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PATHWAYS FOR PREVENTION, DIAGNOSIS, AND TREATMENT OF CERVICAL CANCER IN MEXICO

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Abstract: One of the most serious health threats for women is cervical cancer (CC), and its timely detection is crucial to reducing mortality from this disease. This study analyzes the cancerous agents and natural history of CC; diagnostic methods (cervical screening – or the Papanicolaou (Pap) test, colposcopy, and detection of human papilloma virus - HPV); and strategies for screening of precursor lesions of CC. It reviews screening pathways according to the Official Mexican Regulation NOM-014-SSA2-1994; conduct to follow (based on cytology results) in the case of low-grade intra-epithelial lesions, high-grade intra-epithelial lesions, and invasive cancer; as well as a holistic approach to prevention and control of CC. Furthermore, it discusses types of HPV; HPV vaccines – particularly the types available in Mexico and this nation´s vaccination scheme; the position of the World Health Organization regarding these vaccines; and adverse post-vaccination reactions. It presents: 1) the state of CC in Mexico; 2) existing programs for timely detection of CC based on Health Ministry guidelines; 3) the System of Epidemiological Surveillance of Mexico`s National Cervical Cancer Program; and 4) evolution of CC prevention and control programs in the southeastern Mexican state of Chiapas. We conclude that given limited progress in reduction of CC, there is a need for the Mexican Health Ministry to further train health personnel; periodically evaluate indicators regarding the success of programs addressing CC; increase HPV vaccination; and implement the concept of total quality in healthcare.

Keywords: screening pathways, timely diagnosis, intraepithelial lesions, invasive cancer, human papilloma virus

INTRODUCTION

One of the most serious health threats to women worldwide is cervical cancer (CC), and its timely detection is the most effective strategy for reducing death from this illness.[1, 2] The World Health Organization (WHO) calculates that currently one million women worldwide suffer from CC, although the highest incidence rates are in Central and South America, East Africa, South and Southeast Asia, and the Western Pacific. In 2012, in nations in which the majority of the population have low or moderate incomes, a total of 528,000 new cases were diagnosed and 266,000 women died from this illness. This is due to the fact that these nations lack effective healthcare systems and sufficient healthcare funding. One significant but under-acknowledged factor regarding incidence of CC in many societies is women`s lack of equal access to healthcare. The principal reason for high incidence of CC in nations in which much of the population has a low income is relative lack of effective CC prevention, detection, treatment, and surveillance programs, as well as lack of equal access to such programs. As a result, CC is generally detected in advanced stages, when there is less opportunity for adequate treatment, resulting in high mortality rates.[3, 4]

The CC is the fourth leading cause of death by cancer in women worldwide. An estimated 500,000 new cases occur annually worldwide, and approximately 270,000 women die due to this illness each yea.[5] In Mexico, CC was the second most common cause of cancer in women from 2006 to 2016, with an estimated 13,960 new cases annually in women age 25 and over, or 23.3 cases per 100,000 women.[6] Analysis by Mexico´s National Institute of Statistics and Geography[7] of death records reported by the Health Ministry´s National Information System based on death certificates emitted in Mexico from 2000 to

2015 indicated reduction in mortality from CC in all states. This reduction was attributed to the percentage of the population included in screening programs to test for CC to identify individuals with pathology who had not yet presented symptoms.

While the mortality rate from CC in women age 25 and over in Mexico`s southeastern state of Chiapas - and in Mexico as a whole - is decreasing, a gap continues to exist between Chiapas and the national average. From 2000 to 2015, the mortality rate from CC in Chiapas decreased 29.3% from 24.9 for every 100,000 women to 17.6, while the national rate decreased 39.2% from 18.9 to 11.5 for every 100,000 women.[8] Data indicated that in Chiapas CC was being diagnosed at a later stage than in other states due to a variety of reasons, including lack of access to healthcare, lack of precision of cytopathological diagnosis, and gender-related cultural barriers which prevent many women from seeking medical attention - including the diagnostic test - until they are in an advanced stage of the illness given that their husbands do not allow them be clinically explored.

In 2000, Chiapas had the fourth highest mortality rate from CC in Mexico. However, in 2015 it had the second highest rate after the state of Colima.[8] The reason for which the decrease in the CC mortality rate in Chiapas was less than in other states could be due to the fact that not all women in Chiapas who signed up to receive public healthcare insurance through Seguro Popular (Popular Insurance) were receiving attention regarding CC. Furthermore, it is likely that not all cases were documented as they were not appropriately channeled and detected in a timely fashion, or did not received proper follow-up by the treating physician. This is particularly common for indigenous women who do not speak Spanish. The gradual descent in mortality from CC in women was also occurring in other marginalized states of Mexico; nevertheless, states with better quality medical care had less annual variation in - and a greater rate of descent of - CC-related mortality,[8] and nationwide an incipient annual decrease in CC-related mortality was observed.

In response to this health problem, the 2013 Chiapas state government report regarding healthcare spending indicated that healthcare services had been improved through budget increase. That year, the state reportedly invested over 7.5 billion pesos in cancer prevention in women, principally in actions to reduce CC and breast cancer in women age 25 and over. This report also indicated that 37,381 cervical cytology screenings and 74,359 clinical breast exams were carried out in a timely fashion. Furthermore, the state of Chiapas made an effort to provide the low-income population with membership to health insurance through Seguro Popular. However, data suggests that budget increases had not led to reduction in incidence and mortality from CC in the vulnerable population.[9] This is partly due to sociocultural gender-related barriers which prevent many women from receiving proper follow-up.

As CC is often asymptomatic, by the time symptoms become evident, the cancer is frequently in an advanced stage. In such cases, even if the patient is diagnosed in time, gender dynamics and the family`s economic situation often impede further attention. Thus, many women are vulnerable to contracting and dying from CC. For this reason, CC prevention should focus on reducing incidence, morbidity, and mortality, principally among women from low income families, for whom lack of equal access to screening, prevention, and treatment programs has been documented.[9, 10] For this reason, the WHO recommends that national policies be formulated to guide effective implementation, monitoring, and evaluation

of CC prevention and treatment programs.[1]

This article presents methods of diagnosis and treatment of CC, screening pathways according to the Official Mexican Regulation NOM-014-SSA2-1994, which is currently in effect, and vaccines available for HPV. In particular, a profile of the illness in Mexico and in the state of Chiapas is presented.

BASIC INFORMATION REGARDING CERVICAL CANCER

GENERAL INFORMATION REGARDING CANCER

Cancer initiates as a cellular alteration, provoking invasive growth of abnormal cells that propagate in body tissue, disrupting normal body functioning. Any part of the body is susceptible to cancer, and over 100 types of cancer exist. While no direct cause is understood to provoke its appearance,[1] the International Agency for Research on Cancer (IARC) classifies cancerous agents into three categories:[11]

- Physical cancerous agents: ionizing and ultraviolet radiation.
- Chemical cancerous agents: including tobacco, alcohol, agrochemicals, asbestos, arsenic, and aflatoxins.
- Biological cancerous agents: infections caused by certain viruses, bacteria, or parasites.

Worldwide, smoking - considered to be the principal preventable cause of cancer - is calculated to be the cause of 20% of deaths from cancer. Another 20% of cancer cases are calculated to be due to chronic infections, including HPV which is linked to CC, and hepatitis B linked to hepatic cancer.[3] As a whole, men and women of all ethnic groups and socioeconomic levels contract cancer at similar rates, although a difference is observed in the types of cancer affecting men and women. In 2015, the WHO identified that on a global level, malignant lung, prostate, colorectal, stomach, and liver cancer were the most common cancers affecting men, while for women the most common were breast, colorectal, lung, cervical, and stomach cancer.[1]

In 2013 in Mexico, for women and men age 20 and over hospital morbidity (those hospitalized) for adults with malignant tumors was highest in men for stomach cancer (25%), genital cancer (11%), and hematopoietic cancer (10.6%), and in women for breast cancer (29.5%), CC (18.6%), and stomach cancer (13.8%). Among women age 20 to 29, the highest hospital morbidity for tumors was for genital cancer (10.76), while for women age 30 to 74 it was breast cancer, which appears to be increasing among older women.[12]

CERVICAL CANCER

CC is the most common illness related to HPV infection. The majority of sexually active women and men will contract the HPV infection at some point in their life and some may have recurrent infections. The critical point in which women and men contract the infection is soon after becoming sexually active. While HPV is sexually transmitted, penetration is not necessary for transmission; rather, direct contact with the skin of the genital area is recognized as being sufficient for transmission.[2,13]

Principal risk factors favoring persistence of HPV and its evolution toward CC are: becoming sexually active at an early age, failure to use a condom, smoking, using oral hormonal contraceptives, having multiple partners, and being immuno-suppressed.[14]

Several types of HPV exist, the majority of which do not cause long-lasting lesions (for example, serotypes 6 and 11), which tend to disappear without intervention. However, a small percentage of infections resulting from certain HPV serotypes (principally 16

and 18) may persist and evolve into cancer. Although the majority of infections resulting from HPV involute without intervention and the majority of pre-cancerous lesions disappear spontaneously, all women with HPV run the risk that the infection become chronic and the pre-cancerous lesions evolve into invasive CC, depending on the individual´s immunological system. CC has a latency period of up to 20 years in women with a healthy immunological system, and up to 10 years in immunosuppressed women. Therefore, it is recommended that all women of reproductive age (20 to 49) undergo annual cervical cytology to detect pre-cancerous lesions or cancer in its initial stages.[2]

NATURAL HISTORY OF CERVICAL CANCER

According to González and Núñez,[15] papilloma viruses are small, have double-helix DNA, lack a sheath, and their genome is divided into three regions: i) an early region (E) which codifies the viral proteins necessary for replication of viral DNA (E1, E2, E4, E5, E6, and E7), regulation of transcription, and cellular transformation and immortalization; ii) a late region (L) which codifies structural proteins (L1 and L2); and iii) a regulator region known as the long control region (LCR) which contains the DNA sequence controlling replication and expression of the viral genome.[16] HPV adheres to the cells of the basal layers of the epithelium through a membrane receptor, the molecule a6-Integrin. Once infection has occurred, the virus is established within the nucleus, and through its viral oncoproteins E6 and E7 is capable of: i) immortalizing the cells, conferring them with a high level of chromosomic instability, on some occasions provoking evolution to high-grade lesions with posterior development of cervical neoplasia, or ii) lodging in a latent manner in the epithelial cells, evading detection by the immune system and allowing for future reactivation.

CC involves gradual progression of a series of stages in which cervical cells present pre-malignant histological abnormalities known as cervical intraepithelial neoplasia (CIN) or squamous intraepithelial lesions (SIL), according to the diagnostic system being used (WHO vs. Bethesda, respectively). According to their level of alteration, these are classified as mild dysplasia (CIN1/ LSIL), moderate dysplasia (CIN 2/HSIL), and severe dysplasia or in situ carcinoma (CIN 3/HSIL).[17]

CC evolves into two predominant histological types of cancer: squamous carcinoma and adenocarcinoma. That most common in women is squamous carcinoma (80% of cases), which is most frequently associated with HPV serotype 16. Adenocarcinoma is the second most common, and although it is also most frequently associated with serotype 16, serotypes 18 and 45 are also associated with this type of tumor.[18,19]

Thus, the natural history of evolution of the infection principally depends on the HPV serotype, as well as the age and immunological state of the patient.

In 80 to 90% of cases, CIN1/LSIL lesions undergo spontaneous regression, without the need for treatment. However, this does not tend to occur with CIN 2 & 3 / HSIL lesions, which tend to be persistent, with only a 20% probability of spontaneous regression and a significant risk of transforming into invasive carcinoma.[18]

METHODS OF DIAGNOSIS

DIAGNOSIS OF INFECTION BY HUMAN PAPILLOMA VIRUS

Muñoz et al[20] present the following classification of infection by HPV.

1) Latent infection involves the presence of HPV in apparently normal cells or tissues in a patient without any apparent illness. Nevertheless, the virus is present and sometimes may be detected through specific techniques such as in situ hybridization and polymerase chain reaction (PCR).

2) Subclinical infection is manifested by microscopic changes in the cervical epithelium (koilocytes, dysplasias) detected through cytology or histological cuts of affected tissue. The presence of HPV in the cervical epithelium may be verified using a colposcope that indicates changes in coloration of the cervix upon applying an acetic acid solution; these changes indicate HPV infection and possible premalignant lesion.

3) Clinical infection is manifested by visible tumors with a large amount of HPV-positive tissue. These viruses are capable of infecting other tissues. Nevertheless, illness does not always manifest during this stage, but may remain in a latent or subclinical phase, during which the patient may either acquire a state of resistance or regression of the lesions, or progress toward invasive cancer.

CERVICAL CYTOLOGY (POPULARLY KNOWN AS THE PAP TEST)

Conventional cervical cytology – or the Papanicolaou (Pap) is the most common screening test for detecting preneoplastic lesions. However, this test results in a relatively high percentage of false negatives (failure to identify abnormal cells that are present), largely due to errors in sampling and analysis. Therefore, this technique may be substituted by liquid-based cytology, which allows for obtaining a more complete sample, without damaged, blood or mucous-covered, or inflamed cells. Nevertheless, due to its high cost it is only feasible for a limited population.[6]

COLPOSCOPY

The objective of this test is to locate and evaluate lesions given abnormal cytology; if necessary, a directed biopsy should be taken and stained with 3% acetic acid or using the Schiller test (Lugol staining). The following are abnormal colposcopic findings: acetowhite epithelium, iodine-negative epithelium, changes in coloration (leukoplakia) due to necrosis and keratinization, vascular neoformation, zones with basophilic stippling, mosaics, and irregular surfaces with loss of normal epithelium that become ulcerated.[6]

BIOMOLECULAR TECHNIQUES FOR DETECTING HPV

The following techniques are most widely used to study HPV.

Polymerase chain reaction (PCR). The basis of this technique consists of multiplying the number of copies of a DNA segment present in the sample. This process, known as amplification, is carried out through PCR, and is capable of detecting the presence of very few copies of DNA of the virus, even when they are present in a single cell.[21] (Castaño and Hurtado, 2012).

Hybrid capture. This technique uses RNA sequences capable of detecting several types of HPV. If the sample presents viral infection, an RNA-DNA hybrid is produced which is captured by an antibody that acts specifically against hybrids and is detected through an ELISA reaction, using a chemiluminescent compound to reveal the reaction and provide information regarding the quantity of viral

DNA present in the sample, which appears to have a direct relationship with the presence of high-grade lesions.[21] (Castaño and Hurtado, 2012).

Biomarkers. These are markers of transformation associated with infection by HPV and may be identified during or after active infection. They are grouped as: i) expression markers for oncogenes of HPV (mRNA and proteins), ii) cellular proliferation markers (Ki-67, TOP2a, and p16), and iii) chromosome instability markers (increase of the arm of the chromosome 3q).[22]

Biomolecular determination of HPV together with cervical cytology is the most widely accepted measure for preventing CC. The majority of studies suggest that inclusion of an HPV biomolecular test in the cytology of CC screening may increase identification of precursor lesions by 50-100%. Furthermore, it appears to add several years of life to patients as compared to repeated cytology.[22, 23] Mexico`s 2018 Guide to Clinical Practice for prevention, detection, diagnosis, and treatment of precursor lesions of CC in level 1 and 2 hospitals states that cervical cytology is indicated for women age 25 to 34, while for women age 35 to 69 biomolecular detection of HPV alone or combined with cervical cytology (cotesting) are the most recommended tests for primary screening.[6]

STRATEGIES FOR SCREENING FOR PRECURSOR LESIONS OF CERVICAL CANCER

SCREENING FOR CERVICAL CANCER

For level 1 hospitals, the 2008 Guide to Clinical Practice of Prevention and Timely Detection of CC[6] recommends the following.

1) Screening with cervical cytology (Pap test) should be carried out for all sexually active woman age 21 and over, women under age 21 who have been sexually active for three years, and other women who request it who have never had the screening. The 2018 Guide to Clinical Practice[6] is similar to that of 2008 (SS, 2008), except that it suggests carrying out screening with annual cervical cytology for women age 25 to 69.

2) If the patient is immunosuppressed, the test should be repeated annually.

3) If the patient is not immunosuppressed, is over age 69, and has had 3 or more negative screenings in the past 10 years, screening is suspended.

4) If the patient has had no negative screenings in the past 10 years, cervical cytology should be carried out annually, until 3 consecutive negative tests result, and then continue with screening every 2 to 3 years.

5) If the patient is pregnant or has precedents of partial hysterectomy, cervical cytology should be carried out annually until 3 consecutive negative tests result, and then continue with screening every 2 to 3 years.

6) In case of precedents of malignant or pre-malignant cervical illness in the cervix, the patient should be reviewed in a Dysplasia or Colposcopy Clinic.

PROCEDURES TO FOLLOW BASED ON CYTOLOGY RESULTS

The 2018 Guide to Clinical Practice[6] indicates the following.

1) If a cytology test results negative, a new study should be programmed in 1 year.

2) If the results are negative 2 consecutive years, the next test may be carried out 3 years later.

3) Any woman whose cytology sample was determined inadequate for diagnosis should be scheduled to repeat the test within 21 business days.

4) After 2 cytology tests are determined inadequate for diagnosis, the patient

should be sent for a colposcopy.

5) Women with cytology positive for ASCUS (atypical squamous cells of undetermined origin) should be referred to colposcopy and receive a new study annually

SCREENING PATHWAYS FOR CERVICAL CANCER ACCORDING TO THE OFFICIAL MEXICAN REGULATION

PROCEDURES TO FOLLOW FOR LOW-GRADE INTRAEPITHELIAL LESIONS (LGIEL)

For prevention, detection, diagnosis, treatment, and epidemiological surveillance of CC, the Official Mexican Regulation NOM-014-SSA2-1994[24] establishes the following.

1) If cytology indicates LGIEL and colposcopy is satisfactory (squamo-columnar junction and margins of visible lesions are evident) and does not show evidence of lesion, cervical cytology and colposcopy should be carried out annually.

2) If cytology indicates LGIEL and colposcopy is satisfactory and shows evidence of lesion, a directed biopsy should be taken.

- If the directed biopsy is negative, a new colposcopy should be carried out to verify the diagnosis, and if the treating physician detects a possible lesion, a new directed biopsy or endocervical brushing should be carried out.
- If the directed biopsy indicates LGIEL, the treating physician should provide one of the following conservative (localized) treatments: cryosurgery, electrosurgery, or laser therapy, or the patient may be periodically reviewed in the colposcopy clinic, with colposcopy and cervical cytology taken every six months for 24 months.
- If the directed biopsy indicates high-grade intraepithelial lesions (HGIEL), conservative treatment should be carried out (electrosurgery or laser therapy). In post-menopausal women, conservative treatment should be provided in a colposcopy clinic or extrafascial hysterectomy should be carried out, depending on the anatomical conditions of the cervix.
- If the directed biopsy indicates micro-invasive or invasive cancer, the patient should be transferred to an oncological center for treatment.

3) If cytology indicates LGIEL and colposcopy is not satisfactory, endocervical brushing should be carried out.

- If endocervical brushing is negative, the practicing physician should decide whether the patient will remain under periodic review in the colposcopy clinic or whether she may be referred to her local health center.
- If endocervical brushing indicates LGIEL, it nonetheless should be treated as HGIEL, using conservative excisional methods (cone biopsy), and the case should be reevaluated through a histopathological study.
- If endocervical brushing indicates HGIEL, it should be treated using conservative excisional methods.
- If endocervical brushing indicates micro-invasive or invasive cancer, the patient should be referred to an oncological center.

PROCEDURES TO FOLLOW FOR HIGH-GRADE INTRAEPITHELIAL LESIONS (HGIEL)

The Official Mexican Regulation NOM-014-SSA2-1994[24] for prevention, detection, diagnosis, treatment, and epidemiological surveillance of CC establishes the following.

1) If cytology indicates HGIEL and

colposcopy is satisfactory and does not show evidence of lesion, cervical cytology and colposcopy should be carried out annually.

2) If cytology indicates HGIEL and colposcopy is satisfactory and shows evidence of lesion, a directed biopsy should be taken.

- If the directed biopsy is negative, a new colposcopy should be carried out to verify the diagnosis, and if the treating physician detects a possible lesion, a new directed biopsy or endocervical brushing should be taken.
- If the directed biopsy indicates LGIEL, the treating physician should provide one of the following conservative treatments: cryosurgery, electrosurgery, or laser therapy, or the patient may be periodically reviewed in the colposcopy clinic with colposcopy and cervical cytology taken every six months for 24 months.
- If the directed biopsy indicates HGIEL, conservative treatment should be carried out (electrosurgery or laser therapy). In post-menopausal women, conservative treatment should be provided in a colposcopy clinic or extrafascial hysterectomy should be carried out, depending on the anatomical conditions of the cervix.
- If the directed biopsy indicates micro-invasive or invasive cancer, the patient should be transferred to an oncological center for treatment.

3) If cytology indicates HGIEL and colposcopy is unsatisfactory, endocervical brushing should be carried out.

- If endocervical brushing is negative, the practicing physician should decide whether the patient will remain under periodic review in the colposcopy clinic or whether she may be referred to her local health center.
- If endocervical brushing indicates LGIEL, it nonetheless should be treated as HGIEL, using conservative excisional methods (cone biopsy), and the case should be reevaluated through a histopathological study.
- If endocervical brushing indicates HGIEL, the patient should be treated using conservative excisional methods (cone biopsy).
- If endocervical brushing indicates micro-invasive or invasive cancer, the patient should be referred to an oncological center.

PROCEDURES TO FOLLOW FOR INVASIVE CANCER

The Official Mexican Regulation NOM-014-SSA2-1994[24] for prevention, detection, diagnosis, treatment, and epidemiological surveillance of CC establishes the following.

1) If colposcopy indicates macroscopic tumor, a directed biopsy should be carried out and the extent of the neoplasia carefully evaluated; if the biopsy confirms the diagnosis of micro-invasive or invasive cancer, the patient should be referred to an oncological center.

2) If cytology indicates invasive cancer and colposcopy is satisfactory and indicates a lesion, a directed biopsy should be taken.

- If the biopsy indicates LGIEL, the patient should be treated conservatively, as if she had HGIEL.
- If the biopsy indicates HGIEL, the patient should be treated conservatively.
- If the biopsy indicates micro-invasive or invasive cancer, the patient should be referred to an oncological center.

3) If cytology indicates invasive cancer and colposcopy is unsatisfactory, endocervical brushing should be carried out.

- If endocervical brushing is negative, the practicing physician should decide whether the patient will remain under

periodic review in the colposcopy clinic or whether she may be referred to her local health center.

- If endocervical brushing indicates LGIEL, HGIEL, or invasive cancer, the patient should be referred to a facility with an operating room to carry out a cone biopsy.

HOLISTIC PREVENTION AND MANAGEMENT OF CERVICAL CANCER

The WHO[3] recommends a multidisciplinary holistic approach to prevention and treatment of CC, including healthcare follow-up throughout a woman´s life. Adequate primary prevention begins with vaccination of girls age 9 to 13, before becoming sexually active. Furthermore, it is recommended that women not become sexually active until after puberty, due to the fact that during puberty the ectocervix is immature and the "zone of transformation" (juncture of the flat and cylindrical epithelium) of the cervix is more extensive, thereby facilitating exposure to HPV infection.[25] Furthermore, upon becoming sexually active before age 20, the epithelium is more likely to come into contact with different types of papilloma viruses and be more vulnerable to forming pre-cancerous lesions.[26] It is also important to promote contraceptive use, which is a highly effective, relatively low-cost method of preventing transmission of CC as well as other sexually transmitted diseases.[27]. Women should be warned that smoking may cause alteration in the morphology, size, form, or nucleus of cervicovaginal cells, which could lead to CC, due to the fact that cigarettes contains chemical substances that are carcinogenic and upon coming into contact with the cervical mucous provoke alterations in the central cell pathways, generating cellular mutations or acting as a cofactor for acquiring susceptibility to infections by high-risk HVP.[28]

VACCINES FOR HUMAN PAPILLOMA VIRUS

POSITION OF THE WHO REGARDING HPV VACCINES

In June of 2007, the WHO´s Global Advisory Committee on Vaccine Safety concluded that the vaccines Cervarix (bivalent) and Gardasil (tetravalent) were safe. In December of 2008, the committee examined initial post-marketing surveillance data for Gardasil and confirmed its safety. Clinical trials reported by the WHO[29] documented moderate transitory local reactions (erythema, pain, or inflammation) in the place of the injection in 10 to 20% of vaccinated women, although adverse systemic reactions were not reported. To prevent future adverse effects, the WHO recommended that the vaccine not be administered to those who had suffered serious allergic reactions to prior doses or any component of the vaccine. Some nations recommended postponing HPV vaccination in women presenting any acute illness. While no data published prior to the WHO´s authorization of the vaccine exists that indicates increased risk of syncope following a vaccination, studies posterior to authorization indicate greater frequency of post-vaccination syncope in adolescents vaccinated for HPV than for those receiving other types of vaccines.[3] Aside from this concern, in recent years the vaccine has been controversial due to uncertain efficacy given its coverage of only serotypes 6, 11, 16, and 18 of the more than 200 existing serotypes. The viability of HPV vaccination programs globally is questioned given that it only includes two types of high-risk HPV, leaving recipients unprotected from a broad range of other high-risk serotypes. Furthermore, the information that the population receives regarding HPV vaccines is misleading, generating the false understanding that

vaccinated girls and adolescents will not need to undergo cervical cytology (Pap test) in the future.[30]

Possible adverse effects from the vaccine have been identified as one of the reasons for low rates of immunization against HPV in some nations.[27] Although the WHO has indicated the HPV vaccine`s safety, recent studies indicate that the relationship of the vaccine to development of autoimmune and central nervous system disorders is still uncertain, and therefore there is a need to continue surveillance of the vaccine despite the license having been granted for the vaccine. In 2008, the WHO´s Group of Experts on Vaccines and Recommendations for Immunization recommended that nations consider establishing a system for monitoring the impact of vaccination on the prevalence of the various types of HPV, as well as incidence of abnormalities and premalignant lesions.[29]

ADVERSE REACTIONS TO HPV VACCINATION

Despite the fact that the WHO has approved the safety of the HPV vaccine, the drug has been center of controversy on all continents. Several nations have decided to stop administering it and/or face costly lawsuits by those affected. For example, in Canada, 82 notifications of adverse reactions were reported following application of 162,000 doses in 2007. Of these, in 5 cases the vaccine recipient was hospitalized, including two for appendicitis, one for viral infection, and another for encephalopathy, and additional HPV vaccine recipients were reported to have contracted Guillain-Barré syndrome.[31] In Japan, medical authorities asked the government to discontinue application of the vaccine after over 8 million women had been vaccinated and 1,968 cases of negative effects were reported in 2013, of which 106 were determined to be severe, involving difficulty with movement and convulsions. Japan is the only nation that stopped actively recommending HPV vaccination, resulting in a decreased rate of vaccination from 80% to 1%.[32]

Indeed, adverse effects related to HPV vaccines greatly surpass those recorded for other vaccines.[32] The reasons for these effects are still unknown. One likely explanation is that the vaccines have been designed to maintain extremely high antibody counts during a long period, inducing complex immune reactions through mechanisms similar to those observed in prolonged infections.[33]

Recognizing the potentially negative influence of adverse post-vaccine reactions on the public opinion of many nations, pharmaceutical industries have implemented a strategy of counter-arguments through social networks, which has been accepted by the WHO. The WHO´s Global Advisory Committee on Vaccine Safety[34] affirmed that no safety problem had been found that could change the recommendations for use of the vaccine and publicly criticized the decision by the Japanese Ministry of Health, Labor, and Welfare to retract active recommendation.

However, the media and government agencies regulating healthcare systems worldwide cannot ignore victims´ complaints regarding secondary effects of HPV vaccines. There is a need to increase transparency in all stages of the approval process of pharmaceutical products; to improve post-marketing control systems; to effectively manage conflicts of interest by pharmaceutical companies and multinational organizations; and to develop a system by which citizens have a direct voice in public health decisions.[34]

TYPES OF HPV

According to guidelines for application of vaccines against HPV infection,[35] the types of HPV responsible for CC by order of frequency are: 16, 18, 45, 31, 33, 52, 58, 35, 59, 56, 51, 39, 68, 73, and 82. In the large majority of nations, type 16 is responsible for an estimated 50% of cases of CC, followed by type 18 which is responsible for an estimated 20% of cases. This is the case of Mexico, with some variations according to region and age group.

CERVICAL CANCER VACCINES AVAILABLE IN MEXICO

The objective of immunization is to prevent new sexually active generations from contracting the HPV infection, and thereby prevent CC, by administering the vaccine before the start of sexual activity. In 2012, the HPV vaccine was incorporated into Mexico´s national vaccination scheme to be universally applied to girls in 5th grade and older, as well as girls 11 and older who do not attend school.[36] The following 2 vaccines to prevent CC are available in Mexico.

1. Cervarix: Developed by the Glaxo Smith Kline laboratory, this bivalent vaccine contains high-risk HPV types 16 and 18 (20 mcg of virus-like particles, VLP), with the adjuvants AS04, which is a monophosphoryl lipid A, 500 g), and aluminum hydroxide (50 g). Results published to date for women vaccinated against HPV indicate an 100% efficacy rate against persistent infection 4-5 years later.[35]
2. Gardasil: Developed by the Merck Research and Sanofi Pasteur MSD laboratories, this tetravalent vaccine contains the low-risk HPV types 6 and 11 and high-risk types 16 and 18 (40 mcg VLP of types 6 and 11, and 20 mcg of types 16 and 18), as well as the adjuvant amorphous aluminum hydroxyphosphate sulphate (225 g).[35, 37]

Mechanism of action: The vaccines induce formation of high HPV-specific antibody counts that interfere with viral transmission by adhering to and neutralizing HPV, thereby preventing its penetration into the white epithelial cells. Vaccination is initiated at age 9, given that the response is greater in girls and adolescents younger than 15 years than in those age 16 and over, as well as the fact that women should be vaccinated against HPV before initiating sexual activity. Although the vaccine induces formation of antibodies in women with active infection, it cannot be assured to have therapeutic effects in the case of pre-existing infections.[2]

Vaccination scheme: The 2018 Guide to Clinical Practice[6] recommends administering the bivalent or tetravalent HPV vaccine in two doses with a 6-month interval to all girls age 9 to 13. A 3-dose scheme (an initial vaccine, and posterior vaccines 1-2 months and 6 months later) is recommended for those age 15 and over, as well as for immunosuppressed women and those infected by HIV.

The HPV vaccine does not substitute health education and screening. Women who have received the complete HPV vaccination scheme should be screened for CC.[6] Mexico´s HPV vaccination scheme does not include males, who are principally asymptomatic carriers of the virus, under the argument that the expense is unnecessary given the very low indices of penis and anal cancer in men as compared to those of CC in women.[30]

CERVICAL CANCER IN MEXICO

CURRENT STATE OF CERVICAL CANCER IN MEXICO

In the 1970s, Mexico implemented a national strategy to prevent CC. More recent data show that from 2000 to 2016, the CC mortality rate decreased by almost 40%, from 18.9 to 11.4 deaths per 100,000 women

age 25 and over. In recent years, CC was the second most common cause of death due to malignant neoplasia in women over age 25 in Mexico. According to INEGI, 4050 women died from CC in Mexico in 2016, with a rate of 11.4 deaths per 100,000 women age 25 and over, or 1.32% of all female deaths that year. A majority of these deaths were of women age 25 to 45.[6]

In 2016, the Women`s Cancer Information System (SICAM according to its Spanish initials) of Mexico´s Health Ministry reported 4710 women with cytology positive for HGIEL. Upon analyzing the results by age, those most affected were age 35 to 39, although an increase was observed starting from age 25. Upon age 40, a sustained decrease occurred; the rate was constant from age 50 to 54; and after age 54, the rate gradually decreased.[6] Given the lack of sustained progress in reducing CC, currently there is a need to improve healthcare personnel`s capabilities and periodically evaluate their performance, as well as increase application of the HPV vaccine and implement measures in accordance with the concept of total quality in healthcare.[38]

RESPONSIBILITIES OF DIFFERENT TYPES OF HEALTHCARE CENTERS ESTABLISHED BY MEXICO´S HEALTH MINISTRY GUIDELINES FOR PROGRAMS FOR OPPORTUNE DETECTION OF CERVICAL CANCER

In Mexico, the Department of Women`s Cancer, coordinated by the National Center for Gender Equity and Reproductive Health (CNEGSR according to its Spanish initials) is responsible for coordinating with other government agencies to develop policies for CC management that include: primary prevention, early detection, diagnosis and treatment of precancerous lesions, and palliative care in advanced cases. In 1985, the Institute for Diagnosis and Epidemiology (INDRE according to its Spanish initials) was created, which included a cervical cytology laboratory that began to collaborate with the Program of Opportune Detection of Cervical Cancer to establish a network of laboratories to cover women´s screening needs, fulfilling the objective of this program to detect pre-cancerous CC lesions in women age 25 to 64 through exfoliative cervical cytology. Nevertheless, in 2007, the procedure for detecting precursor lesions was modified, and currently cervical cytology is used to detect HPV in women age 25 to 34, and hybrid capture - or PCR - for women age 35 to 64. If the hybrid capture test is positive, complementary cytology is taken.[39]

The Cytology Laboratory of INDRE`s Department of Pathology and Cytology is a national laboratory that regulates technical aspects and external quality control of the CC diagnostic test through the program Opportune Detection of Cervical Cancer. Currently, the Public Healthcare System has 20 cytology laboratories in the following states: Aguascalientes, Campeche, Chiapas, Chihuahua, Guerrero, Hidalgo, Jalisco, Mexico State, Michoacan, Nayarit, Puebla, Queretaro, Quintana Roo, Sinaloa, Sonora, Tabasco, Tamaulipas, Tlaxcala, Veracruz, and Yucatan. Cytological samples taken at different health centers are sent to the cytology laboratory in their jurisdiction to be evaluated. Results are sent to the corresponding healthcare jurisdiction, which notifies the local healthcare center. If the result is positive, the local healthcare center coordinates follow-up care, involving specialized services such as a colposcopy clinic and pathology laboratory.[39]

To provide quality control in each cytology laboratory, the pathologist or cytologist together with a cytotechnologist should review daily all positive, atypical, and questionable samples. This team, or a cytotechnologist with

over five years of experience according to regulation NOM-014-SSA2-1994, should also carry out a random review of 10% of negative slides. The lead pathologist should endorse all positive cases and report them to INDRE`s Cytology Laboratory, and schedule a meeting to review these cases and obtain the records of the cyto-colposcopic and cyto-histologic correlations.[39]

SYSTEM OF EPIDEMIOLOGICAL SURVEILLANCE WITHIN MEXICO´S NATIONAL CERVICAL CANCER PROGRAM

According to regulation NOM-014-SSA2-1994,[24] epidemiological surveillance of HPV is carried out by analyzing the records of the cytological and histopathological studies with diagnosis of cytopathic changes suggestive of infection. Each healthcare center - whether public or private - should report CC cases that have been detected in its different departments to the Holistic System of Women`s Cancer (SICAM – PROCACU according to its Spanish initials) or the information system corresponding to that healthcare center.

The following send data to these information systems: i) the regional administrative body ("jurisdiction"), ii) laboratory, iii) colposcopy clinic, and iv) oncological center. In the jurisdiction`s online platform, data is first captured for all patients for whom positive cytology or a positive hybrid capture was carried out by a local health center. Three types of cytology are carried out: i) screening cytology, carried out in the patient`s local health center; ii) complementary cytology, to confirm the diagnosis when the hybrid capture test is positive; and iii) follow-up cytology, carried out in the colposcopy clinic with patients under colposcopic surveillance due to cervical alterations during treatment. The second data capture takes place in the colposcopy clinic to provide follow-up to any patient with a positive result.

An initial assessment is carried out through colposcopy to corroborate the previous diagnosis based on cytology or hybrid capture. The conduct to follow depends on which of the following evolutionary stages of the illness are observed through the colposcopy: i) absence of alterations; ii) low-grade intraepithelial lesions; iii) high-grade intraepithelial lesions; iv) neoplasia suggestive of invasion; and v) invasive cancer.

The management plan to be followed depends on the type of lesion the patient presents. The colposcopist chooses among the following options: pharmacological treatment, taking a biopsy for histopathological study, cervical electrosurgery, colposcopic review every six months for two years, and referral to an oncological center. Which of these options is chosen will depend on the availability of funding and infrastructure of the hospital and the judgement of the colposcopist. Aside from the five presumptive diagnoses mentioned in the previous paragraph, diagnosis may result in the following: i) non-specific inflammatory alterations; ii) non-satisfactory samples (the squamocolumnar union and/or the borders of the lesion in the cervix are not visible); and iii) findings not related to CC, including genital atrophy, condylomas, polyps, and vulvar pathology.

After initial assessment through colposcopy, follow-up appointments should be scheduled until finalizing the process. If the patient misses an appointment, discontinues her process, changes residence, etc., her case continues to be on file to be attended to if she resumes communication. The patient must attend all appointments for proper diagnosis and data registry in the electronic system by which the following appointment will be assigned. In the data registry system, an initial appointment allows for advancing

to the following appointment, until the final histopathological diagnosis (through biopsy or cone biopsy) has been obtained (example: appointment 1 = colposcopy; biopsy; wait for histopathological result in order to proceed to appointment 2).

EVOLUTION OF PROGRAMS FOR PREVENTION AND TREATMENT OF CERVICAL CANCER IN CHIAPAS

The 2007-2012 Institutional Program of the Health Ministry of the State of Chiapas[40] mentions that CC programs initiated in the 1940s, when what was then called the Ministry of Health and Assistance instituted an anti-cancer program. However, only in 1995 did Mexico`s National Institute of Cancer begin to train personnel specifically for this purpose.

In 1996, a CC epidemiological surveillance project was initiated to record those patients with CC in order to obtain national indicators for the disease using the software program EPI-CaCu , and in 1997 the Unique Authorized System of Epidemiological Surveillance (SUAVE according to its Spanish initials) was implemented, which groups data for different variables involved in CC in order to identify risk factors for evaluation, treatment, and surveillance of patients with CC.

In 1996 in the state of Chiapas, in accordance with the national Health Ministry, the CC Prevention and Control Program was transferred from the Department of Preventive Medicine to the Department of Reproductive Health. In accordance with national guidelines, the following actions were implemented in Chiapas to detect and attend to this illness: improvement of health infrastructure, establishment of dysplasia clinics, improvement of diagnostic equipment, and training of personnel.

In April of 1998, President Ernesto Zedillo inaugurated the Chiapas State Public Health Laboratory to improve diagnosis and quality control. This laboratory is part of a program which focuses on increasing opportune detection of CC cases through two dysplasia clinics: one with two colposcopists in the General Hospital Dr. Rafael Pascasio Gamboa in the capital of Chiapas, Tuxtla Gutiérrez, and the other in the General Hospital of Tapachula.[40]

In 2010, the second level Hospital of Cultures was opened in San Cristobal de las Casas, Chiapas, with an investment of over 200 million pesos. With 60 beds and all services necessary for a second level medical unit, this hospital attends to inhabitants of the Tsotsil-Tseltal Maya Highlands Region, where the majority of state´s municipalities with the lowest Human Development Index are located. This hospital is administrated by Jurisdiction No. II of the national Health Ministry, which covers the following municipalities: Aldama, Amatenango del Valle, Chalchihuitan**,** Chanal, Chenalho, Huixtan, Las Rosas, Mitontic, Oxchuc, Pantelho, San Andrés Larrainzar, San Cristobal de Las Casas, San Juan Cancuc, San Juan Chamula, Santiago el Pinar, Tenejapa, Teopisca, and Zinacantan. The hospital has carried out a variety of women´s health campaigns, including cervical cytology and mammograms, and has incorporated traditional midwives.[41]

CONCLUSIONS

CC is a significant health problem worldwide, and in Mexico it is the second most common cause of death due to malignant neoplasia among women over age 25.

Timely detection allows for preventing CC, and to reduce mortality from CC in women, there is a need for diagnostic methods to be applied in a timely manner with a high level of quality control.

Detection of lesions caused by HPV through cytology is the most widely accepted method of preventing CC, greatly increasing

identification of precursor lesions.

There is a need for a holistic approach to prevention and treatment of CC, including greater efficacy of screening pathways for early detection of invasive cancer, and clearer delineation of conduct to follow given low- and high-grade intraepithelial lesions (LGIEL and HGIEL, respectively), in accordance with Mexico`s regulations.

A multidisciplinary approach for preventing and controlling CC should involve adequate primary care, including HPV vaccination for girls age 9 to 13 - when vaccination is more effective and before they become sexually active - in order to prevent new generations from contracting the high-risk HPV infection.

The 2 HPV vaccines available in Mexico are bivalent Cervarix, which contains high-risk serotypes 16 and 18, and tetravalent Gardasil, which contains low-risk serotypes 6 and 11 and high-risk serotypes 16 and 18.

HPV vaccines have been very controversial due to their low efficacy, their coverage of only four of over 200 existing serotypes, and above all due to their potentially severe secondary effects.

Adverse effects of the HPV vaccine have been identified as a significant reason for low HPV immunization rates in some regions of the world.

The WHO endorses application of HPV vaccines, stating that they are safe, despite the fact that they have been the center of controversy on all continents.

Given lack of progress in reduction of CC, currently there is a need to increase the capacities of healthcare personnel, as well as provide periodic evaluation of their performance, increase HPV vaccination, and implement the concept of total quality in healthcare.

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