Cáncer de cérvix: una mirada práctica

Cervical cancer, a practical view

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Abstract

Introduction: Cervical cancer (CC) is a public health problem in both developed and undeveloped countries; this pathology has socio-economic repercussions in women of reproductive age.

Objective: To describe the characteristics of cervical cancer prevention, screening, diagnosis, and treatment methods.

Method: An exhaustive bibliographic search was carried out within a period of 6 years (2016-2021) in the database of the Fundación Universitaria del Área Andina using search engines such as Dialnet, Science Direct, Medline, Lilacs, and Scopus to review the general concepts of cervical cancer.

Results: The main etiology of cervical cancer is the human papillomavirus (HPV) which is a preventable virus through adequate education, information, and follow-up of its precancerous lesions. It is the second most frequent cancer in Colombia.

Conclusion: CC is a pathology that mainly affects women of reproductive age belonging to low socioeconomic levels. This type of cancer has high mortality rates, especially in developing countries and in high-risk HPV infections. Regarding the management of this pathology, public health strategies, such as vaccination and conducting screening tests continue being the fundamental pillars.

Key words: Human papillomavirus, cervical cancer, cervical cytology, screening, colposcopy

Resumen

Introducción: El cáncer de cérvix (CC) es un problema de salud pública en países desarrollados y no desarrollados; esta patología tiene repercusiones socioeconómicas en mujeres en edad reproductiva.

Objetivo: Describir las características sobre métodos de prevención, tamizaje, diagnóstico y tratamiento del cáncer de cérvix.

Método: Se realizó una búsqueda bibliográfica exhaustiva con un lapso de 6 años (2016-2021) en la base de datos de la Fundación Universitaria del Área Andina utilizando motores de búsqueda como Dialnet, Science Direct, Medline, LIlacs, Scopus para revisar los conceptos generales sobre cáncer de cérvix.

Resultados: Es el segundo cáncer más frecuente en Colombia, la principal etiología del cáncer de cérvix es el virus del papiloma humano (VPH), el cual es un virus prevenible mediante la adecuada educación e información y seguimiento a sus lesiones precancerosas

Conclusión: El CC es una patología con altas tasas de mortalidad especialmente en países en vía de desarrollo y en las infecciones asociadas a VPH de alto riesgo, afectando principalmente a mujeres en edad reproductiva y estratos socioeconómicos bajos. Los principales pilares para el manejo de esta patología siguen siendo las estrategias de salud pública, como la vacunación y realización de las pruebas de tamizaje.

Palabras clave: Virus del papiloma humano, cáncer de cérvix, citología cervical, tamizaje, colposcopia.

Introduction

Cervical cancer (CC) is considered a worldwide health problem, with high social and economic impact in developing countries, affecting mainly the fourth and sixth decade of life; it is closely related to the Human Papilloma Virus (HPV), which is associated with sexual risk behaviors, such as non-use of condoms, promiscuity, early initiation of sexual relations, lack of knowledge of screening methods such as the HPV-DNA test, cervical cytology and vaccination against HPV; the existence of preventive measures places CC as a preventable cancer, however, inadequate follow-up of premalignant lesions leads to late detection of cervical cancer and therefore an increase in complications and an unfavorable prognosis (1)(2)(3).

Considering that cervical cancer has a high prevalence and mortality rate, it is important to improve the approach to screening and adequate treatment. Therefore, the following literature review describes the characteristics of prevention, screening, diagnosis, and treatment methods for cervical cancer.

Materials and methods

Bibliographic review carried out during 2020 and the first quarter of 2021 on generalities and technical-scientific information of cervical cancer, taking into account international, national and local literature, the information was obtained from different databases such as: Dialnet, Science Direct, Medline, LIlacs, Scopus, under the license of the Fundación Universitaria del Área Andina, in addition to the review of guides and protocols relevant to this pathology, such as those included in the International Federation of Gynecology and Obstetrics (FIGO) and the Ministry of Health in Colombia, articles published between 2016 and 2021 were taken into account. There were 71 articles, of which 12 were rejected because they did not meet the inclusion criteria, leaving a total of 59 articles.

Development

Epidemiology

Worldwide, cervical carcinoma ranks as the fourth most common cancer in women, according to the Pan American Health Organization (PAHO) in 2018, more than 72,000 women were diagnosed with cervical cancer; in Colombia, an incidence of 18.7 per 100,000 women was reported for the year 2012, where the main affected women were between 35 and 50 years old, occupying the fourth cause of mortality. In underdeveloped countries, cervical cancer is the seventh leading cause of cancer and in developing countries it is the second most frequent, as a consequence of health inequalities (4)(5)(6)(7).

Risk Factors

Currently the Human Papillomavirus is considered as a risk agent for the presence of cervical cancer, HPV is a circular double-stranded DNA virus, it has different classifications among these are the non-oncogenic and oncogenic as 16 and 18, the latter are related to more than 77% of cervical cancers. Although this figure is variable in different studies, a study conducted in 2016 where they studied 2134 women mentioned a prevalence of 55% of HPV in cervical cancer (8)(9)(10).

In a study conducted in 2016 in Santiago de Cuba, the beginning of sexual life at an early age and a number of more than 2 sexual partners are named as factors that increase the incidence of HPV infection, since it predisposes the appearance of cervical lesions and subsequent evolution to premalignant and malignant conditions, it is also known exogenous factors that increase the likelihood of CC such as smoking, oral contraceptive use for a long time and multiparity (11) (12).

Birth control methods

Oral hormonal contraceptives, which have an impact depending on the time of use, where prolonged periods longer than 5 years are related as a risk component for cervical cancer, however, multiple studies highlight that after 10 years of abandoning the method, the risk of contracting cervical cancer is similar to that of women who do not use oral hormonal contraceptives. It is noteworthy that among contraceptive methods, barrier methods generate a decrease in HPV infection (13)(14).

Psychosocial factors

In a study conducted in Bangladesh, 2019 (17), they mention the close association between a low educational level and the occurrence of cervical cancer, as a consequence of lower receptivity to screening tests; otherwise, they highlight factors such as living in urban areas, socioeconomic levels, and undergraduate and graduate studies; which contributes positively to the knowledge of the pathogenesis of cervical cancer and the different screening methods to access to timely detection services.

Early initiation of treatment is an important factor in prognosis, according to the report of a study conducted in Taiwan between 2004 and 2010 in women with early diagnosis of cervical cancer, since patients treated after 90 days from diagnosis had a lower overall survival rate compared to patients treated within 90 days; Difficulty in accessing screening programs, psychosocial factors such as fear of surgery and the economic burden on the family are the main causes of delay in initiating treatment in developing countries, in addition to which the location and extent of the tumor directly affects the survival rate (15) (16).

Specific tests

The Papanicolaou test or cervicovaginal cytology is the most important test since it has a high impact on the decrease of incidence and mortality from cervical cancer. Among HPV lesions 70% disappear within a year and 90% within 2 years, however, there is a risk of presenting persistent precancerous lesions that evolve into invasive cancer, which is why it is important to highlight the importance of screening methods for early detection (17)(18)(19).

In Colombia there is Papanicolaou screening, which is indicated for ages between 25 and 30 years in a 1-1-3 scheme, which represents the performance of annual cervical cytology for 2 years in a row, if it reports negative, the next cytology will be performed after 3 years (20).

Human Papilloma Virus Typology

The main HPV serotypes are divided into carcinogenic HPV 16, 18, 31, 33, 35, 45, 51, 52, 56 and 58, HPV 16 and 18 are responsible for 60% and 10-20% respectively of all cervical cancers, while HPV types 31, 33, 35, 45, 51, 52, 56, 58, 59, 68 and 73 constitute 20-30%. In Colombia, cytology combined with high-risk HPV DNA testing is recommended for ages 30-65 years (21) (22).

Genetic susceptibility

In relation to genetic susceptibility, polymorphism in different types of genes has been associated with the development of cervical cancer, the human leukocyte antigen is linked in various ways, since sometimes it stands out as a protective factor and sometimes as a risk factor, there are also genes that disrupt the immune response of the Human Papilloma Virus, such as the chemokine receptor-2 (CCR2) on chromosome 3q21 and the FAS gene on chromosome 10q24. On the other hand, epigenetic alterations have also been associated with the development of cervical cancer, such as aberrant DNA methylation patterns, which may contain points of relevance to guide treatment (23).

Vaccination

Three types of commercially available vaccines are known to reduce the incidence of cervical cancer since they protect against some of the most prevalent serotypes of the Human Papillomavirus, among which the following stand out: Cervarix bivalent (16,18), Gardasil tetravalent (6,11,16,18) and Gardasil nonvalent (6,11,16,18,31,33,45,52,58), which have been approved by the Food and Drug Administration (FDA), these prevent, but do not modify the ongoing infections, so that their administration is recommended in people who have not been exposed to this type of virus, therefore the importance of measures aimed at primary prevention is highlighted (24)(25)(26).

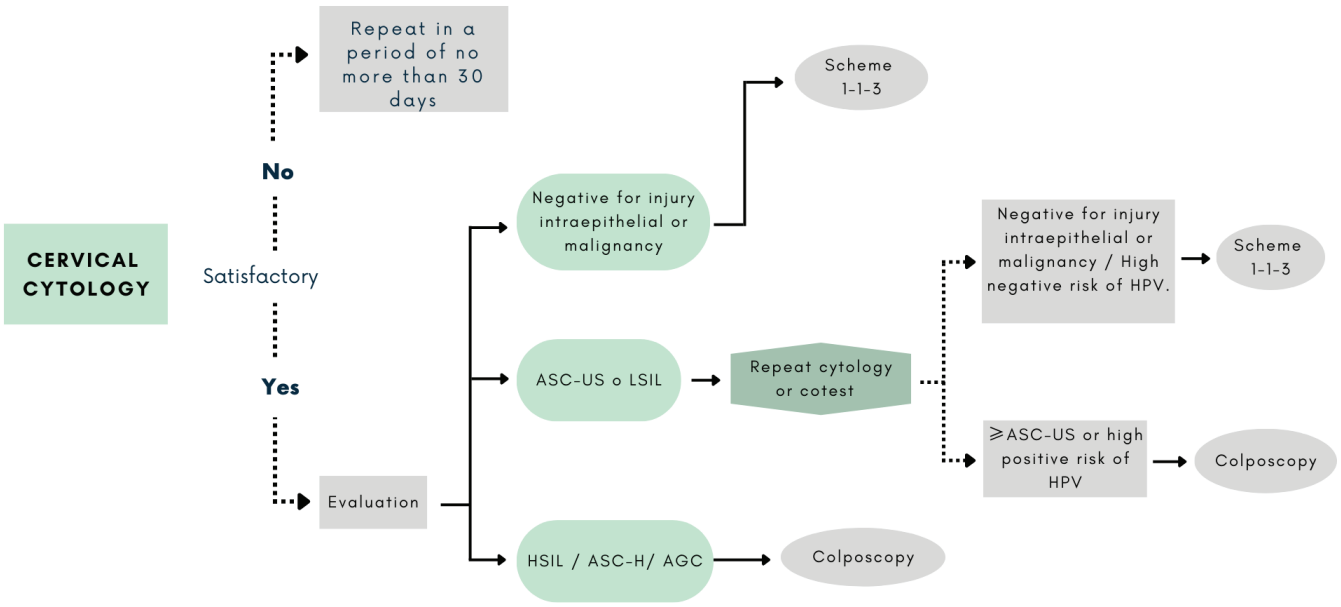
Histopathology

Among the most frequent histopathological types, epidermoid carcinoma is found with 70-75 %, which infiltrates less than 3 mm and has a surface extension < 7 mm, this in turn is subclassified into keratinizing and non-keratinizing, the second most frequent cancer is adenosquamous with 25 %, this is formed by glandular and squamous cells, the endocervical is the most common variant in adenocarcinoma; adenosquamous has been described more commonly in young women and is characteristically more aggressive than squamous cell cancer or adenocarcinoma (27) (28).

Screening

Screening has been recognized as a transcendental action for the reduction of mortality, this is performed by cytology or Papanicolaou, this was developed by Papanicolaou and Triut (1943), since then mortality has decreased by almost 75%; In developed countries it begins at the age of 21-29 years with a follow-up every 3 years, in Colombia the guide of precancerous lesions indicates the performance of cervical cytology from the age of 25 years, the HPV-DNA test begins at 30 years of age and ends at 65 years of age, on the other hand in women with hysterectomy for benign pathology and without a history of cervical disease, it is not recommended to continue with the screening (29) (30)(31)(32)(33). (**Figure 1**)

Figure 1. Diagnostic confirmation algorithm of atypical cervical cytology



ASC-US: Atypical squamous cells of uncertain significance; **LSIL**: Low-grade squamous intraepithelial lesions; **HPV**: Human Papillomavirus; **HSIL**: High-grade squamous intraepithelial lesions; **ASC-H**: Atypical squamous cells cannot exclude HSIL; **AGC**: Atypical glandular cells; **Cotest**: Citology + DNA for HPV; **Scheme 1-1-3**: Cytology every year for two consecutive years and If the result of both are negative, the next citology will be done after 3 years.

Clinic

In early stages the disease is usually asymptomatic, however the symptoms that may occur in women with cervical cancer are irregular, abundant vaginal bleeding and postcoital bleeding, after the tumor spreads to the pelvic cavity can invade bladder and rectum, generating symptoms such as pelvic or lumbar pain radiating to lower limbs, gastrointestinal and urinary symptoms,

due to compression; Some women may have watery, mucoid, purulent or foul-smelling vaginal discharge, which can be confused with cervicitis or vaginitis, however, symptoms and physical examination findings in the early stages of cervical cancer are rare, therefore cervical cytology screening is essential to detect premalignant lesions (34)(35)(36)(37) (**table 1**).

Table 1. FIGO Staging and classification TNM cervical cancer

TNM	Staging FIGO	Definition
Tx		The primary tumor cannot be evaluated
T0		No evidence of primary tumor
T1	I	Cervical carcinoma confined to the uterus
T1a	IA	Invasive carcinoma diagnosed by microscopy. With a maximum invasion depth of 5 mm
T1a1	IA1	Invasion of the stroma < 3 mm deep
T1a2	IA2	Stroma invasion ≥ 3mm and < 5 mm deep
T1b	IB	Invasive carcinoma, with a depth of ≥ 5 mm (greater than stage IA) limited lesion to the uterine cervix
T1b1	IB1	Invasive carcinoma ≥ 5 mm depth of stromal invasion and < 2 cm in the largest dimension
T1b2	IB2	Invasor carcinoma ≥ 2 cm and < 4 cm in the larger dimension
T1b3	IB3	Invasor carcinoma ≥ 4 cm in the larger dimension
T2	II	The carcinoma invades bevond the uterus, but has not spread over the lower third of the vagina or pelvic wall
T2a	IIA	Invasion limited to the upper two-thirds of the vagina without parametric invasion
T2a1	IIA1	Invasive carcinoma < 4 cm in the larger dimension
T2a2	IIA2	Invasive carcinoma ≥ 4 cm in the larger dimension
T2b	IIB	Parametric invasion, without invasion of the pelvic wall

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FIGO Stage

Currently the staging of cervical cancer is performed by the classification generated by the International Federation of Gynecology and Obstetrics (FIGO), in 2018 FIGO presented and published new criteria, through which greater clarity is achieved against the level of involvement, among the main changes include positivity in para-aortic and pelvic lymph nodes, in the initial stages an important modification was made since the lateral extension of the lesion was eliminated and focused mainly on the depth of stromal invasion. Another change that should be highlighted was the elimination of uterine corpus involvement since it did not affect prognosis or management (38) (**table 2**).

Table 2. FIGO Stage

T3a	IIIA	The carcinoma involves the lower third of the vagina without extension to the pelvic wall
T3b	IIIB	Extension to the pelvic wall and/or hydronephrosis or kidney failure
T3c	IIIC	Invasion of the pelvis and or para-aortic lymph nodes regardless of tumor size and extension (with notation r and p)*
T3c1	IIIC1	Metastasis to pelvic lymph nodes
T3c2	IIIC2	Metastasis to para-aortic lymph nodes
T4	IV	The carcinoma extends beyond the true pelvis or has involved the mucosa of the bladder or rectum (bullous edema is not enough to classify a tumor as T4)
	IVA	Tumor that invades adjacent pelvic organs
	IVB	Tumor that invades organs from a distance

*Add the notation with which the finding was made to assign the case to stage IIIC, notation r (images) and p (pathology). TNM: Tumor, Node, Metastases. FIGO: International Federation of Gynecology and Obstetrics.

«Cervical cancer is considered a public health problem, which predominantly affects low socioeconomic strata and women between 30 and 50 years of age.»

Treatment

According to the stage of the cancer indicated by FIGO, in addition to the individual factors in the woman, the type of treatment will be indicated, since this neoplasm occurs significantly in women under 45 years of age, for which the preservation of fertility is an important factor, in addition to the general state of health, age and others, which will define the choice of management (39). In the treatment of cervical cancer multiple physical, emotional, social, and economic side effects are known, therefore it is of great importance to carry out an integral approach aimed at reducing these effects (40) (41).

Among the treatments for cervical cancer are conization, brachytherapy, external beam radiotherapy, chemotherapy, trachelectomy and radical hysterectomy, the colposcopy report can guide the therapeutic decision since if it is reported as adequate it is possible to perform ablation or excision of the cervix, However, if on the other hand it is inadequate or recurrent CIN 2/3, excision should be performed, nevertheless who really guides the treatment is the FIGO staging since it establishes a classification based on the size of the tumor, the dissemination to lymph nodes and metastasis (42)(43)(44).

Discussion

Cervical cancer is considered a public health problem, which predominantly affects low socioeconomic strata and women between 30 and 50 years of age. Most national and international studies show a close relationship between the high mortality rates due to cervical cancer and developing countries, emphasizing health inequalities, as evidenced by the PAHO and the cervical cancer article published in the Lancet in 2019 (45)(46); where reference is made to the relevance of promotion and prevention strategies since, with an adequate implementation of these, the incidence of cervical cancer decreases, including in developing countries (47).

The existence of multiple important risk factors that condition HPV infection is recognized, as described in the article published by Villafuerte Reinante J et al. 2019 (9) and in the article of Medeiros R. 2020 (23) in which factors that influence the risk of progression of HPV infection to malignancy are highlighted, including: smoking and long-term oral contraceptive use, early pregnancy, multiparity, promiscuity and sexually transmitted infections that weaken the immune system and predispose to HPV infection.

HPV is strongly related to cervical cancer, since the presence of DNA of the virus has been demonstrated in cervical cancer cells, and a greater association has been described with HPV 18, therefore vaccination against HPV

has played a fundamental role, showing satisfactory results and positioning itself as one of the main primary prevention strategies, therefore, it is part of the Global Strategy for the Millennium Development Goals. It should be noted that the possibility of access to these interventions has increased, and they are available in 35 countries and the Americas; however, the coverage rates are still not sufficient, since they do not cover 80% of the vulnerable population (6)(48).

The acceptance of preventive measures such as vaccination is influenced by different factors, this is demonstrated in studies such as the one conducted in Bangladesh and Uganda where different factors that determine a better receptivity to strategies that impact on the reduction of cervical cancer are exposed, these include having received vaccination in childhood, having health insurance, greater utilization of medical care, having a health care provider as a source of information among others, therefore in environments of higher socioeconomic development tend to have better rates in terms of vaccination schedules compared to developing countries (49).

In relation to cytological findings, low-grade intraepithelial lesions (LEI) are the most prevalent, coinciding with several investigations such as the one published in 2018 by FIGO Revised Staging for cervical carcinoma where they mention the low-grade intraepithelial lesion as the most common in cytology performed, likewise, the Clinical Practice Guideline shows from a meta-analysis that 76.2% are low grade lesions LEI (CIN I) 54.3% are high grade lesions (CIN II - 3) and 62.2% of invasive cancer (50).

A study conducted in Turkey describes the relationship between oral contraceptives (OCs) for a period longer than 5 years and the presence of cervical cancer, although this association decreases 5 to 10 years after the interruption of the hormonal contraceptive, there are studies that indicate that the benefits of the use of these outweigh the risks, also in non-users of OCs this risk is equalized after 10 years after the abandonment of the method (14).

The present study emphasizes cervical cancer promotion and prevention measures and highlights the need for updated systematic review articles in order to provide complete information to optimize access to it.

Conclusion

Cervical cancer is a very common pathology with high mortality rates especially in developing countries, affecting mainly women of reproductive age, low socioeconomic strata, where Human Papilloma Virus is a major risk factor. It is a preventable virus through adequate education, information, and follow-up of precancerous lesions, so that public health strategies such as cervical cancer screening programs reduce morbidity and mortality, therefore health education, coverage in prevention and promotion programs, vaccination and performance of screening tests, remain the main pillars for the management of this pathology.

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