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Human Papillomavirus Infection in Brazil. Review

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Abstract

Human papillomavirus (HPV) infection is the most common infection transmitted through sexual contact in humans. It is estimated that 291 million women are HPV DNA positive around the world. Some HPV types have a strong association with cervical cancer and its pre-malignant precursors. Prevention and treatment of cervical cancer has improved significantly due to better knowledge about the etiological role of the HPV virus in the pathogenesis of the disease. Despite these advances, morbidity and mortality rates due to cervical cancer remain high in developing countries. Knowledge of HPV disease, HPV vaccines, and HPV-related cancers is consistently low among adolescents and adults worldwide. Strategies to educate potentially vulnerable individuals about HPV and to improve access to HPV vaccination for populations with low vaccination uptake are still needed. In this review, we discuss the epidemiology, ethiopathogeny, risk factors, diagnosis and prevention of cervical cancer in women.

Keywords: *Papillomaviridae; Reproductive Tract Infections; Uterine Cervical Neoplasms*

Introduction

Human papillomavirus (HPV) infection is the most common infection transmitted through sexual contact in humans. Some HPV types have a strong association with cervical cancer and its pre-malignant precursors. HPV-DNA is detected in more than 95% of cervical cancer, its main oncogenic types - HPV types 16 and 18 - are responsible for more than 70% of all cervical cancer and, along with HPV type 45, cause 94% of cervical adenocarcinomas. The morphological diagnosis of endocervical adenocarcinoma is highly difficult, given the multiplicity of histological variants and their different biological behaviour [1-3].

Early sexual activity and multiple sexual partners are factors associated with cervical carcinogenesis [4,5].

Furthermore, several studies have shown that HPV infection is significantly more common among HIV-positive women compared to HIV-negative women [6-8].

Prevention and treatment of cervical cancer has improved significantly due to better knowledge about the etiological role of the HPV virus in the pathogenesis of the disease. Despite these advances, morbidity and mortality rates due to cervical cancer remain high in developing countries. The slow evolution of the disease and the absence of clinical manifestation in early stages may worsen the situation [1,9,10].

The rates of prevention and cure of cervical cancer are high, close to 100% when early diagnosed. In 2012, an estimated 527,000 new cases of cervical cancer were reported around the world. More often the disease starts around age 30 years, and the morbidity and mortality risk increases until after age 50 years [11].

Thus, screening for cervical cancer is important to reduce morbidity and mortality outcomes and to detect precursor precursor cervical cancer lesions [12].

Epidemiology

HPV is the most common sexually transmitted infection worldwide. It is estimated that 291 million women are HPV DNA positive, which means a prevalence of more than 10%, and about 105 million women have an infection caused by type 16 or 18 at least once in a lifetime [11,13]. The acknowledgment of the HPV as the main etiologic factor for cervical neoplasia began in the 1970s, however the association between verrucous cutaneous or mucosal lesions and an infectious agent began in the 1920s [14]. Between 5 and 15% of women without HPV are infected with high-risk HPV types each year, and about 25% of the incidence occurs only in the 15 - 19 age group [15].

HPV infection is a public health problem in Brazil and in many countries. In the United States, cervical cancer accounts for more than 50% of all HPV-associated cancers among women and more than 30% of all HPV-associated cancers [16,17]. In 2012, about 265,000 deaths occurred from cervical cancer worldwide, and around 87% of these events occurred in developing countries. In 2013, 5,430 deaths from cervical cancer occurred in Brazil. In 2016, data from the Brazilian National Cancer Institute (INCA) estimated 16.340 new cases of cervical cancer [11].

Each year about 490,000 women are diagnosed with HPV. In Brazil, cervical cancer is the third most common cancer among the female population just after non-melanoma skin cancer and breast cancer, and it ranks as the second leading cause of cancer death among women. Cervical cancer is the second most frequent cancer in the North, Central-West and Northeast regions of Brazil (23.97 cases per 100,000 women; 20.72/100000; and 19.49/100000, respectively). In the Southeast region, it is the third most common type of cancer (11,13/100,000), and the fourth most common type in the South Region (15,17/100,000) [1,9-11].

In South America and Central America, the most common types of HPV are 16,18,45,31 and 33. In Brazil, the prevalent type of HPV is the type 16 followed for the types 31 and 33 in Northeast and Midwest regions [18,19].

In Brazil, approximately 28% of the tests with abnormal cytological findings were performed in adolescent women less than one year after the first intercourse. Although HPV is acquired through sexual intercourse, in most cases HPV undergoes a sort of clearance within two years [20,21].

The prevalence of low-grade squamous intraepithelial lesions (LGSIL) was 0.8% among all documented cytopathological tests in Brazil in 2009. Considering only the tests with abnormal results, the prevalence of LGSIL was 31%, the second most frequent cytopathological diagnosis, requiring additional investigation or follow-up, preceded only by the ASC-US category [6].

In a survey of indigenous women in Brazil between 2005 and 2011, 2,903 cytological tests were performed in sexually active women, covering 93.4% of the female population. 9.1% of the tests showed cytological changes with atypia of indeterminate or greater significance (ASC-US) [22].

With the introduction of vaccination programs, HPV-acquired infections and their cancer-related outcomes can now be safely and effectively prevented [23]. In addition, it is important to state that when they reach the recommended age, even women who are vaccinated must undergo the preventive examination, since the vaccine does not prevent all oncogenic types of HPV. In Brazil, the Ministry of Health recommends the screening of cervical cancer through cytopathological examination in women between 25 and 64 years old [24].

HPV tropism for epithelial cells leads not only to cervical infection, but also causes infection in other areas of the body (i.e.: benign skin and mucosal lesions, cutaneous mucinous tumors, such as non-melanoma skin cancers, oropharyngeal cancer and genital carcinomas [25]. In almost all cases of cervical cancer, HPV is also present in other sites: it is associated with 85% of anal cancer cases, 40% of vulvar cancer cases, 70% of vaginal cancers and 50% of cases of penis cancer cases, 35% of oropharynx cancers, 10% of larynx and 23% of mouth cancers [26].

Ethiopathogeny

The HPV virus is a small DNA virus, measuring approximately 55 nm in diameter. The viral genomic DNA consist of a single double-stranded DNA molecule of about 8,000 nucleotides and is divided mainly in 3 major regions: An Early region, involved in viral replication; a Late region which encodes viral capsid proteins that form the structure of the virus; and a Long Control Region (LCR or noncoding region [NCR]).

The HPV capsid is non-enveloped, having icosahedral symmetry formed through the interaction among 72 pentamers of the major capsid protein, L1 [27,28].

Human Papillomaviruses infect keratinocytes in the basal layer of stratified squamous epithelia, then replicate and assemble exclusively in the nucleus. HPV genomes are often integrated into the host chromosomes in cervical cancers and become disrupted and its replication defective through the years [1,29,30].

High-risk mucosal HPVs encode three transformation proteins, E5, E6 and E7, the main regulators being the E6 and E7 oncoproteins. Viral oncoproteins E6 and E7 induce tumor initiation and also play an important role in the malignant progression of the lesion through the induction of genomic instability and other mechanisms. In the process of malignant progression, E6 and E7 oncoproteins promote the acquisition of unlimited proliferative potential, independent growth factor, evasion of apoptosis and sensitivity to cytostatic signals, induction of invasive and metastatic properties and sustained angiogenesis [31].

Mucosal HPV infections are associated with benign genital warts, carcinomas of the cervix and anogenital region, and also cervical cancer, oropharyngeal cancer, anal cancer, vulvar cancer, vaginal cancer, penile cancer and recurrent respiratory papillomatosis. This plethora of morbidities is likely to contribute to both increasing health related burden and worsening health outcomes [30,32].

High-risk HPV infections can cause intraepithelial lesions that are risk factors for malignant progression, but most of these infections do not result in clinically apparent lesions, and those that develop spontaneously tend to regress with high frequency. The integration of HPV genome sequences into a host cell chromosome is common during malignant progression [32].

According to epidemiologic classification of HPV types, HPV viruses can be classified as low and high-risk. Low-risk types are generally found in vulva genital condylomas and high-risk types are associated with cervical cancer. Fifteen high-risk types were classified, among them the types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, and 58. Three types (26, 53, and 66) should be considered probable high-risk types. The low-risk types are: 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81. While types 34, 57, and 83 have not been detected to date in any sample and were therefore considered to be associated with undetermined risk. The incidence of high-risk HPV infections is higher than low-risk infections. Many infections are asymptomatic and transient, but persistent infection with oncogenic types of HPV is a serious health problem, as it favours the development of precancerous lesions and, subsequently, neoplasia [1,33].

HPV genomes are found in the nuclei of infected cervix carcinoma cells, where infectious viral particles can be isolated. In some low-grade lesions and in most high-grade lesions and cervical cancer, HPV genomes are found integrated into the chromosomes, and this integration is the central point of oncogenic cell transformation [28].

Integration of HPV DNA deregulates the expression of E6 and E7, which interact with p53 tumor suppressor genes and RB proteins, respectively. This process impairs the function of the onco-suppressor gene, involving DNA repair, decreased apoptosis, and eventual cell death. Chromosomal mutations cause functional modifications such as loss of heterozygosity and pro-oncogene, and activation of mechanisms that allow the induction of cervical carcinogenesis [25,34].

Individuals with HPV infection may develop lesions (intraepithelial neoplasia) that lead to cancer of the uterus, vulva, vagina, penis, and anus. On the other hand, most people infected with HPV may never have the infection diagnosed if they do not develop clinical lesions or do not perform laboratory tests [26]. The role of sexual partners of HPV-infected women in disease progression is still unknown. However, any infected partner may be responsible for the re-infection of the woman, and it is important that sexual partners be evaluated, as they benefit from the test and may eventually transmit the infection to new partners [35,36]. According to the guidelines on Sexually Transmitted Diseases (STDs), each sex partner of an infected woman should be examined in order to identify, treat and prevent further disease [37,36].

Risk Factors

The number of sexual partners is the main risk factor for HPV infection. Therefore, it is necessary to clarify the population about the forms of transmission, diagnosis, treatment and forms of prevention of infections caused by HPV. In addition, in most populations, peak prevalence of HPV infection occurs a few years after the average age of sexual initiation [12,17,38,39].

Socio-demographic, behavioural, sexual, contraceptive, reproductive and clinical aspects make women more susceptible to factors directly involved in cervical carcinogenesis, such as local inflammation and HPV infection. Epidemiological studies have shown that in cytologically normal women, HPV infection precedes the development of precancerous lesions of the cervix. Currently, important aspects are considered for the reduction of high rates of death due to cervical cancer in Brazil, such as sociocultural, political and economic aspects, with emphasis on schooling, access to cervical cancer prevention and management services, life habits, as well as the different age groups and their geographic region [10,29].

Currently, women's health in Brazil is an issue that involves the social, educational and public health dimensions, as well as the biological vulnerability due to the anatomical difference (Transformation Zone).

The high prevalence of HPV infection among adolescents and young women can be explained by the fact that this is the age group in which many women initiate their sexual life, with more frequent sexual activity, partner turnover and search for new partners, irregular use of contraceptive methods, in addition to the psychosocial characteristics of this age group, which normally does not seek health services for preventive purposes with the same regularity as older women [40].

Women's greater knowledge of the acquisition forms, risk factors and frequency of HPV infection may contribute to a better perception of the risk of developing cervical precancerous lesions and in consequence this may influence their permanent adherence to the activities of colpocitology and promote important behavioural and lifestyles changes in order to reduce risk of HPV infection [10].

The understanding of viral pathogenesis by the population is important to stimulate primary and secondary prevention. Sexual transmission, including anal and oral transmission, is considered the primary form of transmission of HPV and is directly related to the number of sexual partners, however, there are other forms of HPV transmission that should be noted, such as fomites and vertical contamination during childbirth [17].

Diagnosis

The primary goal of cervical cancer screening is to prevent the morbidity and mortality. The ideal screening strategy should efficiently and accurately identify those precursor (preneoplastic) cervical lesions that may evolve into invasive cancers and avoid the unnecessary detection and treatment of transient HPV infection and its associated benign lesions [12].

The National Cancer Control Program was created by the Brazilian Ministry of Health in the 1970's, originally aimed at screening women for cervical cancer. In the 1980s, the Program for Integral Attention to Women's Health (PAISM) was implemented, which stimulated routine Papanicolaou tests (Papanicolaou) in gynaecological consultations. The Oncology Program (PRO-ONCO) was then created and later absorbed by the National Cancer Institute (INCA) with the creation of the Brazilian Unified Health System (SUS) in 1988. In the same year, the Cervical Cancer Information System (SISCOLO) started monitoring the actions developed for the control of cervical cancer. In 2005, the National Policy on Cancer Care (PNAO) focused on control and prevent cervical and breast cancer. According to the Brazilian Guidelines for the screening of cervical cancer, cytopathologic examination is the standard method of screening for cervical cancer and its precursor lesions. The interval between examinations should be three years after two negative exams with annual interval, and the first test should occur at age 25 for women who have initiated sexual activity. The examinations should continue until the age of 64 and should be discontinued when, after that age, women have had at least two consecutive negative tests in the last five years. For women, over 64 years and who have never performed the cytopathological examination, two exams should be performed with interval of one to three years; If both exams are negative, these women may be exempted from further examination. These recommendations do not apply to women with prior history of cervical cancer precursor lesions [41].

Liquid-based cytology (LBC) has been used as an alternative to conventional Pap cytology testing since the late 1990s. The test begins with the clinician-collected gynaecologic sample, then the sample is added to a vial with collection medium (Sure Path Preservative fluid) rather than being spread on a microscope slide as in the conventional Pap testing protocol. Additionally, samples may be submitted to molecular and cytological analyses. As a result of these improvements in sample quality, the clinical sensitivity and specificity of LBC in the detection of high-grade lesions is significantly higher compared to conventional Pap test. LBC and the conventional Pap test have been considered the cervical cytology approaches of choice in cervical cancer screening programs in many countries, including Brazil [42-44].

Colposcopy is the method of choice to detect Cervical Intraepithelial Neoplasia (CIN), the abnormal cells on the surface of the cervix. The colposcopy results can be classified as: normal, low-grade, high-grade, keratosis, erosion, inflammation, polyps, condyloma, non-visualized transformation zone [45].

According to the Brazilian guidelines for cervical cancer screening, if the result of two repeated cytologies is equal to or suggestive of intraepithelial lesion or cancer, the woman should be referred to the reference unit to colposcopy [11].

Basic skills are needed to colposcopically assess cervical intraepithelial neoplasia, and the lack of professional qualification compromises the reliability of the results of the colposcopy exams. Therefore, it is strongly recommended that colposcopy be performed by physicians who have specific authorization in the application of this technique. The association of colposcopy, oncotic cytology and histology is the so-called "diagnostic tripod" that allows diagnosis of neoplastic and pre-neoplastic lesions in more than 90% of cases. This is important since colposcopy or cytology alone have high sensitivity, but low specificity [46].

A cervical biopsy should be done after evaluation of colposcopy results (direct biopsy). When colposcopy cannot be performed or properly evaluated, the biopsy can be done in areas without cervical lesions or less affected areas. However, biopsy is recommended for all women with high-grade cytologic abnormalities, even with inconclusive colposcopy [45].

Molecular biological methods have an advantage of being capable of detecting virus DNA which is a cause of cervical cancer, thereby performing accurate diagnosis [47]. In order to prevent and detect early cervical cancer, it is important not only to detect intraepithelial cervical changes, but also to identify the presence of high-risk HPV and its type. HPV virus can be detected in the cervix through molecular biological methods such as PCR (Polymerase Chain Reaction), hybrid capture, in situ hybridization and immunohistochemistry.

PCR is the most common method of DNA amplification in molecular biology, and it consists of amplifying specific segments of the HPV viral DNA, followed by hybridization. Hybrid Capture detects specific HPV DNA sequences through the analysis of excised uterine cervix cells, identifying abnormal cells present in pre-cancerous and cancerous lesions, based on the modification of the architectural structure [1,45,48].

The HPV test uses the same type of cervical sample that is used in the cervical swab test. However, cervical cells are not smeared on a glass slide, as is done in cytology, instead they are transferred to a vial of liquid preservative. This test has higher sensitivity for detection of CIN III than cytology, despite its low specificity.

Therefore, this test should not be used alone for cervical screening. HPV testing is typically done through automated molecular amplification or hybridization techniques. It identifies the presence of 13 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68). The clinical cut point to positive tests is 1.0 pg/ml of HPV DNA [12,49].

In a study to test different approaches to detect pre-invasive cervical lesions and cervical cancer in Brazil, 1,040 women were tested for Hybrid Capture II, and 184 (17,5%) were tested positive for both methods (self-sampling or doctor's collection), although with a frequency for positive samples higher through self-collection (21% vs 16%). It was also observed that 137 of these women had normal Pap smears with positive hybrid capture [50].

In Brazil, there are still no nationwide organized screening programs for cervical cancer as well as no reliable data on the women who undergo HPV testing. Therefore, there are currently no means to ensure that the interval between controls will be effectively extended from the adoption of the HPV test, which is a necessary condition to obtain some favourable cost-effectiveness results. This is a major obstacle to the use of HPV testing at the present time. Although the diagnostic performance of molecular tests in specific age groups and cytopathological tests in positive cases has been promising, implementing these measures in Brazil at the current level of organization of cervical cancer screening will not transform these potential benefits into real benefits [41].

Prevention

In women without routine screening, the risk for cervical cancer is evidently higher than in women who undergo routine screening tests. Once the routine Papanicolaou tests favour early diagnosis. As a standard protocol adopted in Canada, routine serial Papanicolaou screening resulted in reducing cervical cancer mortality by 50% in the past 30 years. In Brazil, the national cervical cancer prevention strategy stimulates women between 25 and 64 years old who have or have had sexual intercourse to undergo a cytopathological examination every three years, after two initial examinations with negative results with a minimum interval of one year between them. In addition, the use of condoms in sexual intercourse hold be encouraged [24,51,52].

Consistent condom use during sexual intercourse can provide some protection against infection, and it is associated with STD preventive behaviour. Its consistent use decreases the risk of acquiring condylomata acuminate and high-grade lesions in the cervix. However, even with the use of this preventive method, if HPV infection is present in the vulva, in the pubic, perineal or perianal region, or in the scrotum, HPV can be transmitted. The female condom also covers the vulva, and this reduces transmission more effectively since it is correctly placed on at the beginning of sexual activity [26].

Male circumcision has a protective effect against HPV infection and cervical cancer in female partners, and should be considered in countries where HPV vaccination programs and screening for cervical cancer are not available. The mechanism by which circumcision may have a protective effect against HPV infection is uncertain. In uncircumcised men, the foreskin is pulled back during sexual intercourse, and the surface of the inner mucosa of the foreskin is exposed to vaginal and cervical secretions. Thus, removal of the foreskin may minimize the possibility of viral entry, either due to the reduced surface area of the mucosal surface vulnerable to HPV or because of the small possibility of mucosal trauma during sexual intercourse [39,53].

Ideally, circumcision should be a process conducted before potential exposure to HPV through sexual contact. However, this recommendation should be consistent with other factors, such as culture and the specific needs of different populations [39].

Primary prevention of cancer is considered the "most desirable option from a societal perspective". Prophylactic HPV vaccination dramatically improved primary prevention of cervical and other HPV-associated cancers, at a time when prevention was performed mostly at the secondary level [17,54].

Cervical Cancer and Preventive Vaccination

Knowledge of HPV disease, HPV vaccines, and HPV-related cancers is consistently low among adolescents and adults worldwide. Thus, strategies to educate potentially vulnerable individuals about HPV and to improve access to HPV vaccination for populations with low vaccination uptake are still needed [55,56].

Current recommendations for HPV vaccination in adolescents include preventing persistent infections and the occurrence of anogenital warts, which begin in young adulthood, and to prevent cervical, vaginal, vulvar and anal cancer occurring later in life [17,16]. It is important to reinforce the need for vaccination among preadolescents and adolescents, since the vaccine does not benefit women who are already infected or injured [51,57,58].

Many developed countries have already decided to introduce the HPV vaccine into their regular immunization programs. However, only few developing countries, in which cervical cancer constitutes a significant public health problem, have already made this decision [59,60].

A key determinant of HPV vaccine coverage is its acceptability in the population. Barriers to acceptance of the vaccine include the cost of the vaccine, patient's age, and knowledge-related barriers like uncertainty over the side effects and the duration of the effectiveness of the vaccine, low awareness of infection risk, the fear of experiencing pain during injections, among others. In addition, the overall effectivity of the vaccine in is not well established, as the vaccination does not replace the screening programs [54,61].

Studies evaluating the effectivity of HPV vaccination on cervical cancer incidence and mortality are few, and follow-up studies on large populations are needed to assess the real impact of vaccination on the prevention of invasive cancer [57].

The HPV vaccine safety profile is comparable to other licensed prophylactic vaccines. The vaccine consists of human papilloma virus-like particles (VLP) particles - viral capsids - lacking DNA and infecting viral structures. The vaccines are prepared from VLPs produced by recombinant technology: the major structural protein of the capsid L1 self-assembles to form empty shells that resemble HPV VLPs, inducing immune response [29,30,33,54,62-64].

There are two types of licensed vaccines available for use: bivalent and quadrivalent vaccine. The bivalent vaccine protects against viral types 16 and 18, while the quadrivalent protects against types 6, 11, 16 and 18. The bivalent vaccine prevents pre-cancerous cervical lesions related to HPVs 16 and 18. The quadrivalent vaccine prevents pre-cancerous lesions - related to HPVs 16 and 18 - in the cervix, vulva and vagina in women, and anal precancerous lesions in both sexes; as well as anogenital warts related to HPVs 6 and 11, in both women and men. Thus, the quadrivalent vaccine provides additional protection for anogenital condylomas that are associated with HPV 6 and HPV 11 infection [57,58]. The vaccines have different indications according to sex and age group. Unlike the quadrivalent vaccine, indicated for women and men between 9 and 26 years of age, the bivalent vaccine is indicated for women from 9 years of age, without restriction of age [58]. Recently, a third vaccine was approved by the Food and Drug Administration (FDA): the nonvalent vaccine, which adds prevention against HPV types 31, 33, 45, 52, and 58 to the quadrivalent vaccine [23].

Although vaccination against HPV 16 and 18 is highly effective in preventing CIN II and CIN III among women who have not previously been exposed to these types of HPV, routine cervical cancer screening should not be ignored after vaccination. In vaccinated populations, women protected by vaccination could have less intensive screening and also start it at a later age, as they are likely to have a lower risk of cervical cancer in the future. However, once the first generation of vaccines only covers HPV 16 and HPV 18, about 30% of cervical continue to occur. As the Advisory Committee on Immunization Practices recommends that vaccination programmes include women up to 26 years-old many women may be vaccinated after HPV infection has already been acquired, when efficacy is redecide [12].

The HPV vaccine prevents the first infection, persistent infection and cervical cancer only for individuals who have not previously been exposed to the virus, preferably before starting sexual life, from 9 to 26 years-old, since the infection usually occurs soon after the onset of sexual life. HPV vaccination is also recommended for women aged 13 to 26 years and men aged 13 to 21 years who have not been previously vaccinated, as well as men aged 22 to 26 years who may also be vaccinated. HPV vaccination programmes tend to follow the manufacturers' recommendations instead of the optimum age from a public health perspective in this age group, the highest antibody levels were found after vaccination and girls who were not infected by any of the four serotypes present in the vaccine will have greater benefits. In women between 9 and 15 years-old, the vaccine is highly immunogenic [16,54,60,62].

HPV vaccines have an efficacy greater than 95% in preventing cervical dysplasia and genital warts that are caused by the types of HPV contained in the vaccines. With the quadrivalent vaccine a reduction in the cumulative incidence of anogenital warts is expected [65].

The distribution of the quadrivalent vaccine by immunization programs is a recent strategy, adopted in some countries after approval by the FDA, in June 2006. In Brazil, The Brazilian Health Regulatory Agency (ANVISA) has approved its commercialization. Currently, the quadrivalent vaccine is part of the National Vaccination Calendar in Brazil, and it is applied in two doses in women between 9 and 14 years-old, with a six-month interval between doses. Adolescents aged 14 can start the vaccination schedule since they complete the treatment until age 15, with a minimum interval of six months between doses. There is a three-dose regimen (at the baseline, after two and six months) for women between 9 and 26 years diagnosed with HIV/AIDS. From 2017 on, the male population will be included in the vaccination strategies of the National Immunization Program (PNI) to prevent penile cancers, genital warts and contamination of partners. There is also a three-dose scheme (at the baseline, after two and six months) for boys and men with HIV/AIDS, between 9 and 26 years-old. In the first year of introduction of the quadrivalent vaccine for boys, it will be available for the age group of 12 to 13 years in two doses, with a six-month interval between doses. By 2020, boys aged 9 years or older will be included [66].

In addition, health policies related to cervical cancer should focus on the detection of precursor lesions and their treatment and clinical follow-up. HPV vaccines prevent infection but do not change the natural history of the disease in individuals already infected. HPV vaccine is contraindicated for pregnant women due to possible teratogenicity, also during febrile conditions, for individuals with known hypersensitivity, previous severe allergic reactions to the vaccine or with haemorrhagic disorders. It can be administered to immunosuppressed women, as they are at higher risk of acquiring HPV infection, but there is no evidence of efficacy in this group [1,30,54,62,65]. There is also the possibility of non-acceptance of the vaccine due to lack of knowledge of the adolescents' parents, since most parents do not have sufficient knowledge about the vaccine and affirm that it could stimulate promiscuity, with few parents considering considering the vaccine an innovative, promising technology capable of protecting against a sexually transmitted infection [16,61].

Without specific vaccination, HPV contamination can only be completely avoided through complete sexual abstinence. The HPV vaccine does not prevent infections caused by other STDs and its introduction does not eliminate the need for screening for cervical cancer. The Pap smear remains essential in detecting cancer and precancerous changes caused by other types of HPV, as well as any cancer in women who have not been vaccinated or who have already become infected with HPV [33,62].

Conclusion

HPV infection is a public health problem in Brazil. [16]

In Brazil, the prevalent type of HPV is the type 16 followed for the types 31 and 33 in Northeast and Midwest regions [18,19].

Currently, important aspects are considered for the reduction of high rates of death due to cervical cancer in Brazil, such as sociocultural, political and economic aspects, with emphasis on schooling, access to cervical cancer prevention and management services, life habits, as well as the different age groups and their geographic region [10].

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