HPV infection in women:
psychosexual impact of genital warts and intraepithelial lesions

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Abstract

Introduction: Genital Human Papillomavirus (HPV) infection is the most commonly occurring sexually transmitted viral infection in humans. HPV is a wide family of DNA viruses, which may cause benign skin and mucosal tumors (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 on the uterine cervix.

Aims: This review analyses the impact of: a) genital warts and their treatment; b) HPV related genital, oral and anal precancerous lesions on women's sexual function.

Methods: A Medline search was carried out. Search terms were HPV, genital warts, intraepithelial neoplasia, cervical cancer, anal cancer, oral cancer, epidemiology, HPV risk factors, sexual dysfunctions, desire disorders, arousal disorders, dyspareunia, vulvar vestibulitis, vulvodynia, orgasmic difficulties, sexual repertoire, couple sexual problems, depression, anxiety, pap-smear, screening program, therapy, vaccines.

Main outcome measures: Sexual consequences of HPV infection in women, specifically genital warts and intraepithelial HPV related neoplasia.

Results: Psychosexual vulnerability increases with number of recurrences of HPV infections. Depression, anxiety and anger are the emotions most frequently reported. However, to date there is no conclusive evidence of a specific correlation between HPV infection and a specific female sexual disorder. The relationship between HPV and vulvar vestibulitis/vulvodynia related dyspareunia seems not direct. Counseling problems, the role of vaccine anti-HPV, and the concept of high-risk partner are discussed. The reader is offered a practical approach with clinically relevant recommendations that may prove useful in his/her daily practice when dealing with HPV infected women and couples.

Conclusion: The evidence of psychosexual consequences of HPV related genital warts and intraepithelial lesions is limited. Specific research on the sexual impact of genital warts and intraepithelial HPV related lesion in women is urgently needed.

Key words: HPV, genital warts, intraepithelial neoplasia, cervical cancer, anal HPV infection, oral HPV infection, female sexual dysfunctions, dyspareunia, psychosexual issues, HPV vaccine, high-risk partners, anxiety, depression

Introduction

Genital Human Papillomavirus (HPV) infection is the most commonly occurring sexually transmitted viral infection in humans[1]. HPV is a wide family of DNA viruses which may cause benign skin and mucosal tumors (genital, anal or oral warts), or malignant cancers in different organs. Women are more susceptible to the oncogenic effect of HPVs, mostly at the genital site and on the uterine cervix[2].

The literature on HPVs is substantial and increasing. The main areas of research include the virological characteristics of HPVs, epidemiology, medical and oncological impact of the infection and related diseases, prevention strategies through appropriate barrier contraception, pap-smear screening and the potential role of vaccines[3-4].

However, research investigating the relationship between HPV infections and sexual dysfunctions in women is limited. It is only in recent years that research in this area has increased. This has occurred in parallel with the growing rate of infections and consequent psychosocial burden.

HPV related disease may have a significant impact on women's sexuality because:

a) it is a sexually transmitted disease affecting particularly the vulva and the uterine cervix. For biological, emotional and symbolic reasons they are key organs for women's eroticism. HPV related disorders may: i) threaten personal and genital health; ii) convey the sense of something degrading, and/or a connotation of stigma, which may induce the woman to feel ashamed, "dirty", inadequate[5-14]; iii) question the health of the partner and his loyalty and commitment to the couple thus potentially affecting sexual function and raising critical issues for the relationship [8];

b) it may contribute to vulvodynia and sexual pain disorders, namely dyspareunia, associated with and/or consequent to vulvar laser treatment[15];

c) it is a potentially oncogenic disease, which may convey a more serious threat for the woman's genital and general health, specifically increasing fear and anxiety[5-10, 12-14]. Worry associated with repeated exams and consultations, and invasive and painful treatments, which increase in case of recurrences, adds further vulnerability to the woman's emotional and sexual well-being[8].

The paper will analyze the impact of HPVs infections on women's psychosexual health. Medical consequences such as urogenital and proctological comorbidity will be included when they interfere with the sexuality of the woman and the couple.

Method

Given the complexity of the topic, this paper will focus on the impact on women's sexuality of genital warts and intraepithelial precancerous lesions. The analysis of HPV psychosexual impact relies mainly on levels of evidence 2 and 3, along with the clinical experience of the authors (implied when no data are referenced). Key papers and reviews are summarized in primis to give the reader a full, although concise understanding of the main characteristics of HPVs, mechanisms of action, mode of infection, prevention, principles of diagnosis and treatment, and after that the literature review was focused on HPV infection's consequences on women's psychosexual health. The search was conducted in Pub Med. Explicit search terms that enable the search to be replicated were used. They include: HPV, genital warts, intraepithelial neoplasia, cervical cancer, anal cancer, oral cancer, epidemiology, HPV risk factors, sexual dysfunctions, desire disorders, arousal disorders, dyspareunia, vulvar vestibulitis, vulvodynia, orgasmic difficulties, sexual repertoire, couple sexual problems, medical comorbidities, psychosexual issues, anxiety, depression, pap-smear, screening program, therapy, vaccines. There was no restriction on geographic setting. The search was limited to English literature.

A total of 123 studies were collected. Abstracts and papers were reviewed independently by the Authors. A final list of articles was then determined. Only 17 articles investigated HPV infection's psychosexual consequences as their primary

aim. However, only one was a controlled study[9]. Given the paucity of the controlled studies, all 17 studies were considered, and level of evidence was defined as follows: 1a – systematic review of randomized controlled trials; 1b – Individual randomized controlled trial; 2a – Systematic review of cohort study; 2b – Individual cohort study; 3a – Systematic review of case-control studies; 3b – Individual case-control study; 4 – Case series; 5 Expert opinion. Editorials and papers with no abstract were excluded.

Epidemiology

It is estimated that in the United States alone 20 million individuals are infected with HPV. Age-standardized HPV prevalence worldwide has been shown to vary, nearly 20 times between populations, from 1.4% in Spain to 25.6% in Nigeria[16]. Epidemiological studies suggest that about 80% of women will have acquired genital HPV by age 50, which makes HPV infection the norm rather than the exception[17-19].

Epidemiology of HPV-related lesions is further usually differentiated between benign and precancerous/cancerous lesions.

Genital warts

Dinh et al. collected data on genital wart diagnosis history, and on sociodemographic and sexual behavior variables, from 8849 sexually active men and women aged 18 to 59, to determine the percentage of subjects who reported having been diagnosed with genital warts in the United States from 1999-2004. Overall, 5.6% of 18- to 59-year-old subjects reported having ever been diagnosed with genital warts. The percentage resulted higher in women (7.2%) than in men (4%). Genital wart diagnosis peaked among 25- to 34-year-old women (10.4%) and 35- to 44-year-old men (6.0%)[20].

Focusing on women, the incidence of genital warts varies in different countries. Robust epidemiological data for genital warts in Europe comes from the UK, where genital warts are a notifiable disease. Epidemiological data for genital warts are limited for other countries in Europe. In France, a recent prospective observational study estimated an overall incidence of 228.9 x 100.000 in women 15-65 years[21].

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 reported that 1 in 10 women in the Nordic countries experienced genital warts before the age of 45, with an increasing occurrence in younger birth cohorts[22]. In Southern Europe, a Spanish study found that 16.9% of women aged 16-20 visiting STDs clinics were affected by GW [23]. In Greece, a cross-sectional study performed in STD clinics showed that 47% of the sample of 829 women had GW[24]. A recent Italian publication estimated the incidence of genital warts 4,3 x1000 women in general female population attending gynecological visit [25].

Intraepithelial neoplasia and cervical cancer

HPV types that infect the genital area are classified as oncogenic low-risk (e.g., 6, 11, 42, 43, 44) or as oncogenic high-risk types (e.g., 16, 18, 31, 33, 45, 52), according to their associated lesions.

High risk HPV causes almost all cases of intraepithelial and invasive cervical cancer. This cancer is the second most common cancer among women worldwide, with an estimated 493,000 new cases and 274,000 deaths in 2002[26] with 80% of new cases occurring in developing countries[27, 28]. Overall, 70% of ICC cases were associated with either HPV16 (55%) or 18 (15%). The six next most common types, namely HPV31, 33, 35, 45, 52 and 58 accounted for an additional 18% of cases [29].These cancers take many years to develop, with a peak in risk at about 35-55 years of age [27, 28].

Cervical cancer is an important cause of lost years of life in relatively young women. Worldwide, the ratio of mortality to incidence is 55%, with higher survival rates and with quite good prognosis in low-risk regions but with lower survival in developing countries, where many cases are present at relatively advanced stages[26].

Main Characteristics and mechanism of action of HPV

Characteristics

HPVs are a group of small DNA viruses. The double-stranded, circular DNA genomes of all HPVs are approximately 8 kb in size.

To date, over 100 different viral types have been identified, and about one third of these infect epithelial cells in the genital tract. The viral types that infect the genital tract fall into two categories: high risk and low risk. The high-risk types are associated with the development of anogenital cancers, while infections by the low-risk HPVs induce mainly benign genital warts[30].

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[31]. L1 genes determine variations in the protein of the viral capsid, i.e., the container of the DNA virus. Vaccines contain the different proteins identifying genotypes no. 6, 11, 16 and 18, thus inducing antibodies able to selectively protect against the viruses specifically identified by the protein-number-plate[31]. (Box 1)

The virus infects keratinocytes in the basal layers of stratified squamous epithelium of critical sexual areas such as mouth, vagina, and anus. Cells in the basal layer consist of stem cells and transit-amplifying cells that are continuously dividing and provide a reservoir of cells for the suprabasal regions. 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 [32].

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 DNA synthesis and express markers for cell proliferation[32].

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[32].

Most HPV infections are “cleared” by the immune system and do not result in clinical diseases[33]. The majority of sexually active adults will be infected with HPV at least once in their lives. However, sexually active women less than 25 years of age consistently have the highest rates of infection[32]. The anatomical characteristics of female genital tract, mainly in the genital mucosal histology, may in part explain gender female vulnerability for clinical sequelae.

Precise mechanisms determining the final outcomes are currently unknown. When immunocompetence is weakened and/or the virus belongs to one of the more aggressive oncogenic subtypes, cancer may finally occur[34]. In the case of High Risk HPV infection that cause the cervical cancer development, the viral life cycle is perturbed in two ways: the loss of terminal differentiation on cell cycle that leads to a cellular state that cannot support the full viral life cycle and the circular viral DNA genome, which normally resides as a nuclear plasmid, often becomes integrated into the host genome and thereby becomes disrupted and its replication defective.

Types of HPVs, such as HPV-16, HPV-18, which are designated “high-risk” or “oncogenic,” have been recognized as causative agents of cervical, anal, vulvar and laryngeal cancers. These sexually transmitted viruses are associated with more than 70% of cervical cancer cases[34,35].

Clinical consequences

Clinical sequelae in cases of low-risk HPV infection consist of genital warts, which can cause significant physical and

psychosocial distress.

Respiratory tract papillomatosis are associated with HPV types 6 and 11; these HPV types are also commonly associated with genital warts. The incidence of respiratory tract papillomatosis in young adults is increasing[36-38]. It has been postulated that oro-genital contact is the means of transmission in this age group. In view of the high infectivity of genital warts, it is interesting to note the low prevalence of oro-pharyngeal warts in adults indulging in oro-genital contact. Clinical manifestations of high-risk HPV cervical infection include a wide range of cytological/histological abnormalities, like: abnormal Pap test results, low-grade squamous intraepithelial lesions (LSIL), high-grade squamous intraepithelial lesions (HSIL) and cervical cancer. Other genital sites, such as vulvar and vaginal, could be the target for HR HPV carcinogenesis with comparison of precancerous (high grade VIN or VaIN) or invasive cancer.

Oral HPV is strongly associated with oral squamous cell carcinoma (OSCC), suggesting that HPV-16 and -18 are risk factors for oral cancer[37,38]. A significant association with tobacco and alcohol has been confirmed. In addition, a family history of cancer is associated with OSCC[36-38].

Anal HPV infections in women are usually underestimated because women do not think or report they had unprotected anal sex and physicians usually do not ask about this sexual practice. The health risks of unprotected 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 almost universally lower for anal than for vaginal intercourse[39]. A 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[39].

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-positive men and women who practice receptive anal intercourse are at the highest risk of AIN[40]. The incidence of AIN has increased significantly in the last decades[41].

Also, the progression of the disease has an impact on sexual health. The sense of a health threat can be very different depending on the grade of the lesions: LSIL vs HSIL or cancer in situ, as they require a different aggressiveness of treatment and follow up.

One of the main biases in the studies surveyed is that they cluster together lesions of all degrees. Currently, there are neither effective means of preventing HPV transmission nor cures for clinical manifestations: infection can only be totally prevented via complete sexual abstinence. Good but not total protection is achieved when there is consistent condom use during every type of intimacy (oral, vaginal, anal) and the condom is applied prior to any contact. Prophylactic VLP L1 vaccines are now available. They protect women against clinical consequences of some types of HPV, like cervical cancer and high grade Cervical Intraepithelial Neoplasia (CIN) HPV 16-18 related for bivalent and quadrivalent formulations, with also indication for protecting from vulvar and vaginal precancerous lesion and genital warts HPV 6,11,16,18 related for the quadrivalent one. Treatment for clinical sequelae such as genital warts and precancerous cervical lesion consists of removing the problematic cells and watching for recurrence. This method consumes significant health care resources and is costly[42]. Some costs are difficult to estimate (personal distress, psychological comorbidities, and negative sexual outcomes).

Diagnosis

The diagnosis of HPV infection and the clinical consequences can be made following an abnormal smear test or HPV testing.

Cervical HPV-related lesions are typically asymptomatic but in the case of invasive diseases some symptoms like atypical vaginal blood losses, smelly vaginal discharge, urinary or anorectal symptoms and weight loss could arise as consequences of malignant proliferation and cancer.

For genital warts normally visual inspection is sufficient for diagnosis.

Therapy

Treatments of precancerous HPV related lesions include a wide range of interventions, according to the type and site of lesions, extension and severity. For genital warts both medical and surgical treatment are available.

Early and late recurrences of the infection and related pathologies are frequent. They may have a very 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.

Psychosexual impact of HPV infections

Despite HPV infection being amongst the most common STDs seen in clinical practice, attention has only begun to focus on the psychological or psychosexual impact of this diagnosis on the individual. The few studies that exist suggest adverse psychological and psychosexual sequelae may be common[43, 44].

Regarding the evaluation of the specific psychosexual impact for different forms of clinical HPV sequelae, whilst much research has been published on the mode of transmission of HPV-related oral lesions, epidemiology and other oral disease-related issues, to the author's knowledge no studies have been published on the psychosexual consequences of oral HPV infections. The same consideration could be made of HPV related anal lesion; in fact, no specific published literature exists on psychosexual consequences of anal HPV infections. So the available studies are focused on genital – i.e., vulvar/vaginal/cervical – lesions. However, oral and anal infections are increasing and should be investigated from the point of view of their potential psychosexual impact as well.

In the clinical setting, women with flourishing, massive, disfiguring genital warts may express specific "cosmetic" concerns, at the risk of persistent modification of the genitals and fears of being rejected by partners. However, no mention of this specific issue can be found in the clinical literature published thus far. Given the increasing focus women have of the cosmetic appearance of their genitals and its impact on their self-image and self-esteem the cosmetic impact of flourishing genital warts deserves to be specifically evaluated[45].

The evidence emerging from the literature and from our clinical experience suggests the existence of several peaks of vulnerability due to HPV infection. Different stages in the diagnosis and treatment of HPV infection may have a different impact on women and couples. The "timing" effect can overlap with a number of variables, causing psychosexual impairment or leading to overt sexual dysfunctions.

Psychosexual impact of the diagnosis

HPV testing may offer a number of advantages to conventional cervical screening, such as increased sensitivity to 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. 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 abnormality[46, 47].

Conaglen et Al, in their individual case control study on 101 consecutive clients attending an STD clinic, evaluated with 4 validated questionnaires, found that those diagnosed with first episode of HPV had considerable psychological difficulties (25% of the HPV positive group complained suffering for social dysfunction vs 7,9% of the HPV negative group; 17,9% reported severe depression vs 10,5%); 29% of men and 10% of women with a first episode of genital warts could be

classified as having sexual concerns at their first visit. However, the diagnosis of HPV was not associated with a greater psychological or psychosexual impact than that reported for other sexually transmitted infections[5].

Similar results were reported in a study by McCaffery et Al.[6] A postal questionnaire survey was sent to 428 women aged 20–64 to measure psychosocial and psychosexual consequences of HPV infection. Anxiety, distress and feelings about current, past and future sexual relationships were also investigated. Women with normal cytology who tested positive for HPV (HPV+) were significantly more anxious and distressed than HPV negative women 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+ 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 of anxiety. The HPV+ women felt significantly worse 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.

Even in this investigation, the findings suggest that testing positive for HPV may have an adverse psychosocial impact, with increased anxiety, distress and concern about sexual relationships[6].

To assess the psychosocial impact of HPV testing as an adjunct to cytology in routine primary cervical screening a controlled study was carried out. The trial provides a randomized setting of revealed HPV results versus concealed results permitting valid comparisons for assessing true psychosocial impact. The intervention was a revealed high-risk HPV test result in addition to cervical cytology. The main outcome was measured using the General Health Questionnaire (GHQ-28), Spielberger State-Trait Anxiety Inventory and Sexual Rating Scale (SRS). Among women with mildly abnormal or normal cytology, receiving an HPV (+ve) result did not impact significantly on GHQ caseness and mean scores or on Spielberger State and Trait scores when compared with women in whom the HPV (+ve) test result was concealed. Among women with normal cytology, receiving an HPV (+ve) result was associated with a reduction in the Sexual Rating Scale compared with similar women whose HPV (+ve) result was concealed. We can conclude that HPV testing does not add significant psychological distress when combined with cytology in routine primary cervical screening[9].

Maggino et Al.[7] evaluated the impact of the communication of an HPV diagnosis on the cognitive-behavioral aspect, emotional experiences, psychic-physical well-being and psychosexual sphere in young women between the ages of 20 and 45. Three self-evaluating questionnaires (the CBA-20, the SAT-P, and the BISF-W) were administered to 36 women who had been diagnosed with an HPV infection and 36 women who had never been diagnosed with HPV. 36% of the experimental group reacted to the diagnosis with fear, 29% reacted with anxiety, while only 3% of women did react with anger. Significant differences emerged in two samples regarding state of anxiety and obsessive and compulsive aspects, while there were no significant differences between the two groups regarding the subjective satisfaction with life quality and sexual function. A significant positive correlation was found between the sum of anxiety and fear expressed at the time of the diagnosis and the trait anxiety reported in the Cognitive Behavioral Assessment 2.0. The results indicate that the prevalent emotions felt at the time of the diagnosis are fear and anxiety. The persons who were diagnosed with an HPV infection resulted as having higher levels of trait anxiety, obsessions, compulsions, and behaviors and worries related to hygiene[7].

To evaluate the psychosocial impact of taking part in repeated testing for HPV, Waller used in-depth interviews that were carried out with 30 women who were HPV positive with normal cytology at trial baseline, and attended for a repeat HPV test 12 months later[8].

This excellent qualitative study indicates that feelings of shock, confusion and distress about testing HPV positive were common. These feelings are frequently related to the sexually transmitted nature of HPV and concerns. They were articulated about: a) where the virus had come from; b) anxiety about the health implications of HPV. Anxiety was triggered by lack of knowledge about HPV and followed by seeking further information about HPV from the Internet.

Once some of the confusion had been resolved, women seemed able to put the result to the back of their mind until the next test. Particularly reassuring was the knowledge that the virus could lie dormant for a long time, so exposure was not necessarily recent and its presence did not mean that a partner had been unfaithful [8].

Women were also reassured by the fact that HPV does not cause symptoms, is highly prevalent and can clear spontaneously without treatment. The pattern of initial anxiety is modulated by the attitude of the physician: reassuring vs neglecting to clarify the most critical questions and/or referring the woman to the net.

Not surprisingly, emotional responses following the *second* HPV test varied greatly by whether or not that test was positive. Negative feelings included fear and anxiety about cancer and becoming ill, concerns about fertility, feelings of being unclean because of the sexually transmitted nature of HPV, concerns about transmission and sexual relationships, a negative impact on feelings about sex, and relationship issues including blaming a partner for the infection. Overall, 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[8].

Psychosexual impact of the therapy

HPV genital lesions' treatment (physical-chemical therapy, diathermocoagulation and laser therapy or pharmacological therapy with imiquimod) is usually long and painful and can cause sexual impairments[43, 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[43, 48]. Unfortunately, whilst the etiology of the psychosexual impact has been discussed in different papers, controlled studies on the impact of different therapies are lacking. 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: CO2 laser ablation, intramuscular interferon-alpha, CO2 laser ablation plus intramuscolar interferon-alpha. Results indicated 57% of the patients experienced sexual impairments after therapy. The main reasons for sexuality change were: the disease itself, fear of infecting the partner, pain during the intercourse, forced use of condom. Sixteen percent of the patients reported a worsening of the relationship with the partner. No difference was found between the different treatment groups[48].

HPV infection, vulvodynia and dyspareunia

It seems that a link between genital warts and vulvodynia is not due to the clinical HPV related disease itself but as consequences of the treatment of the genital lesions. "Vulvodynia is a prevalent and highly distressing disorder, with major consequences for interpersonal and psychological well-being[49]. Vulvodynia impairs the psychological, physical, and reproductive health of approximately 10% of women at some point in their lives[49-51].

Two studies in fact, do not support the association between vulvar HPV infection and vulvodynia or vulvar vestibulitis: Smith found that a history of genital infections is associated with an increased risk of VVS: bacterial vaginosis (BV) (odds ratio, OR = 9.4), Candida albicans (OR = 5.7), pelvic inflammatory disease (PID) (OR = 11.2), trichomoniasis (OR = 20.6), and vulvar dysplasia (OR = l5.7) but no risk associated with HPV, Atypical Squamous Cells of Undetermined Significance (ASCUS), cervical dysplasia, genital warts, chlamydia, genital herpes or gonorrhea[52].

Gaunt et al. investigated the prevalence of HPV in patients with VVS by using a polymerase chain reaction (PCR) primer set that detects known HPV types. They retrospectively identified 38 patients with VVS who underwent therapeutic surgical excision of the vestibule. Eleven controls without vestibulitis who underwent vestibular excision for conditions unrelated to HPV infection were identified prospectively. Surgical specimens were examined for the presence of HPV DNA by PCR amplification. DNA sequencing was used to determine HPV type. They found that the prevalence of HPV among patients with VVS was 21% vs. 36% among controls. Group B HPV types accounted for 4 of the 10 (40%) HPV types found in patients with VVS. Overall, in both patient and control samples, a spectrum of HPV types were identified,

encompassing many branches of the HPV phylogenetic tree. No etiologic association was apparent. The low rate of observed infection in women with and without VVS and the diversity of HPV types identified suggest incidental virus carriage rather than direct cause and effect. The underlying cause of this debilitating condition remains unknown[53].

Morin[15] found that there was an association between *treatment* for vulvar HPV infection and vulvodynia. This can occur when either pharmacologic (Imiquimod) or physical treatment (either laser or DTC) cause persistent introital/vulvar pain as a persistent side effect of treatment. This negative outcome is common when physical treatment is:

a) extensive, due to the magnitude/extension of the vulvar genital warts;
b) repeated due to warts' recurrence or re-infection;
c) overzealous (with deep lesions and neuropathic pain);
d) associated with a defensive contraction of the elevator ani, because of the iatrogenic pain. This, in turn, can contribute to introital dyspareunia, reflex inhibition of lubrication, vaginal dryness and micro-abrasion of the introital mucosa (during intercourse subsequent to treatment) and chronic introital inflammation leading to vulvar vestibulitis and vulvodynia.

The silent carrier or the high risk man: the he-partner

A specific issue to be dealt with when counseling women which HPV infections relates to "who infected whom" [8]. This question becomes more painful when oncogenic HPV strains are etiologically related to precancerous lesions that can progress to cervical or vulvar cancer[7, 8]. Studies assessing the carrier or infected status of partners of HPV infected women indicate that subclinical lesions are far more common than diagnosed by simple visual genital examination[54,55].

Penile lesions were seen in 68% of the male sexual partners of women with intraepithelial cervical neoplasia, when examined by visual inspection or, when available with the colposcopic instrument. More than one lesion type was diagnosed in 15% of cases. Flat lesions, papular lesions, and condylomata acuminata were seen in 83%, 29%, and 4%, of cases respectively. HPV was detected in 59% of the penile scrapings, containing mainly oncogenic HPV types. When penile lesions were present, 67% of penile scrapings were positive for HPV, whereas 37% were HPV-positive when no lesions were visible. Penile lesions are frequently found in sexual partners of women with cervical intraepithelial neoplasia, *when appropriately examined*. Most of these lesions are *subclinical* (i.e., only visible after acetowhite staining and/or with HPV DNA test of the partner). They are often associated with the presence of high-risk HPV, indicating that male sexual partners of women with cervical intraepithelial neoplasia might constitute a reservoir for high-risk HPV[54, 55].

Discussion

Women have a gender-specific vulnerability to the health and sexual consequences of HPV infections. They have almost twice the percentage of genital warts in comparison to men[20]. Women have a higher vulnerability to oncogenic HPV, mostly at cervical and vulvar site. (The age-standardized incidence of vulvar cancer averages between 1 and 2 per 100,000 women in Western countries. Epidemiological studies have identified sexual factors, particularly HPV infection, as increasing risk) [56].

The health and sexual risks linked to HPV infections are currently underestimated by women themselves.

Research on the specific impact of genital warts and intraepithelial neoplasias on sexual function and relationship in women is limited. Research focuses more on general psychological outcomes, such as depression, anxiety, guilt, anger, rage, or sexuality as a general issue rather than focusing on specific dimensions of women's sexuality[5-14]. To the author's knowledge, no studies using validated sexual questionnaires, such as the Female Sexual Function Index or Profile of Female Sexual Function, have been published. The only disorder investigated to explore if it could be related to HPV infection is dyspareunia via the link with vulvodynia/vulvar vestibulitis. However, the relationship between HPV and

vulvar vestibulitis-related dyspareunia appears to be eventually a sequelae of the HPV related diseases treatment rather than the HPV infection itself[15, 52, 53].

In previous studies, couple-related psychosexual issues have only been explored as part of a broader analysis, with no follow-up studies specifically examining couple outcomes after treatment for genital warts or intraepithelial neoplasia.

More data have been produced on the impact of HPV diagnosis on the emotional and psychosexual well-being.

Communicating the diagnosis, through correct and exhaustive information on HPV infection and its psychosexual meaning should be consistently offered by the clinician to HPV positive women and their partners (if the couple is willing to be consulted together). Many women are surprised and upset upon learning about HPV[5-7, 10]. Many search for information on the Internet and report being even more scared. Partners may present with a wide range of negative affects, that should be addressed in parallel[12]. Ensuring that women are aware that HPV is a common condition and limiting potential negative consequences by appropriate follow-up and medical interventions (when needed) may reduce the negative feelings and anxiety experienced by women with HPV[13].

Clinical experience indicates 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. However, controlled studies are needed to support this claim. Vulnerability increases in women experiencing dysfunctional sexuality prior to diagnosis; in single women; in women with troubled relationships; or when the infection strongly suggests the partner has had unprotected sex outside of the relationship[8]. 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 their partner.

Overall, preliminary data indicate that sexual morbidity is more correlated to frequency of recurrences than to different treatments per se[48]. Prevention and early diagnosis of recurrences may reduce the long-term sexual consequences of HPV infection in women. Active counseling on potential female sexual dysfunctions worsened or precipitated by HPV infection should be part of the routine medical approach.

Physicians should also actively investigate previous unprotected anal sex in women with genital HPV infection, to avoid the collusion of silence and the risk of undiagnosed highly aggressive AIN[39-41]. After the diagnosis of perianal or anal HPV-related diseases, 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 even transgressive.

Health care providers should actively inform women against the risk of unprotected anal sex.

Women are frequently very disturbed to discover that a partner they loved may have infected them. “What is the role of men who are sexual partners of women with genital HPV infection and/or cancer?” This is a sensitive question increasingly raised in clinical consultation by both affected women and their partners[8]. HPV testing of the partner, or penis examination, should be considered part of the diagnostic assessment of partners of HPV infected women[54,55]. The sexual impact of being an inducer or a carrier or HPV infections should be investigated. Psychosexual and informative counseling to *both* partners is critical to prevent further negative psychosexual outcomes during diagnosis and treatment of HPV related lesions. Husbands and couples express their relief and gratitude when these issues and potential difficulties and/or misunderstandings are openly and spontaneously raised by the physician during the consultation and when practical suggestions are given to overcome physical and emotional problems. Guilty feelings may be pervasive, rooted in the past personal sex life. On the other hand, aggressive feelings against the partner considered responsible for the infection (of having "caught" it) and the subsequent precancerous or cancerous lesions may dominate the clinical picture in a minority of cases[7, 57, 58]. Individual and couple counseling is critical to addressing these feelings that may affect the motivational-affective roots of desire and couple commitment.

Overall, the published data indicate that many more questions remain unaddressed than answered in this emerging field of STDs. More research is needed on all the aspects that remain neglected in the evaluation of psychosexual outcomes

of genital warts and intraepithelial neoplasias. The evidence is more consistent regarding the outcomes of treatments after cervical, genital and anal cancers. This will be reviewed in a separate paper.

Conclusions

Women are at an increasing risk of HPV infections and related lesions, with a specific and underestimated vulnerability to the risk of anal infections. Psychosexual vulnerability increases with the number of recurrences of HPV infections. Fear, anxiety, anger and depression are the emotions most frequently reported[5-14]. However, to date there is no conclusive evidence of a correlation between HPV infection and a specific female sexual disorder. The relationship between HPV and vulvodynia/vulvar vestibulitis related dyspareunia seems indirect[15,52,53]. Vaccine anti-HPV may reduce the incidence of HPV infection and the related psychosexual consequences[59]. However, no data have been produced so far on this issue. The potential of a "high-risk partner" should be considered and diagnosed while counseling HPV infected women. Specific research on the sexual impact of genital warts and intraepithelial HPV related lesion in women is urgently needed.

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Box 1. The new HPV vaccines: a hope for the future

New prophylactic HPV vaccines promise to dramatically reduce the incidence of clinical consequences of HPV infection, mainly precancerous cervical lesion cervical cancer, and also other precancerous genital lesions, genital warts, and cytological abnormalities. The quadrivalent vaccine currently approved by FDA and EMEA utilizes 4 different "virus like particles", thus enabling the immune system to protect against HPV viruses corresponding to genotypes 6,11, 16 and 18. This will have a prophylactic impact on about 90% of condylomata and more than 70% of invasive cervical cancers (the remaining being caused by others genotypes).[25]

Among children 9-15 years old and young women aged 15–26 years not previously infected with vaccine-type HPV strains, prophylactic HPV vaccination appears to be highly efficacious. 26

Vaccination is not a substitute for routine cervical screening. Since no vaccine is 100% effective and not provide protection against non-vaccine HPV types, or against existing HPV infections, routine cervical screening remains critically important and should follow local recommendations.

the HPV vaccines do not protect against other sexually transmitted diseases, therefore appropriate precautions against sexually transmitted diseases should continue to be used.

Tab 1. HPV infection risk factors and gender vulnerability in women

Youth	Moscicki Ab, 2007[60]. Saleh MM, Seoud AA, Zaklama MS, 2007[61]. Winer RI, Feng Q, Hughes JP et Al, 2008[62].
Gender (female)	Steben M, Duarte-Franco E, 2007[63]. Hariri S, Dunne EF, Sternberg M, et Al, 1991[44]. Dinh TH, Sternberg M, Dunne EF, 2008[20].
High number of sexual partners	Moscicki Ab, 2007[60]. Saleh MM, Seoud AA, Zaklama MS, 2007[61]. Winer RI, Feng Q, Hughes JP et Al, 2008[62].
Non consistently protected sex	Epstein RJ, 2005[65].
Co-infection with Chlamydia trachomatis	Anttila T, Saikku P, Koskela P, et al. 2001[66]. Bosch FX, de Sanjosè S., 2007[67]. Ault KA, 2006[32].
Coinfection with Herpes Simplex virus	Smith JS, Herrero R, Bosetti C, et al, 2002[68]. Bosch FX, de Sanjosè S., 2007[67].
Smoking	Castellsaguè X, Munoz N. 2003[69]. Bosch FX, de Sanjosè S., 2007[67].
Immunosuppression (HIV, immunosuppressive therapy)	Strickler HD, Burk RD, Fazzari M, et al. 2005[70]. Cameron JE, 2007[71].
Pregnancy	Strickler HD, Burk RD, Fazzari M, et al. 2005[70].