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Clinical Manifestations of Genital HPV Infection

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1. Introduction

The Human papillomavirus infection is the sexually transmitted infection most frequent in man and woman (Koutsky, 1997; Worda, 2005). The probability of transmission of HPV through sexual intercourse varies from 5 to 100% with an average of 40%. The probability of transmission per partner (male-female) is estimated at 60% for HPV 16 and 60% for HPV that causes genital warts. Detection of HPV DNA by the molecular biological methods, does not necessarily represent the manisfestation of a disease (Burchell et al, 2006). According to The World Health Organization (WHO), more than 630 million men and women (1 in every 10 people) are infected with HPV in the world (Ferlay et al, 2004; CDC, 2007). Clinical manifestation is present in less than 10% and the infection is often asymptomatic and can be unnoticed by the patient even though a lesion is present. It is believed, that approximately 1/3 of all women en the world have some form of clinically manifested HPV infection. Also, half of all the women of the world sexually active are infected with this virus (Snoeck, 2006).

It is believed as well that after exposure to HPV, the virus infects the entire lower genital tract epithelium (Shepherd & Bryson, 2008). The incubation period is highly variable, ranging from a few days to many years (20 to 30 years or more) (Sinal & Woods, 2005) (Figure 1). When the infection process starts, there is a proliferation phase ranging from from 3 to 6 months, when many lesions many lesions appear. After the response of B and T cells to the infection, what follows is the containment phase that also lasts for 3 to 6 months, when regression will occur to more than 80% of the lesions. The other 20% will have an active disease or recurrence after variable disease-free intervals (Franco & Steben, 2007). The clinical manifestations are variable and are associated with systemic and local immune response of each individual, with different environmental factors. Dependent on the host immune system, the course of the infection can take one of the three following forms. The most frequent is the Latent Infection, where no clinical manifestation of the infection occurs, and it is only detected by the HPV DNA detection methods. The second form is the Subclinical Infection with minimal clinical manifestation, that is usually diagnosed by colposcopy, cytology and histology. The third form, that is the least common is the Clinical Infection. In this form there is an active expression of the disease, manifested mainly by genital warts, precancerous lesions and invasive cancer (Chow et al, 2010). The

different manifestations are also dependent on different types of HPV (currently more than 200 types) and also the host immune system (Bernard, 2005). The low-risk HPV will mainly produce warts (condyloma) and the high risk HPV will mainly produce an intraepithelial lesion (Trofatter, 1997).

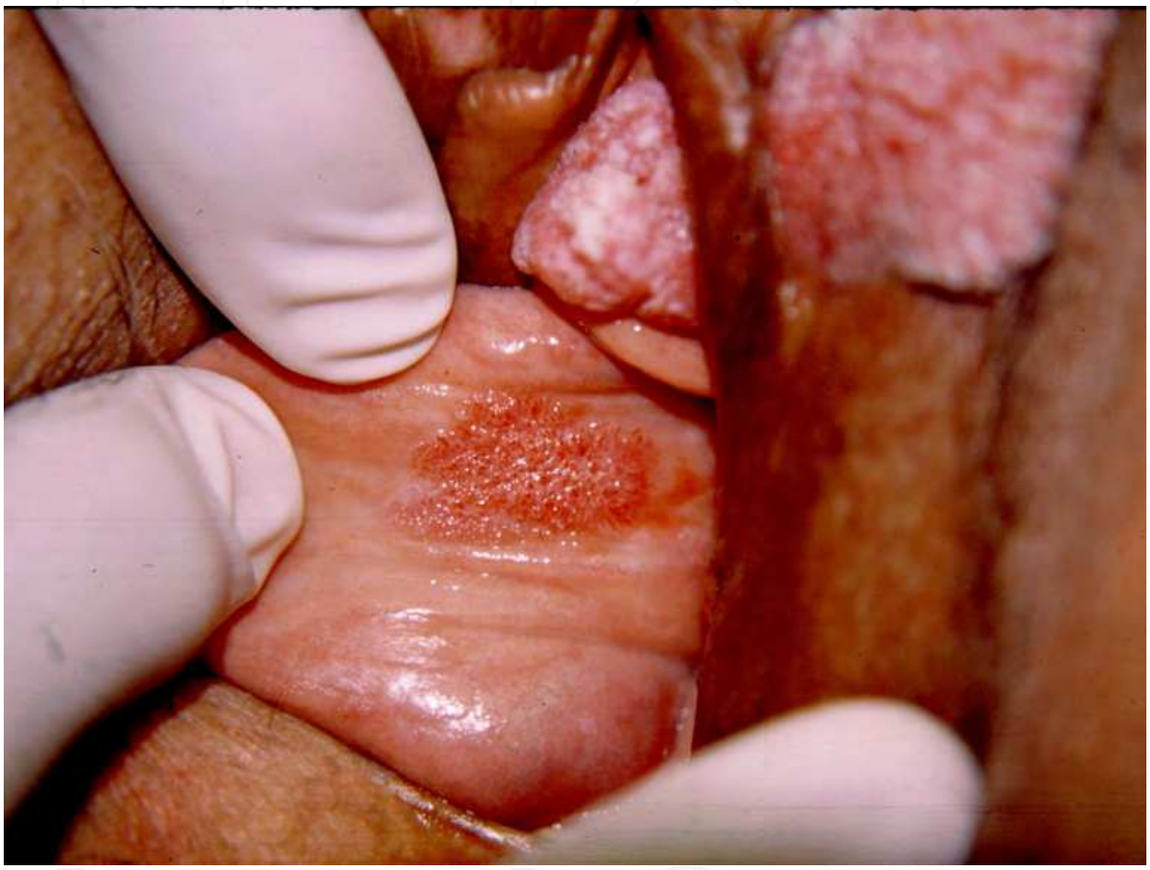

Fig. 1. A 75-year-old woman sexually inactive for 25 years showing a wart on the vulva that appeared 6 months ago. There is also a VAIN 3 and an urethral cancer HPV 16 induced.

2. Clinical lesions

Clinical lesions (only 2 to 3% of HPV infections) are mainly represented by condyloma acuminatum, Bowenoid papulosis (vulvar intraepithelial neoplasia usual type) and Buschke-Loewenstein tumor. The presence of acuminate lesions on the cervix (Figure 2) are infrequent (in 6% of the women that have vulvar condyloma) and this represents an indication of high-risk HPV infections (20% of these infections have associated an intraepithelial lesion) (Scheurer et al, 2005). Genital warts are easily recognized by papillary epithelial proliferations, often with vascular loops inside. Lesions may be single or multiple, scattered or confluent (Sadjadi et al, 2003) (Figure 3 and 4).

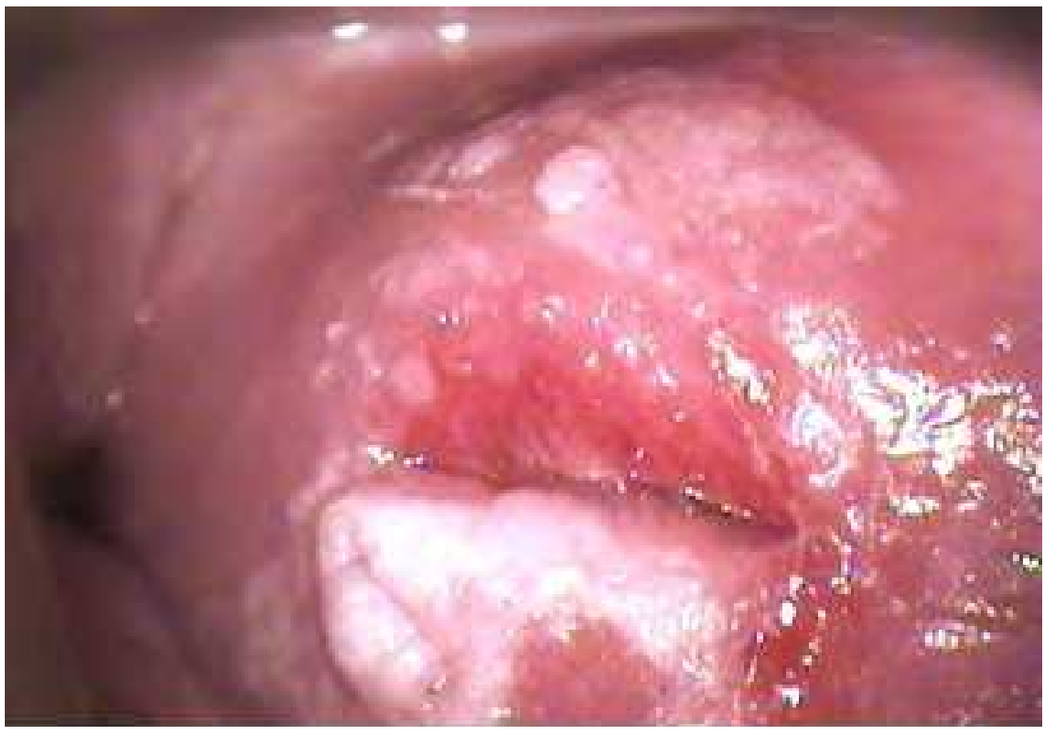

Fig. 2. Condyloma acuminata in the cervix

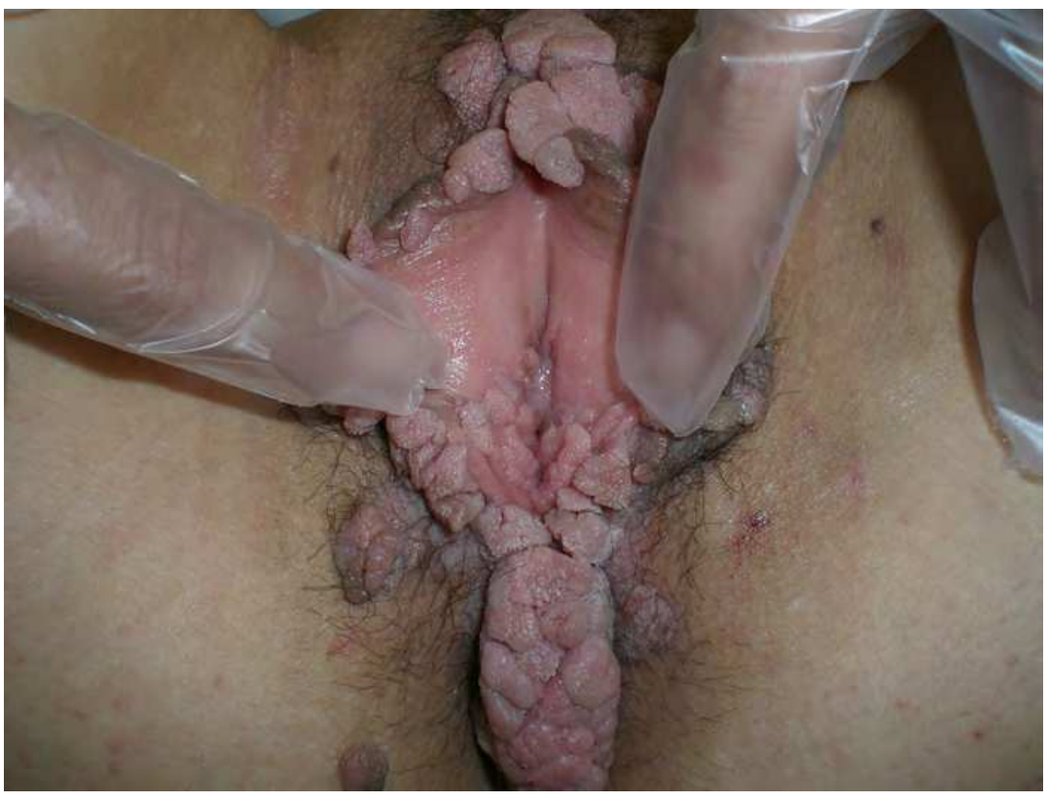

Fig. 3. Multiple condyloma acuminata on the vulva

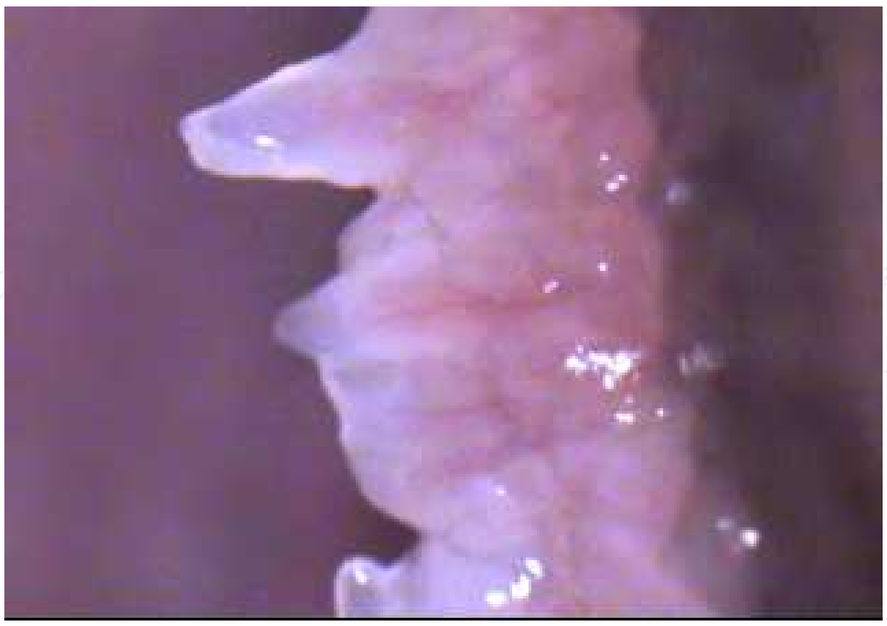

Fig. 4. Detail of a condyloma acuminatum with a characteristic central vessel.

Vaginal warts can be detected by careful examination in more than one third of the cases of women who have vulvar warts. Generally, they are usually small and multiple and can be hidden by the speculum. The lesions may involve the entire length of the vagina, but most frequentely occur in the upper and lower thirds of the vagina (Figure 5). Although vaginal warts are usually asymptomatic, vaginal discharging and itching can occur, and less often, post-coital bleeding, may be present (Row et al, 1981).

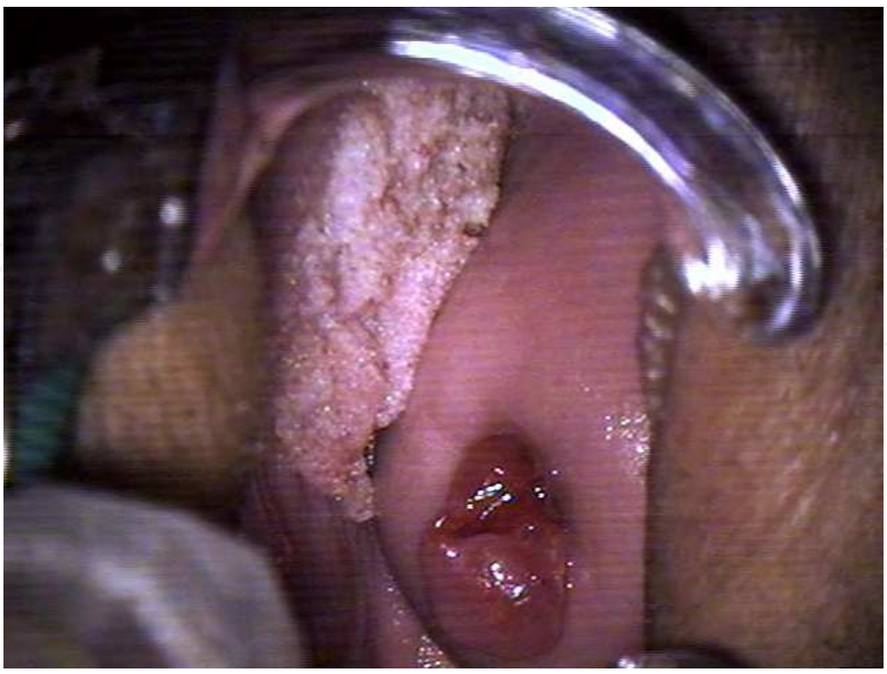

Fig. 5. Multiple vaginal warts in the upper third of the vagina

The verrucous lesions in the vulvar region have increased in numbers in recent years, affecting mainly younger women. Vulvar warts generally occur in moist areas of the skin and in places subjected mostly to trauma during intercourse.

About 25% of the women with vulvar warts have these lesions in the anal and perianal region as well, and are not necessarily associated with the practice of anal sex (Figure 3). These lesions may be sessile or pedunculated, papular, hyperkeratotic or hyperpigmented. Vulvar manifestations depend on each individual, ranging from small lesions (Figure 6) to gigantic such as in the cases of a Buschke-Loewenstein tumor (Ambriz-Gonzalez et al, 2005) (Figure 7). Papular and hypercrhromic vulvar lesions (vulvar intraepithelial neoplasia (VIN) usual type) (Figure 8) represent today, a high-grade intraepithelial neoplasia (Forcier & Musacchio, 2010).

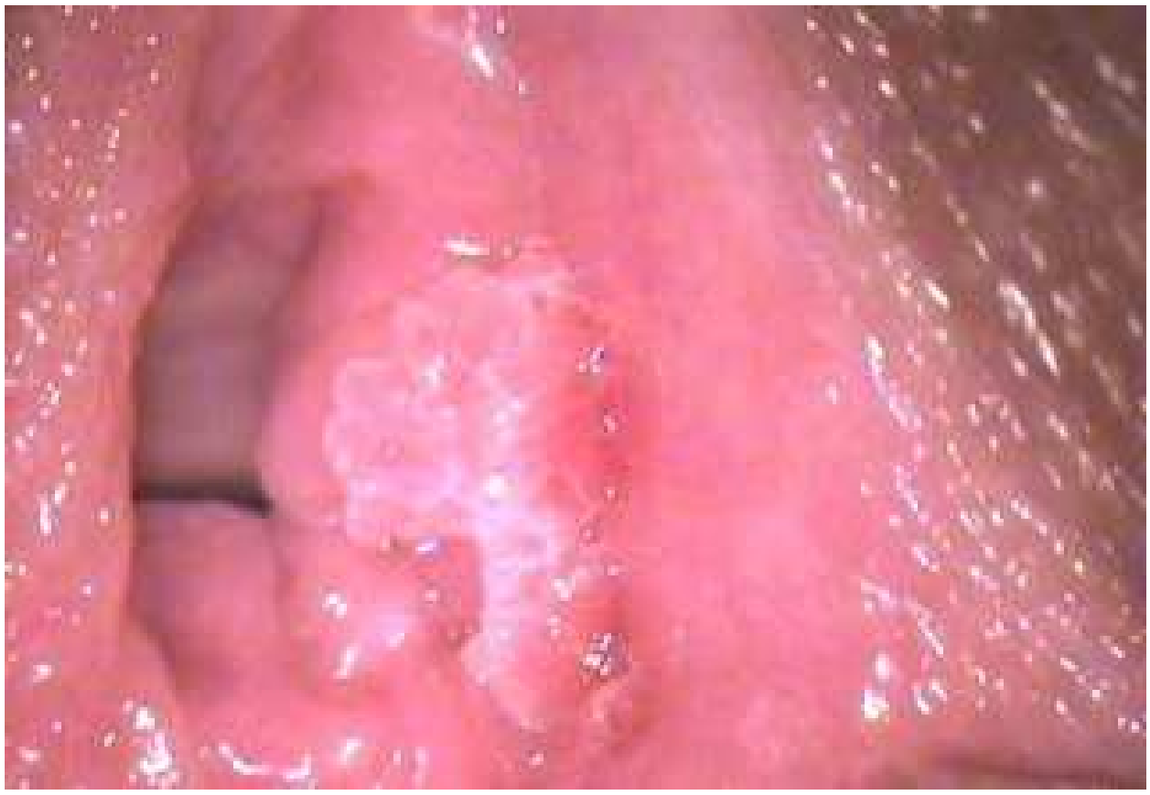

Fig. 6. Small vulvar wart

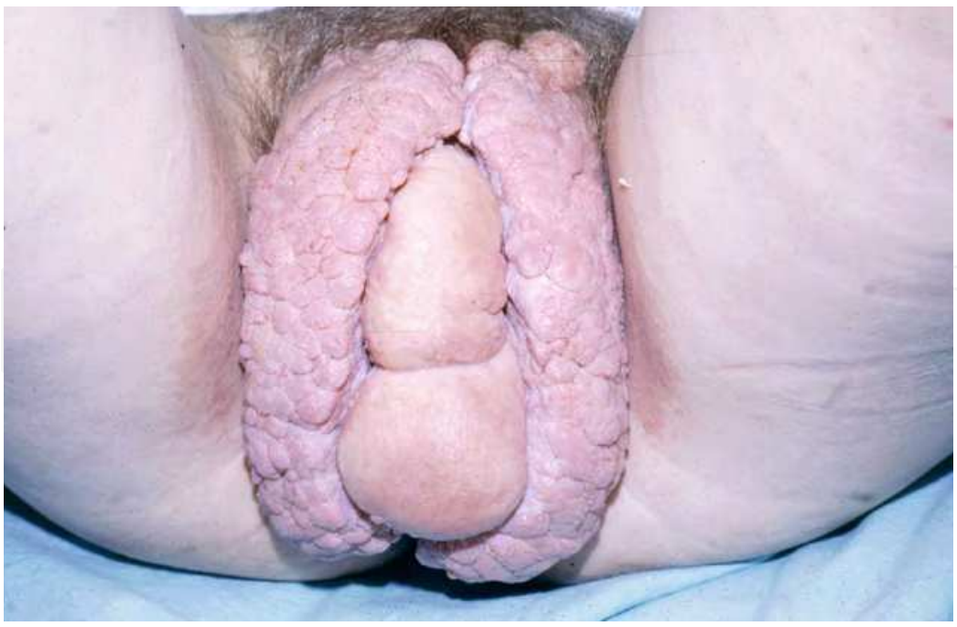

Fig. 7. Buschke-Loewenstein tumor in a woman of 18 years who begun sexual activity 6 months before with only the same partner

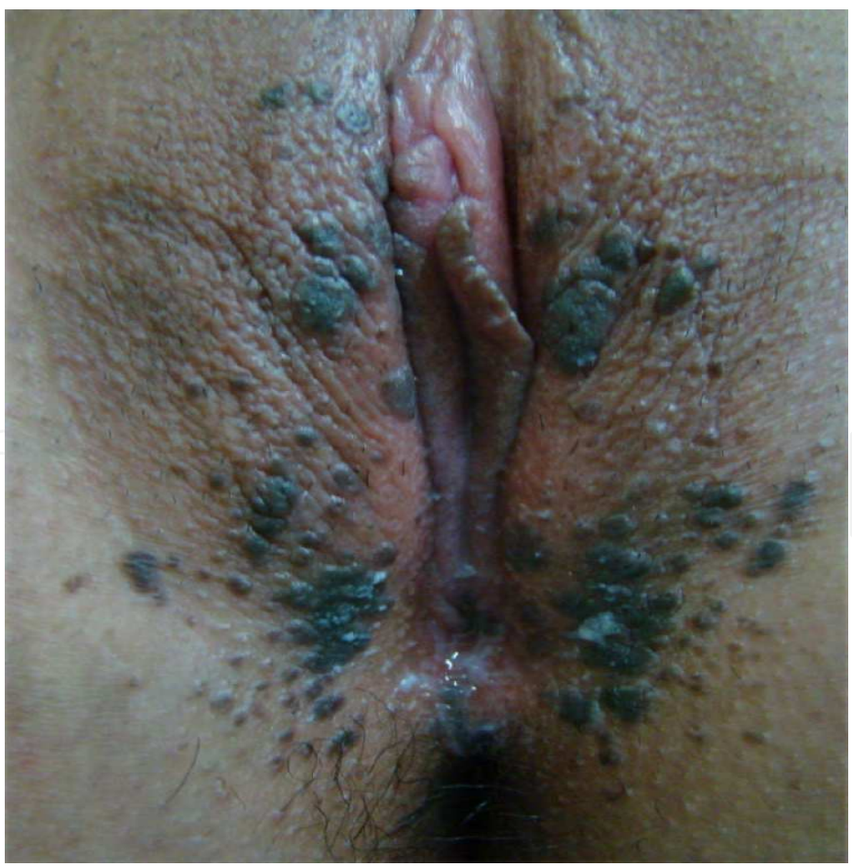

Fig. 8. A typical example of VIN usual type with hyperchromic papules coalescing

Approximately 18% of women with vulvar condyloma have anal and perianal warts as well (Figure 9). Depending on the extent of the injuries, discomfort or bleeding may occur during evacuation. In these cases, the rectal examination should also be performed, since approximately 10% of women with anal warts, exhibit rectal lesions (Nadal et al, 1999).

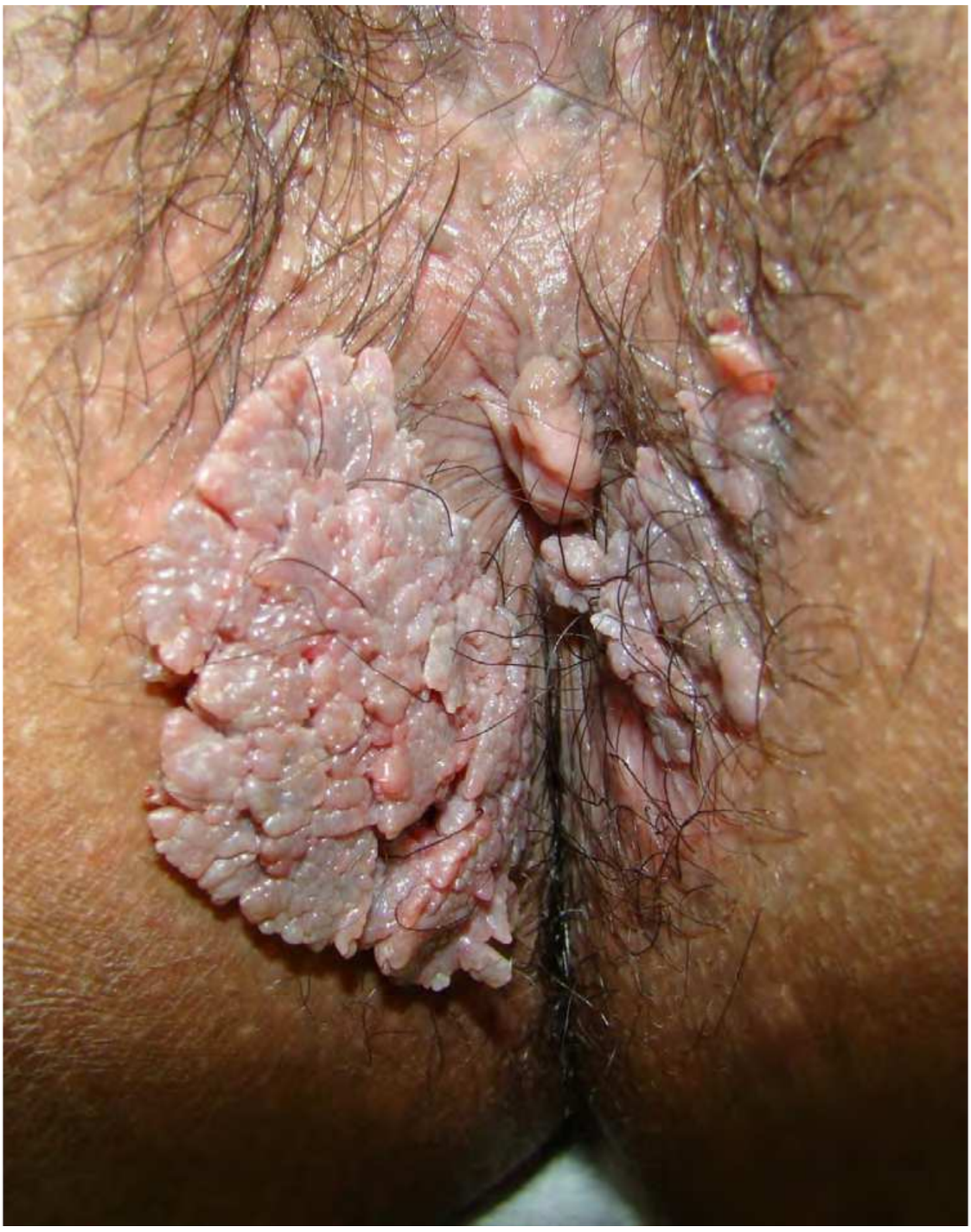

Fig. 9. Multiple condyloma acuminatum in the anal and perianal region

When evaluating male partners of women with genital disease associated with HPV, approximately 40 to 50% of them also have lesions. The lesions may manifest as penile warts, papules or papillae. The lesions appear mainly in areas of trauma, especially related to sexual activity (the penile shaft, preputial cavity, coronal sulcus and glans) (Figure 10). Urethral involvement (Figure 11) is more frequent in men than women (10 to 28% of the men with genital warts and less than 5% of the women with genital diseases associated with HPV) (Buechner, 2002).

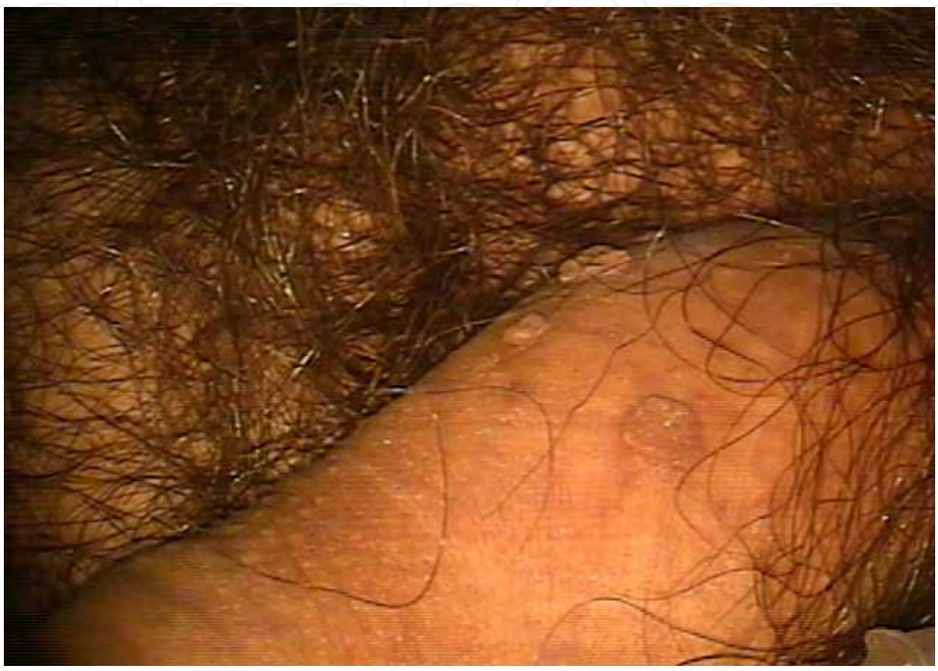

Fig. 10. Genital warts at the base of the penile

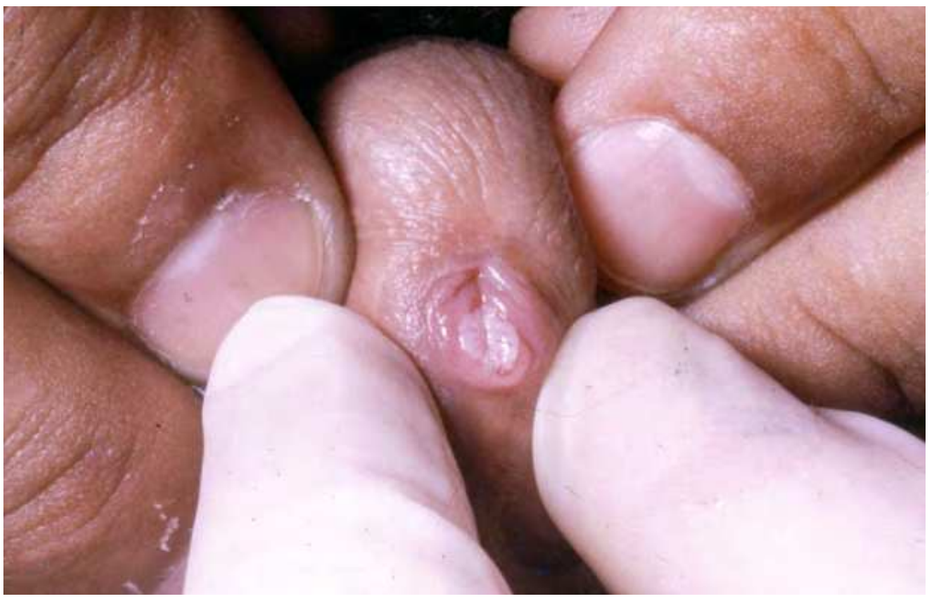

Fig. 11. Condyloma in the urethra of a young man

3. Sub-clinical lesions

Subclinical lesions represent 60% of the cases of external anogenital HPV and 95% of the cases of cervical HPV infection. The main symptoms are micropapillary, micropapular, spike, and keratotic lesions. The diagnosis of these lesions is accomplished primarily by colposcopy, cytology and histology (Forcier & Musacchio, 2010).

The cytopathic effects of HPV infection, specifically koilocytotic atypia, dyskeratosis and the cellular multinucleation are detected in 2 to 3% of routine Pap smears (Figure 12). The cytological and histological patterns of HPV-induced lesions are essentially the same (Wright, 2006) (Figure 13).

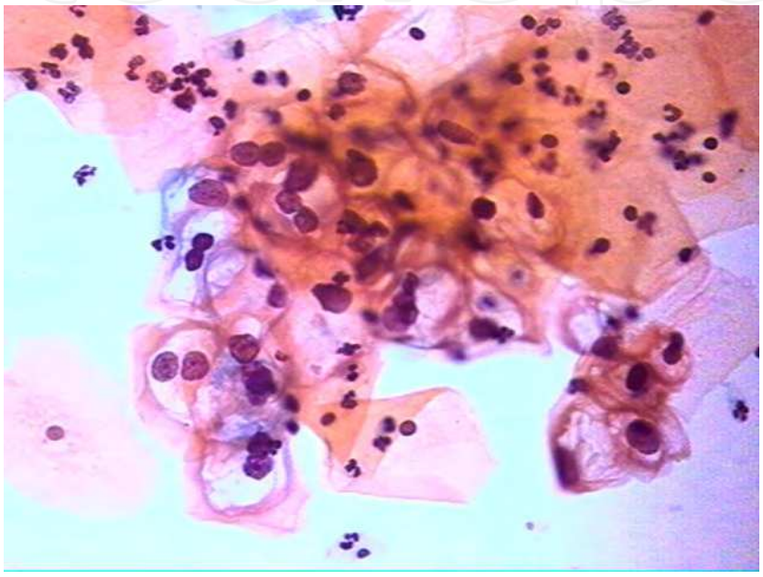

Fig. 12. Cytopathic effects of HPV infection (koilocytotic atypia)

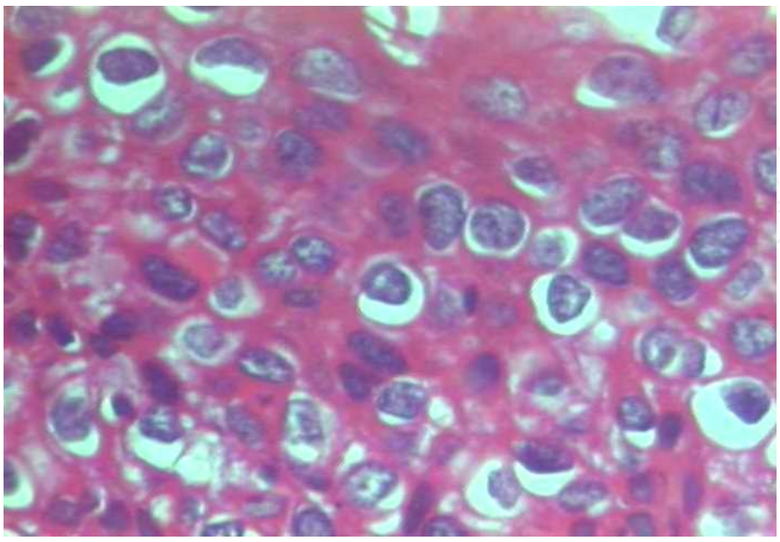

Fig. 13. Histology of a cervical intraepithelial neoplasia with cytopathic effects of HPV infection (koilocytosis)

Cervical intraepithelial neoplasia (CIN) is the most common manifestation of HPV in the cervix. These lesions are manifested by colposcopy using acetic acid that produces aceto-white epithelium, punctation or mosaic. At the colposcopic exam, the cellular changes in the low-grade squamous intraepithelial lesions (LSIL) are discrete (Figure 14) while in high-grade lesions (HSIL) are bigger (Figure 15), including an atypical vascularization. An aceto-white lesion outside the cervical transformation zone is highly suggestive of an HPV infection (Figure 16). The low-grade lesions often regress spontaneously, ranging from 25 to 60% in one year. The regression rate for high-grade lesions is much smaller (Chase et al, 2008).

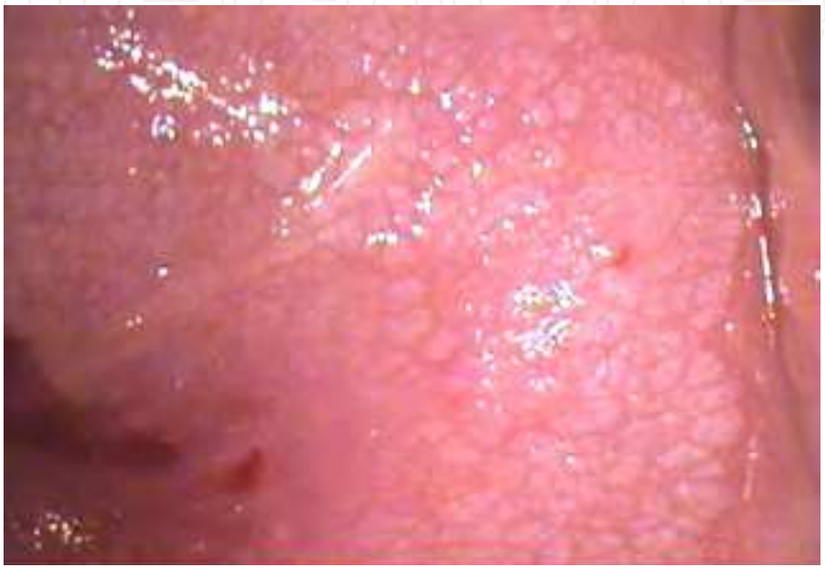

Fig. 14. Colposcopy of a low-grade squamous intraepithelial lesion caused by the HPV infection (mosaiciform lesion)

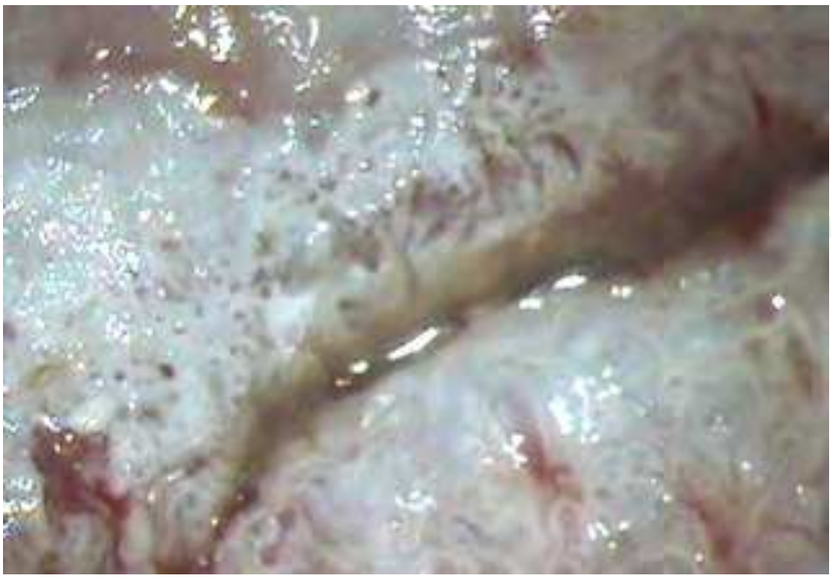

Fig. 15. Colposcopy of a high-grade squamous intraepithelial lesion caused by the HPV infection (atypical vessels)

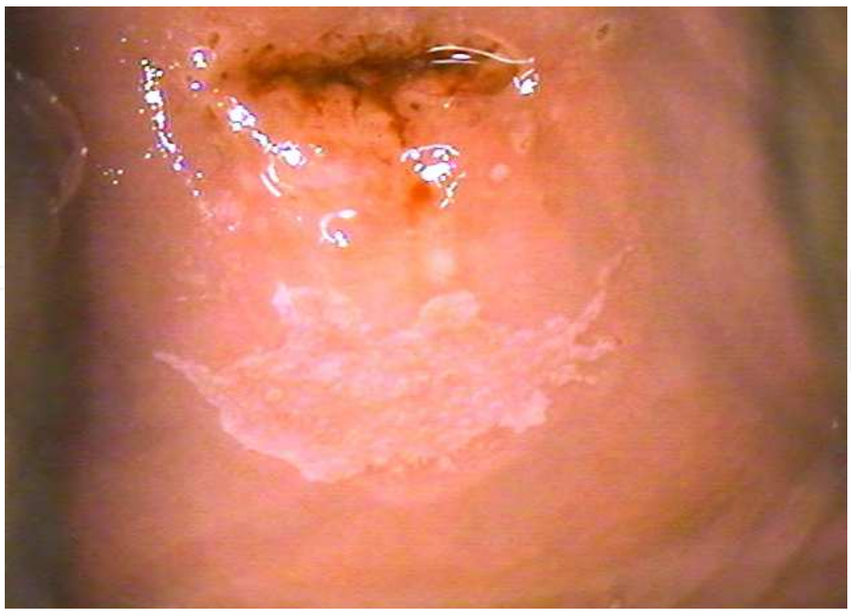

Fig. 16. Aceto-white lesion outside the cervical transformation zone due to the HPV infection

The manifestations of the HPV infection in the vagina is poor. Changes are usually aceto-white, flat or the micropapillary lesion that are visible after the application of acetic acid at 2 to 5% (Figure 17) and are better visualized after applying Lugol's iodine (Figure 18). The punctation and mosaics caused by HPV should be differentiated mainly from the congenital transformation zone and may be related to a vaginal low or high-grade intraepithelial neoplasia (Davis, 1993) . The natural history of vaginal intraepithelial neoplasia (VAIN) based on a 3-year follow-up study of no treatment suggests a regression rate of 78%, 13% persistence, and 9% progression to cancer (Aho et al, 1991).

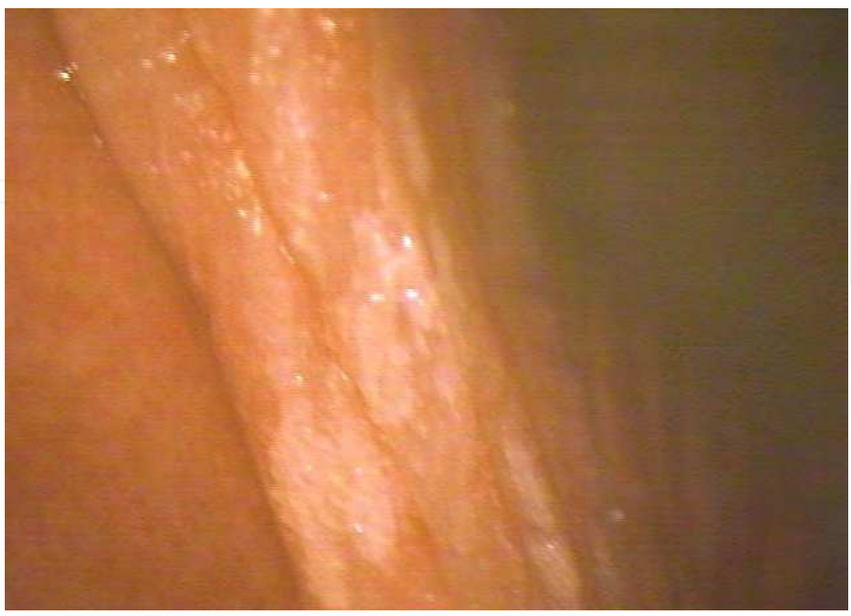

Fig. 17. Colposcopy of a vaginal intraepithelial neoplasia after applying acetic acid 2%

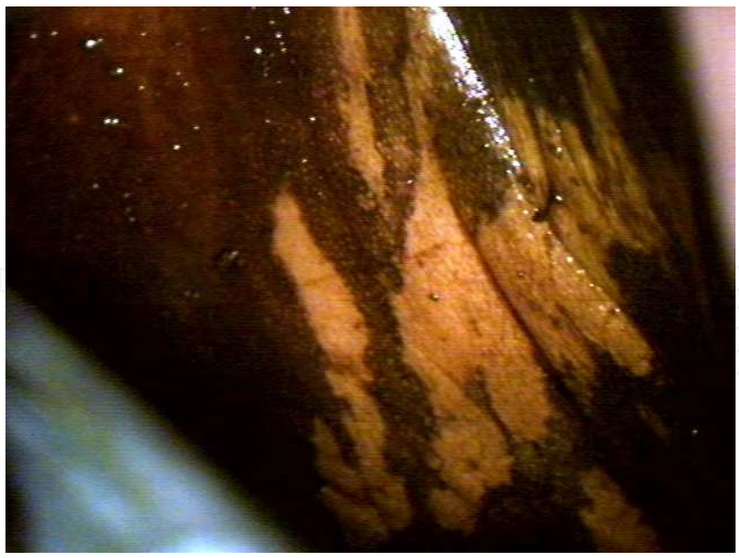

Fig. 18. The visualization of a vaginal intraepithelial neoplasia with colposcopy is better after applying Lugol's iodine solution

The colposcopic examination of the vulva after the application of acetic acid at 5% permits the identification of the minimum changes associated with HPV, usually expressed by the aceto-white epithelium. These changes are often multifocal and commonly involve the vaginal fourchette and labia minora. It is necessary, however, to have an expert colposcopist to differentiate the subclinical alterations induced by HPV from inflammatory changes (Gagné, 2008). The vulvar intraepithelial neoplasia (VIN) associated with HPV (VIN usual type) has a very small risk of progression to an invasive lesion. The most severe intraepithelial lesions (VIN differentiated type, that are not associated with HPV) tend to be multicentric and multifocal. These lesions may be associated with pruritus and local irritation (Heller, 2007).

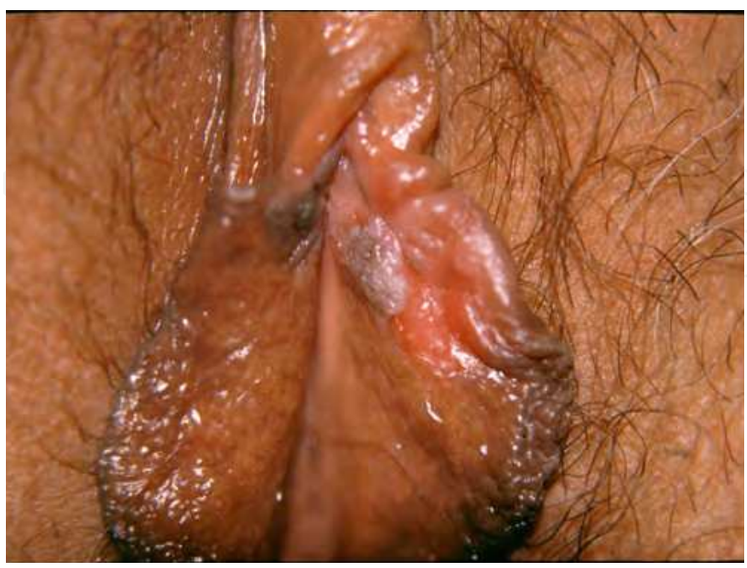

Fig. 19. A hyperpigmented and aceto-white lesion of a vulvar intraepithelial neoplasia (VIN usual type) of the minor labia observed by colposcopy after applying acetic acid 5%.

Subclinical changes in the perianal and anal area are much less frequent and pratically all are associated with an aceto-white epithelium of varying severity after the use of acetic acid at 5% (Chin-Hong & Palefsky 2002) (Figure 20).

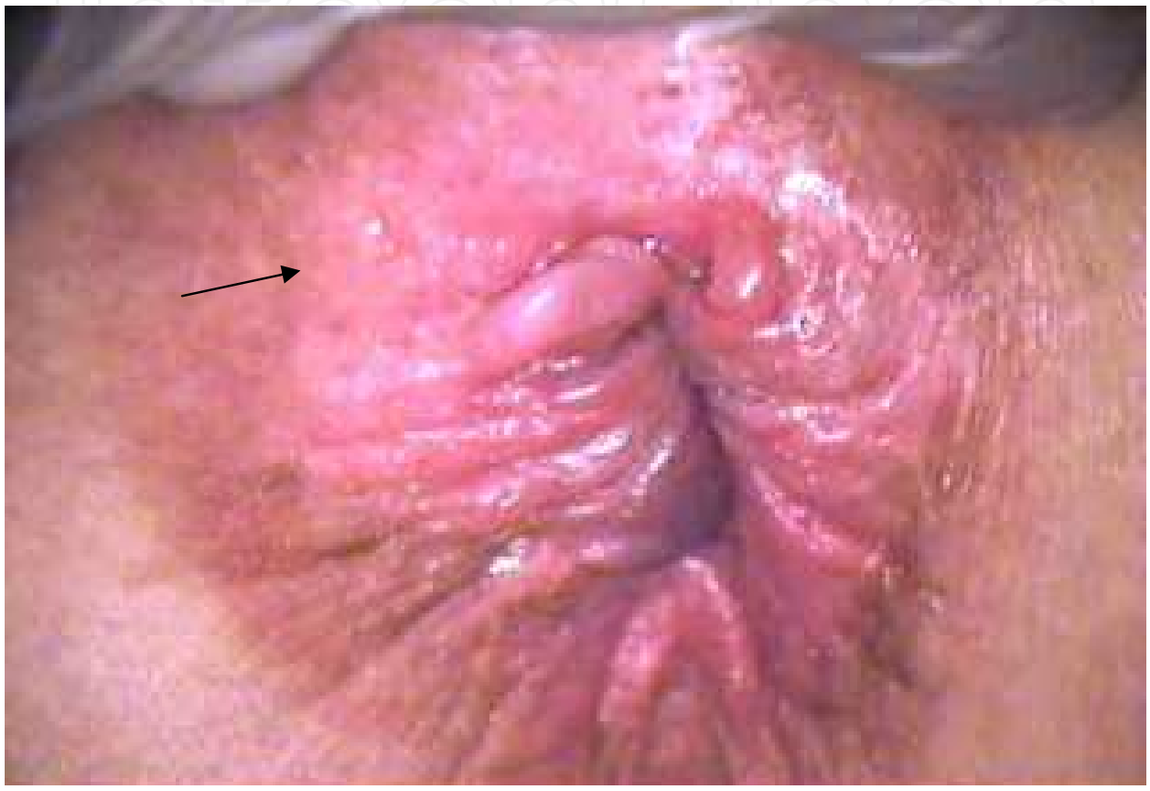

Fig. 20. Aceto-white epithelium of an anal intraepithelial neoplasia observed by colposcopy after applying acetic acid 5%

When evaluating with colposcopy (peniscopy) and acetic acid on male partners of women with genital disease associated with HPV, approximately 40 to 50% of them also have lesions associated with HPV. About 20 to 30% of partners of women with cervical intraepithelial neoplasia also have a penile intraepithelial neoplasia (PIN). Half of these lesions are subclinical. Circumcised men have a lower prevalence of subclinical disease due to the majority of the lesions being located on the foreskin. Penile intraepithelial neoplasias may also exhibit a hyperchromic (Figure 21) or reddish lesion. Rarely these lesions are symptomatic, but when this occurs, itching or burning is more frequent (Krebs & Schneider, 1987).

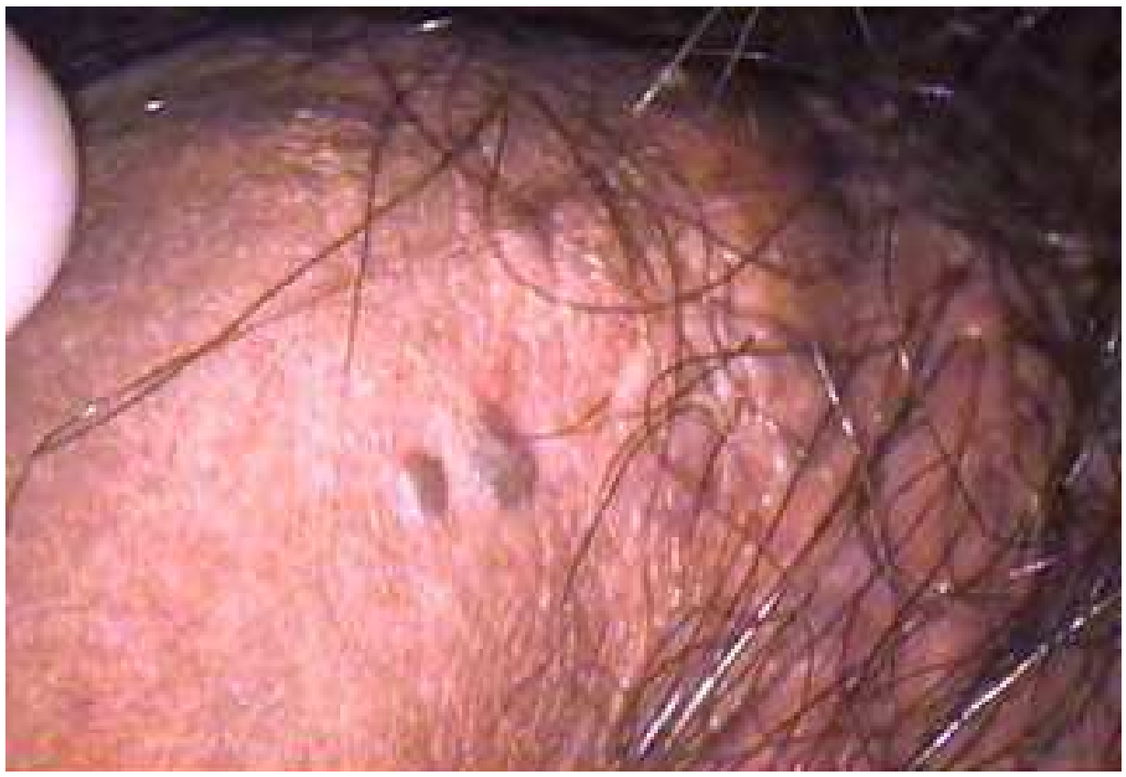

Fig. 21. Penile intraepithelial neoplasia observed by peniscopy after applying acetic acid 5% exhibiting hyperpigmented papules on the foreskin

4. Latent infection

In latent infections there are no clinical manifestation. In the general female population, the prevalence of the HPV infection ranges from 2 to 44%. Infection also occurs in approximately 8% of women who are not yet sexually active and approximately 20% in women who have had sexual activity with women only. In men, the percentage of HPV infection can reach as high as 45%, depending on the population studied. The diagnosis of latent infection is performed using molecular biology methods, especially the hybrid capture and polymerase chain reaction (PCR) methods, due to the clinical examination, colposcopy, cytology and histology are normal (Chow et al, 2010).

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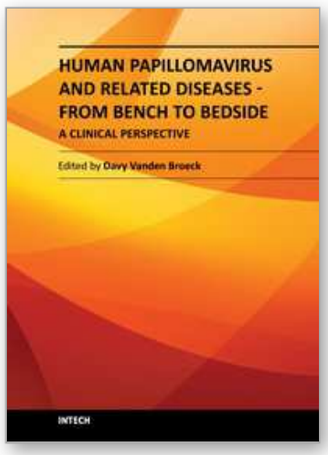

Human Papillomavirus and Related Diseases - From Bench to Bedside - A Clinical Perspective

Edited by Dr. Davy Vanden Broeck

ISBN 978-953-307-860-1
Hard cover, 348 pages
Publisher InTech
Published online 20, January, 2012
Published in print edition January, 2012

Cervical cancer is the second most prevalent cancer among women worldwide, and infection with Human Papilloma Virus (HPV) has been identified as the causal agent for this condition. The natural history of cervical cancer is characterized by slow disease progression, rendering the condition, in essence, preventable and even treatable when diagnosed in early stages. Pap smear and the recently introduced prophylactic vaccines are the most prominent prevention options, but despite the availability of these primary and secondary screening tools, the global burden of disease is unfortunately still very high. This book will focus on the clinical aspects of HPV and related disease, highlighting the latest developments in this field.

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Edison Natal Fedrizzi (2012). Clinical Manifestations of Genital HPV Infection, Human Papillomavirus and Related Diseases - From Bench to Bedside - A Clinical Perspective, Dr. Davy Vanden Broeck (Ed.), ISBN: 978-953-307-860-1, InTech, Available from: http://www.intechopen.com/books/human-papillomavirus-and-related-diseases-from-bench-to-bedside-a-clinical-perspective/clinical-manifestations-of-genital-hpv-infection

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