017, 2018, and 2019, respectively. Compatible with a previous study in other countries[3], the highest prevalence was demonstrated in Thai people aged 15 to 24 years. However, the reported prevalence of AGW is likely to be lower than the actual prevalence because some patients did not go to the hospital or receive any treatment due to mild or no symptoms.

Prevention

The primary prevention includes refraining from skin contact, especially sexual relation, and receiving HPV vaccine. Personal hygiene is as important in that personal items such as underwear and towels should not be shared[3]. HPV vaccination schedules are two doses for young people aged 9 to 15 years and three doses for older ones. At the moment, booster dose of HPV vaccine is not recommended.

The aim of vaccination is to enhance both innate and adaptive immunity to prevent STIs. Normally, innate immunity is the main pathway to defend against HPV infection. Currently, there are three types of HPV vaccine, 2-valent HPV vaccine (HPV types 16 and 18), 4-valent HPV vaccine (HPV types 6, 11, 16, and 18), and 9-valent HPV vaccine (HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58). However, 9-valent HPV vaccine is not available in Thailand at the moment. The three landmark studies of HPV vaccination, including FUTURE I[12], Broad spectrum HPV vaccine study[13], and V501-020[14], support that 4-valent and 9-valent HPV vaccination reduce incident AGW. However, 4-valent vaccine has some superiority. A review of the impact and effectiveness of the 4-valent HPV vaccine in 10 years of clinical experience (2007 to 2009) in Canada among girls aged 9 to 14 years old showed that the incidence of AGWs deceased by up to 45%[15].

For the 'HPV vaccination as a treatment modality', a prospective report was conducted in 26 Korean patients with AGW who received either the HPV vaccine or surgical excision. Some patients in the vaccine group requested the surgical removal of the lesion before completing the vaccination course. At a mean follow up time of 8.42±3.27 months, 10/10 patients (100%) who received HPV vaccine did not show any recurrent lesions[16]. This study was limited by a small number of cases and some unreported data.

For the 'combination across HPV vaccine', a study in 2018 by Gilca et al showed that 371 boys and girls were randomized (1:1) into three groups, 1) two doses of 9-valent HPV vaccine, 2) a first dose of 2-valent HPV vaccine followed by 9-valent HPV vaccine six months later, or 3) a first dose of 9-valent HPV vaccine followed by 2-valent HPV vaccine six months later. Blood samples were collected from all participants to measure HPV antibodies level by ELISA at one- or six-month post-first dose and one month post-second dose[17]. The summary was that 9-valent HPV vaccine can be used as the second dose following the first dose of 2-valent HPV vaccine.

Hintze and O'Neill demonstrated that gender-neutral vaccination provided a cost-effective benefit for preventing HPV-related diseases. The benefit of HPV vaccination for girls is to prevent premalignant cervical cancers and other HPV-related cancers. For men or boys who received the vaccination, the effect is not only for personal benefit, but also a herd immunity for women or girls by preventing the

transmission of HPV[18]. This is demonstrated in the HPV-vaccine leading nation like Australia. National policy in Australia starting in 2007 required all girls aged 12 to 13 years to get HPV vaccine. The updated policy in 2009 recommended all women who are younger than 26 years to get free HPV vaccine. In 2013, boys aged 12 to 13 years were included in the vaccination program and in 2014, 14 to 15-year-old boys were further included too. At the beginning of January 2018, Australian vaccine policy launched a new policy to switch from 4-valent HPV vaccine to 9-valent HPV vaccine.

Conclusion

AGW is a STI that has negative effects on psychological and social issues. The annual report based on the passive surveillance might show a lower number of cases than the actual prevalence. Apparently, the most effective method of prevention is to avoid direct contact and HPV vaccination. As both preventive methods are not 100% efficacious, AGW remains one of the STIs' never-ending stories.

Conflicts of interest

The authors declare no conflict of interest.

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