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HPV infection in women: clinical consequences, psychosexual impact and the chances of prevention

A. Graziottin

Director, Center of Gynecology and Medical Sexology - H. San Raffaele Resnati, Milan, Italy

ABSTRACT

HPV infection in women: clinical consequences, psychosexual impact and the chances of prevention.

Introduction. Human Papillomavirus (HPV) infection is the most common genital viral infection in humans. It is highly prevalent and increasing, due to promiscuity and unprotected sex. HPV is a wide family of DNA viruses, which may cause benign skin and mucosal tumours (genital, anal or oral warts), intraepithelial neoplasias and/or malignant cancers in different organs. Women are more susceptible to the oncogenic effect of HPVs, mostly at the genital site.

Aims. This paper analyses the main characteristics of HPVs, the clinical consequences of their infections in women, with the current epidemiology; some highlights on the actual measure of prevention, with a focus on the psychosexual consequences of HPV infections.

Conclusion. The HR-HPVs (High Risk Human Papillomavirus) have been causally related to several cancers in human (cervical, vulvar, vaginal, anal), and the LR-HPV (Low Risk Human Papillomavirus) types related mainly to a benign sexually transmitted disease: genital warts.

Primary measures of prevention such as vaccination can protect against a panel of HPV related diseases, while secondary prevention, such as pap test or HPV test are specific for a precocious diagnosis, and is currently standardized as a screening measure, only in the field of cervical cancer. To guarantee the most effective preventive strategies both measures had to continue together.

Psychosexual vulnerability increases with number of recurrences of HPV infections. Depression, anxiety and anger are the emotions most frequently reported. However, no specific correlation has been proved so far between HPV infection and a specific female sexual disorder. A practical approach is offered to the reader with clinically relevant tips, useful in his/her daily practice, when dealing with HPV infected women and couples.

SOMMARIO

Infezione da HPV nelle donne: conseguenze cliniche, impatto psicosessuale ed opportunità di prevenzione.

Introduzione. L'infezione da Papillomavirus umano (HPV) è la più comune infezione genitale virale che colpisce l'essere umano. L'infezione ha un'elevata prevalenza che è in aumento a causa della promiscuità e di rapporti sessuali non protetti. Quella degli HPV è una grande famiglia di virus a DNA che possono causare tumori benigni della mucosa e della pelle (condilomi genitali, verruche anali e orali), neoplasie intraepiteliali e/o cancri maligni in differenti organi. Le donne sono maggiormente suscettibili all'effetto oncogeno degli HPV, soprattutto nell'area genitale.

Obiettivo. Questo articolo analizza le principali caratteristiche degli HPV, le conseguenze cliniche delle infezioni da HPV nelle donne alla luce dell'attuale epidemiologia e affronta alcuni aspetti delle attuali misure di prevenzione, con un'attenzione particolare alle conseguenze delle infezioni da HPV nella sfera psicosessuale.

Conclusioni. Gli HR-HPV (HPV ad alto rischio) sono causalmente correlati a diversi tipi di cancro nell'essere umano (cervicale, vulvare, vaginale e anale) mentre i tipi LR-HPV (tipo a basso rischio) sono correlati soprattutto a patologie benigne a trasmissione sessuale: i condilomi genitali.

Una misura di prevenzione primaria come la vaccinazione può offrire protezione da diverse patologie da HPV, mentre la prevenzione secondaria come il Pap-test o l'HPV test è specifica per effettuare una diagnosi precoce, ed è al momento standardizzata come misura di screening solo per il cancro cervicale. Per garantire le migliori strategie di prevenzione entrambe le pratiche devono essere continuate.

Con l'aumentare della ricorrenza delle infezioni da HPV aumenta anche la vulnerabilità a livello psicosessuale. Depressione, ansia e ira sono le emozioni più frequentemente riportate. Tuttavia, nessuna correlazione specifica è stata dimostrata fino ad oggi tra l'infezione da HPV e specifici disordini femminili relativi alla sfera sessuale. Un approccio pratico offrirà al lettore suggerimenti utili alla sua pratica quotidiana nell'interfacciarsi con donne e coppie colpite dall'HPV.

Correspondence to: A. Graziottin

Key words: HPV, genital warts, intraepithelial neoplasia, cervical cancer, anal HPV infection, psychosexual issues, HPV vaccine.

Parole chiave: HPV, condilomi genitali, neoplasia intraepiteliale, cancro del collo dell'utero, infezione anale da HPV, complicazioni psico-sessuali, vaccino HPV.

INTRODUCTION

Human Papillomavirus (HPV) infection is the most common genital viral infection in humans (1). HPV is a wide family of DNA viruses with a tropism for skin and mucosa (genital, anal or oral), that can cause several benign or malignant diseases (2). More than 100 HPV types have been identified, and several types have been defined to be oncogenic by the International Agency for the Research on Cancer (IARC), the HR-HPV (High Risk), whilst others have been classified as LR-HPV (Low Risk) (3).

The HR-HPV has been causally related to several cancers in human (cervical, vulvar, vaginal, anal), and the LR-HPV types related mainly to benign sexually transmitted diseases: genital warts.

HPV are widespread and it's estimated that about 50-75% of sexually active people may have encountered the virus during their sexual life (4).

Women are more susceptible to the oncogenic effect of HPVs, mostly at the genital site, on the uterine cervix (5).

Tumors related to HPVs are rare consequence of the persistence of the High Risk Human Papillomaviruses. Currently, extremely effective measures of prevention are established, like secondary prevention (pap test and HPV test), and primary prevention (vaccines).

This paper summarizes the main characteristic of HPVs, the clinical consequences of their infections in women, with the current epidemiology, some highlights on the actual measure of prevention, with a focus on the psychosexual consequences of HPV infections.

MAIN CHARACTERISTICS AND MECHANISM OF ACTION OF HPV

Papillomaviruses (PV) are a group of small DNA tumor viruses that infect various animals from birds to mammals, including humans (6). To date, more than one hundred human and animal PV genotypes (types) have been completely sequenced (3). Depending on the genotype, Human Papillomavirus may cause benign or malignant tumors. The taxonomic status of HPV types, subtypes, and variants is based on the sequence of their L1 genes which differ from each other by at least 10%, 2-10%, and 2%, respectively (3). L1 genes determine variations in the main protein that builds the viral capsid, i.e. the container of the virus.

Virus infects the keratinocytes in the basal layers of a stratified squamous epithelium or the mucosal cell lining of critical sexual areas such as mouth, vagina, and anus (3). HPV infection of these cells leads to the activation of a cascade of viral gene expression that, perturbing the epithelial cell differentiation, results, at the end of this cell cycle, in the production of HPV virions (3).

In fact, normally, when basal cells undergo cell division, the daughter cell that migrates into the suprabasal compartment withdraws from the cell cycle and initiates a program of terminal differentiation. However, in HPV-positive human keratinocytes and cervical epithelial cells the suprabasal cells continue the DNA synthesis and express markers for cell proliferation.

Within this suprabasal compartment, cells support the amplification of the viral genome, expression of capsid genes and assembly of progeny virus, and final encapsidation of HPV DNA to generate new virus occurs within the terminally differentiated cell compartment (3).

HPVs does not always cause productive or clinically detectable lesion. They can a) be exfoliated with the superficial keratinocytes, leaving no traces of the previous infection; b) remain silent within the guest cell DNA; c) remain active in the DNA, inducing: c1) benign proliferation (condylomata) or c2) promote the positive transformation of a normal cell into a cancerous one (7).

Fortunately, most HPV infections are cleared by the immune system and do not result in clinical complications. Persistent infection with high-risk HPV types has been linked first to the development of cervical cancer.

VACCINES AND THE PRIMARY PREVENTION OF HPV RELATED DISEASES

Infection can only be prevented via complete sexual abstinence. Good protection, but not total, could be obtained when *every* type of intimacy (oral, vaginal, anal) is consistently protected with condom prior to any sexual contact.

a) HPV Vaccine: the pharmacology

Primary prevention with a vaccine is now achieved for the two most dangerous HR HPV types 16 and 18 and for other two LR types 6 and 11 with quadrivalent VLP-L1 vaccine (10), whilst the bivalent vaccine protects only against the two oncogenic HR HPV types 16 and 18. In the US only the quadrivalent has been approved, whilst in the majority of the other European countries, in South America and Australia both vaccines are used.

VLP (Virus Like Particle) is a recombinant DNA technology with a plasmid-induced yeast production of large amount of L1, the main immunological type specific protein of the empty capsomere of HPV (11). Once produced in this large amount, L1 has the intrinsic capacity of self assemble, generating empty particles that resemble originating virus on surface but without any DNA information inside, thus completely unable to infect cells and causing diseases (11). HPV only infects humans, but animal studies with analogous papillomaviruses suggest that the efficacy of L1 VLP vaccines is mediated by the development of a humoral immune response. Several animal system demonstrated that when injected intramuscularly, these VLPs can stimulate immune system to react against them, as if they were the originating HPV virus, so that when the animal is rechallenged with HPV it is protected by the clinical consequences of this infection (12-14). Large and prolonged clinical trials in humans have definitively showed that bivalent vaccine can protect against the clinical consequences of HR-HPV 16 and 18, whilst the quadrivalent vaccine can protect woman against cervical, vaginal, vulvar precancerous lesions and also against genital warts (15-19).

The quadrivalent vaccine contains four VLP-L1 (for HPV 6: 20 micrograms; for HPV 11: 40 micrograms; for HPV 16: 40 micrograms and for HPV18: 20 micrograms) adsorbed into a new adjuvant system, the AAHS: amorphous aluminum hydroxyphosphate sulphate adjuvant (225 micrograms Al).

This AAHS has been selected because it has been shown to induce a larger amount of antibodies than other classical alum-hydroxide salt (20), with a well known safety profile, because AAHS has already been administered to million subjects in several others vaccines.

b) HPV Vaccine: mode of administration

The primary vaccination series consists of 3 separate 0.5 ml doses administered according to the following schedule: 0, 2, 6 months.

c) HPV Vaccine: indications

The current indication for quadrivalent vaccine are the prevention of premalignant genital lesions (cervical, vulvar and vaginal), cervical cancer and external genital warts (condyloma acuminata) causally related to Human Papillomavirus (HPV) types 6, 11, 16 and 18.

HPV 16 and HPV 18 are estimated to be responsible for approximately 70% of cervical cancers; 80% of adenocarcinoma in situ (AIS); 45-70% of high-grade cervical intraepithelial neoplasia (CIN 2/3); 25% of low grade cervical intraepithelial neoplasia (CIN 1).

HPV 16 and 18 also cause approximately 70% of HPV related high-grade vulvar (VIN 2/3) and vaginal (VaIN 2/3) intraepithelial neoplasia, instead the low risk types, HPV 6 and 11 are responsible for approximately 90% of genital warts and 10% of low grade cervical intraepithelial neoplasia (CIN 1).

d) HPV Vaccine and pap smear: the perfect strategy

Vaccination is *not* a substitute for secondary prevention methods and screening. In

fact, with new HPV vaccines, not all types of HR-HPV are prevented. Even if quadrivalent vaccine has demonstrated a rate of cross-protective benefit, the clinically relevance of that phenomenon has not yet established. Furthermore, the optimal vaccine benefit is achieved in naïve adolescents/young women, i.e. before they have naturally encountered papillomavirus vaccine types (21), and it has also to be considered that primary and secondary prevention pursue different objectives.

Primary measure of prevention such as vaccination can protect against a panel of HPV related diseases, while secondary prevention, as pap test or HPV test is for a precocious diagnosis, and is currently standardized as such screening measure, only in the field of cervical cancer, and not for other HPV related diseases.

It is therefore critical that women continue the screening program also in the vaccine era. Vaccination campaigns could indeed help to achieve an even better screening compliance. Recent data from six European countries (Denmark, German, Portugal, Spain, Sweden and France) based on a questionnaire carried out before (2006) and after (2008) the introduction of bivalent and quadrivalent vaccine, showed that mothers of vaccinated girls tended to attend screening for themselves more often than other mothers (22).

EPIDEMIOLOGY OF HPV INFECTIONS IN WOMEN

It is estimated that 20 million individuals in the United States are infected with HPV, with 5.5 million new infections occurring each year among cytologically normal women (24).

Age-standardized HPV prevalence has been shown to vary nearly 20 times between populations, from 1.5% in Spain to more than 35% in Honduras and Kenya, with a mean value of 10% worldwide (25).

In Europe the HPV types distribution, in general population of women without cytological abnormalities has shown HPV 16 as the most common in all countries, followed by other types as HPV 18, 31, 33, 35, 39, 42, 45, 66 and HPV 6, with a different grading distribution between North, Est ,West and South Europe (26) (Table 1).

THE ONCOGENIC PROCESS HPV MEDIATED

The majority of HPV infections are cleared by the immune system without any clinical complication. The persistence of the infection with an oncogenic HPV types is necessary to promote the transformation process of a normal cell in a precancerous and, progressively, in a cancerous invasive one.

Other contributing factors include smoking, early age at sexual debut, multiparity (high), other STDs and so on (Table 2). Cytological manifestations of high-risk HPV infection in women include Abnormal Pap test results, and Low-grade Squamous Intraepithelial Lesions (LSIL), High-grade Squamous Intraepithelial Lesions (HSIL), and cervical cancer. Others precancerous lesions or invasive cancers from anogenital sites like vagina, vulva and anus are linked to HR-HPV types.

The histological classification of these lesions identified with the term CIN (Cervical Intraepithelial Neoplasia) has different grading of disease.

The initial lesion or CIN 1 (corresponding

Tab. 1 - Distribution of prevalence rate of HPV types in Europe (mod de Sanjosé S, Lancet Infect Dis 2007).

North Europe (prevalence %)	West Europe (prevalence %)	Sud Europe (prevalence %)	Est. Europe (prevalence %)
HPV 16 (3,0)	HPV 16 (1,6)	HPV 16 (1,2)	HPV 16 (7,4)
HPV18 (1,0)	HPV18 (0,7)	HPV 66(0,3)	HPV 31 (3,2)
HPV 31 (0,7)	HPV 31 (0,7)	HPV 45 (0,3)	HPV 18 (1,9)
HPV33 (0,6)	HPV35 (0,4)	HPV31 (0,2)	HPV 66 (1,6)
HPV 6 (0,5)	HPV 33 (0,3)	HPV 42 (0,2)	HPV 39 (1,3)

Tab. 2 - HPV infection risk factors and gender vulnerability in women.

Youth	Moscicki Ab, 2007[14] Saleh MM, Seoud AA, Zaklama MS, 2007[15] Winer Rl, Feng Q, Hughes JP et al. 2008[16]
Gender (female)	Steben M, Duarte-Franco E, 2007[17]
High number of sexual partners	Moscicki Ab, 2007[14] Saleh MM, Seoud AA, Zaklama MS, 2007[15] Winer Rl, Feng Q, Hughes JP et al. 2008[16]
Non consistently protected sex	Epstein RJ, 2005[18]
Co-infection with Chlamydia trachomatis	Anttila T, Saikku P, Koskela P, et al. 2001[19] Bosch FX, de Sanjosè S, 2007[20]
Coinfection with Herpes Simplex virus	Smith JS, Herrero R, Bosetti C, et al. 2002[21] Bosch FX, de Sanjosè S, 2007[20]
Smoking	Castellsague X, Munoz N, 2003[21] Bosch FX, de Sanjosè S, 2007[20]
Immunosuppression (HIV, immunosuppressive therapy)	Strickler HD, Burk RD, Fazzari M, et al. 2005[23] Cameron JE, 2007[24]
Pregnancy	Strickler HD, Burk RD, Fazzari M, et al. 2005[23]

to LSIL), involves only one/third of the epithelial tissue; it spontaneously regresses very often, so the general clinical management is monitoring over time this kind of only potentially precancerous lesion, with repeated pap test, colposcopy, and direct biopsy when indicated (27). Instead, CIN 2 and mainly CIN 3 (involving 2/3rd or all 3/3rd of the epithelial tissue, and corresponding to HSIL) are considered definite precancerous lesions: their regressive potential, although described, is minimal, whilst they possess a significant risk of progression to invasive cancer. The clinical management requires their surgical removal after diagnosis (27).

The distribution of HPV types in women with cervical abnormalities world wide is quite different from that of women in the general population. Globally it has been registered a HPV prevalence of 71,6% in low grade lesion and of 84,9% in high grade lesions (28). Table 3 shows the different type distribution in low grade and high grade lesions.

Different HPV types patterns seem to be involved with increasing grade of the lesion. Some authors observed that women with HPV 16, 31, 33 seem to have the highest risk to develop high grade lesions, while women with HPV 18, 39, 51, 52, 56, 58 have intermediate risk. Instead they noted no excess risk for HPV 35, 45, 59, 66 (29).

In Europe the HPV-HR prevalence in high grade lesions is 88%, with HPV 16 being usually the most frequently proven, followed by HPV 31, 33, 18, 58, 52, 51, and 56 (30). Finally in invasive cervical lesion, virtually 100% of HPV presence is described (31).

THE HPV-HR BURDEN ON WOMEN'S HEALTH

The worldwide female population is 2.329,08 millions women, and for age from 15 years old it has been calculated that each year 493.243 women receive a cervical cancer diagnosis, with 273.505 death cases (28). Cervical cancer results the second most frequent can-

Tab. 3 - HPV types prevalence in low grade and High grade lesion in European women (mod X. Castellsagué Vaccine 2007)

Low grade HPV types prevalence world wide (percentage %)	High grade HPV types prevalence world wide (percentage %)
HPV 16 (20,3)	HPV 16 (46,4)
HPV31 (8,3)	HPV31 (8,7)
HPV 51 (8,3)	HPV 33 (7,3)
HPV53 (7,8)	HPV58 (7,8)
HPV 52 (6,9)	HPV 18 (6,9)

cer in female world population, and also the second in the younger age (between 15 to 44 years old women) (28).

HPV 16 (54,4% of prevalence) and 18 (15,9% of prevalence) cause more than 70% of invasive cervical cancer worldwide, and for the others HR-HPV types the distribution is the following: HPV 33 (prevalence 4,3%), HPV 45 (3,7%), HPV 31 (3,5%), HPV 58 (3,3%), HPV 52 (2,5%) and HPV 35,59 and 51 (comprehensively 3,4%).

In Europe the distribution is moderately different with HPV 16, 18, 33, 31, 45, 35, 58 and 56 in descending order of frequence (30).

GENITAL WARTS: KEY ASPECTS

Genital warts (GWs), known also as *condyloma acuminata*, are related to HPV infection, and 90% of cases are related to HPV 6 and 11. GWs are a benign condition, extremely frequent with very different local extension. GWs are often accompanied by psychological distress (32, 33), sometimes higher than their medical consequences.

Fear of developing cancer and some impact on sexual life and relationships are often reported (34). Diagnosis is primarily clinical. The treatment goal is the removal of warts and therapy can be chemical or surgical (35). Topical treatments (Imiquimod, Podophyllotoxin, Podofilox or Trichloroacetic acid) could be applied directly on the skin. To remove larger warts or warts not responding to medication cryotherapy, electrocautery, surgical excision, or laser can be used. Biopsy and viral typing is usually not recommended for patients with typical lesions.

Switching to a new treatment is appropriate if there is no response after three cycles of medical or surgical treatment. Routine follow-up is recommended, in order to monitor the response to therapy and to evaluate possible recurrences.

To assess the burden and correlates of genital warts in women a population-based cross-sectional study in 69,147 women (18-45 years of age) randomly chosen from the general population in Denmark, Iceland, Norway, and Sweden was performed. Information on clinically diagnosed genital warts and lifestyle habits was collected using a questionnaire. The data suggested that 1 in 10 women in the Nordic countries experience genital warts before the age of 45 years, with an increasing occurrence in younger birth cohorts (36).

THE ROLE OF VACCINE IN THE PREVENTION OF GENITAL WARTS

The quadrivalent vaccine contains also VLP to prevent HPV6 and 11 related condyloma acuminata, and clinical trial has shown a 99% of preventive efficacy at the end of the study.

Genital warts commonly need a shorter time to clinical development (usually between 3-8 months) than the estimated time of ≥ 1 year necessary to develop evaluable precancerous lesion related to HPV HR types.

To evaluate the effective benefits attainable with the introduction of a new vaccine into the female general population in real life, we may use benign lesions (GWs) both as a measure of what we could reach immediately in terms of disease reduction and as an earlier indicator of what we could expect to reach in terms of prevention of lesion due to HR types.

For example the recent report of an obser-

vational study in Australia, comparing the proportion of genital warts diagnosed in the total number of diagnoses of sexually transmitted diseases at the Melbourne Sexual Health Centre before and after the introduction of vaccination with quadrivalent vaccine, documents a 48 % decline in this proportion only one year after vaccination (in women younger than 28 years) (37). Australia administered quadrivalent vaccine since April 2007 to school girls between 12 and 18 years and since July 2007 to women less than 26 years of age outside of the school based programme. The coverage rate in the region where the study took place is between 65% and 75%.

The reduction in genital warts' diagnoses is an important benefit in itself. In addition, it can be considered an early and significant marker of the range of benefits that a vaccination programme with the quadrivalent vaccine is expected to provide in terms of reducing other malignant or premalignant HPV related diseases (37).

DIAGNOSIS

The diagnosis of the HPV clinical consequences or infections can be made either on:

symptomatic women: generally in older stages of HPV- related diseases, presenting with vulvar, anal or oral lesion; atypical vaginal blood losses, smelly vaginal discharge, urinary or anorectal symptoms, weight loss for malignant proliferation and cancer.

asymptomatic women: most often following an abnormal smear test or HPV testing.

HPV testing may offer a number of advantages to conventional cervical screening, such as increased sensitivity for high grade precancerous disease, the potential to increase screening intervals for HPV negative women and the reduction of unnecessary colposcopies among women with borderline smears (ASC-US). However, HPV testing has been criticized for its lack of specificity and the potential for large numbers of women to test positive in the absence of clinically significant cytological abnormalities (38, 39).

THERAPY

Treatments include a wide range of interventions, according to the type and site of lesions, extension and severity. Key interventions are:

Pharmacologic;
Physical;
Surgical.

Early and late recurrences of the infection and related pathologies are frequent. They may have a vary different impact from the psychosexual point of view, according to the severity of lesions, aggressiveness of related treatments and their side-effects, frequency of recurrences and their severity, and quality of psychosexual support from relatives and healthcare providers.

ANAL HPV INFECTIONS

Anal HPV infections in women are usually underestimated because women do not report they had unprotected anal sex and physicians usually do not ask about this sexual practice.

The health risks of anal sex appear to be severely underestimated by a substantial proportion of sexually active women and men. Among heterosexuals reported rates of condom use are nearly universally lower for anal than for vaginal intercourse. U.S. survey and other data suggest that, in terms of absolute numbers, approximately seven times more women than homosexual men engage in unprotected receptive anal intercourse (40).

Anal intraepithelial neoplasia (AIN) is a consequence of chronic HPV infection in the anal canal and appears to be driven by high viral loads of HPV. AIN natural history resembles that of cervical intraepithelial neoplasia. Low-grade lesions frequently resolve, but high-grade lesions are much more stable. HIV-positives men and women who practice receptive anal intercourse are at highest risk of AIN (41).

The incidence of AIN has increased significantly in the last decades (42).

Globally annual rate of incidence of anal cancer varied from 0, 1 to 2, 8 cases for 100.000 men and from 0, 0 to 2, 2 for 100.000 in women (43).

After the diagnosis of perianal or anal HPV related infections, many refuse any further anal intimacy. In the clinical setting,

the most frequently reported feeling is a sense of guilt, anal sex still being considered in many countries as inappropriate or frankly transgressive.

PSYCHOSEXUAL IMPACT

Despite HPV infection being amongst the most common STDs seen in clinical practice, few studies have been carried out describing adverse psychological and psychosexual sequelae (33, 44).

The evidence emerging from the literature and from our clinical experiences suggests the existence of several peaks of vulnerability due to HPV infection. The available studies are focused on genital – i.e. vulvar/vaginal/cervical lesions. However, oral and anal infections are increasing and should be considered also from the point of view of their potential psychosexual impact.

Conagle found that the first episode of HPV can cause considerable psychological difficulties. However, the diagnosis was not associated with a greater psychological or psychosexual impact other than for other sexual health concerns (45).

McCaffery et al. (46) found that women with normal cytology who tested positive for HPV (HPV+) were significantly more anxious and distressed than women who were negative (HPV-) using both a state anxiety measure [$F(1,267) = 29$, $P < 0.0001$] and a screening specific measure of psychological distress [$F(1,267) = 69$, $P < 0.0001$]. Women with an abnormal or unsatisfactory smear result, who tested HPV positive:

were significantly more distressed than HPV negative women with the same smear result [F (1,267) = 8.8, P 1⁄4 0.002], (but there was no significant difference in state anxiety);

had significantly worse feeling about their sexual relationships. Approximately one-third of women who tested positive reported feeling worse about past and future sexual relationships compared with less than 2% of HPV negative women.

The findings suggest that testing positive for HPV may have an adverse psychosocial impact, with increased anxiety, distress and concern about sexual relationships (46). The emotional impact of testing positive a second time was greater for many women, sometimes causing them to overcome their embarrassment about having a sexually transmitted infection in order to disclose their result and seek support. Women appeared to be more distressed by a second HPV positive result than a single one, and expressed a clear preference for immediate colposcopy over continued surveillance (47).

In the clinical setting, a specific "cosmetic" issue involves women with flourishing, massive genital warts, disfiguring the aspect of their genitals. Concerns over the risk of persistent modification of the genitals and fears of being rejected by partners because of that is expressed to the listening physician, but no mentions to this specific issue have been found in the clinical literature.

HPV lesions' treatment (physical-chemical therapy, diathermocoagulation and laser therapy or pharmacological therapy with imiquimod) are usually long and painful (44, 48). The higher the number of the interventions, the more painful the technique and the severity of the scarring, the more severe is the potential psychosexual impact. Unfortunately, whilst the etiology of the psychosexual impact has been discussed in different papers, controlled studies on the impact of different therapies are lacking (48, 49).

Genital HPV infection can lead to self-inflicted blame and hypochondriac fears as well as to problems with sexuality. Filiberti assessed the psychological and psychodynamic aspects of patients with widespread genital HPV infection entering into a clinical trial in which they were randomly assigned to three treatment groups: CO_2 laser ablation, intramuscular interferon-alpha, CO_2 laser ablation plus intramuscular interferon-alpha. Results indicated a high percentage of sexual impairments after therapy, presence of fear of cancer and worsening in the emotional relationship with the partner. No difference was found among groups of treatment (50).

Furthermore, an American survey of people affected by HPV found that sexual enjoyment and activity were negatively affected and more then ¾ of respondents reported associated feelings of depression and anger (51).

Clinical experience indicate that women with a satisfying sexuality before the HPV diagnosis are those less vulnerable to the long term negative consequences of genital warts and their treatments. Vulnerability increases in women with a dysfunctional sexuality before the diagnosis, in single women, in women with a troubled or conflicting relationships, or when the infection strongly suggests an unprotected affair of the partner. Clinical correlates include loss of sexual desire, more difficult mental and genital arousal, dyspareunia, less frequent intercourse, and a qualitative and quantitative reduction of the repertoire of sexual behaviors. After HPV genital infection, many women refuse further passive oral sex for fear of infecting the partner.

CONCLUSIONS

Women are at increasing risk of HPV infections and related lesions, with a specific and underestimated vulnerability to the risk of anal infections.

Although the research on oncogenic potential of HPV was focused mainly on cervical cancer, now it is clear that this specific cancer is only the tip of the iceberg, with a larger and heavier (in term of number of cases, costs and consequences) base composed by several others precancerous and cancerous diseases.

In this field secondary prevention showed very well the complexity of the pathway through the diagnosis and management of precancerous/cancerous lesions.

The possibility to increase the primary prevention through HPV quadrivalent vaccine cannot be underestimated, as it will reduce benign lesions such as genital warts, a great part of precancerous lesion at cervical, vulvar and vaginal level and also cervical cancers.

In parallel, secondary prevention through the pap-smear and related investigations – when indicated – should be maintained. They must be used and recommended as an alliance, in order to exploit to the best both preventive measures.

Psychosexual vulnerability increases with number of recurrences of HPV infections. Depression, anxiety and anger are the emotions most frequently reported. No specific correlation has been proved so far between HPV infection and a specific female sexual disorder. Vaccine anti-HPV may reduce also the psychosexual impact of HPV infections. However, no data have been produced so far on this issue, that certainly deserves prospective controlled studies.

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