REVIEW ARTICLE

Challenges in screening of sexually transmitted viral infections of the female genital tract: Where do we stand? — A scoping review

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Abstract

Globally more than a million sexually transmitted infections occur daily, and over 53 000 [47,000-60,000] women aged 15 and over were living with human immunodeficiency virus / acquired immunodeficiency syndrome in Pakistan by the year 2020. This situation becomes graver when the sexually transmitted infections exist as co-infections while remaining undiagnosed or under-diagnosed. Additionally, herpetic or papillomavirus lesions are more recurrent, more extensive and have more serious consequences in human immunodeficiency virus-positive patients. Literature shows a dramatic increase in morbidity and mortality due to the occurrence of malignancies in genital co-infections. There is a key concern that every single adolescent female living in Pakistan is at a high risk of acquiring viral sexually transmitted infections along with malignancy of the cervix. As such, the health and future of this age group is already imperilled. Needless to mention that the practice of routine cervical screening and diagnostic laboratory services offered to a common woman in Pakistan have been less than satisfactory for decades. Therefore, to meet the minimum expectations regarding the Millennium Development Goals for sexual and reproductive health and rights 2030, it has now become imperative for the health sector to develop and implement scientific and community-based policies for comprehensive and multidisciplinary diagnostic strategies leading to early and effective management of viral sexually transmitted infections and subsequent neoplasia.

Keywords: Cervical cancer, STIs, Sexually transmitted infections, HIV, Human immunodeficiency virus), HPV, Human papilloma virus, HSV, Herpes simplex virus), Screening.

DOI: https://doi.org/10.47391/JPMA.4166

Introduction

Cervical cancer is the fourth most frequent malignancy among females and the seventh commonest malignancy overall, globally.[1] According to recent Globocan statistics, approximately 62.8 million women all over the world are at risk for developing cervical carcinoma with an annual number of reported cases and deaths being 569,847 and 311,365, respectively.[2] The prevalence of cervical malignancy has increased in Pakistan as almost 20 women develop cervical cancer every day, making it the third most common cancer in Pakistani women aged 15-44 years, and about 5,233 new cases per annum.[3] Though its incidence is rising with every passing year, cervical carcinoma is believed to be the most preventable cancer among the relevant human malignancies owing to the successful screening options available. In industrialised nations, there is a significant decrease in incidence and death rate of cervical cancer due to the implementation and broad coverage of cytology-based screening programmes.[4] Pakistan bears an increased burden of this carcinoma mainly due to late presentation and diagnosis, thus resulting in a poor survival rate.

Aetiology of Cervical Cancer

Smoking (3.4%), increased rate (3.8%) of total fertility in terms of live births per women, use of oral contraceptives (1.6%), age <17 years at first intercourse or first childbirth, multiparity, having multiple sex partners, obesity, weakened immune system, prolonged intrauterine device (IUD) use, low socioeconomic grade, subjection to diethylstilbestrol (DES) and family history of cervical cancer are some of the leading risk factors for the development of carcinoma of the cervix.[5] According to the United States Centres for Disease Control and the Prevention (CDC), the factors considered hazardous for the progress of cancer of cervix include low immunity, infections with human papilloma virus (HPV), human immunodeficiency virus human immunodeficiency virus (HIV), Chlamydia (C.) trachomatis and, most probably, herpes simplex virus (HSV), never or rarely screened cases and history of lower genital tract neoplasm (vaginal, vulvar or anal).[6]

Cervical cancer is considered to be the result of an already existing HPV infection of distinct cell populations at the squamocolumnar junction between endocervix and ectocervix. This leads to a cellular transformation from pre-cancer and then to an invasive cancer. Although the progression of cervical cancer is slow, the clinical course is

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rapid once the invasion has developed.[7]

Screening Services in Pakistan

Studies from Pakistan have highlighted that the increasing burden of cervical cancer is mainly attributed to its diagnosis at an advanced stage, lack of screening awareness and increased cost of treatment, thus resulting in poor survival rate. Mass screening programmes on the national level and ensuring quality public health education is therefore imperative to save the women from this cancer.[8] Fortunately, literature reveals that cervical carcinoma has a slow progression rate and because of its monocausal genesis, earlier detection in pre-cancerous stages can save many lives. This can be achieved by reinforcement of cytology-based programmes implemented decades ago and more efficient screening of HIV, HPV and HSV women aged 30 years or older. Cytology-based screening programmes have markedly reduced the incidence and mortality of cervical malignancy in the developed countries compared to the developing countries where such facilities are not freely available.[9] Screening analysis for women associated with this disease is too low in the developing countries due to barriers including limited knowledge about the disease, lack of awareness of preventable diseases, and non-availability of resources and encouragement from family and community.[10]

Cervical Cytology Classification Systems

The World Health Organisation (WHO) system for histological classification of dysplasia of the cervix includes mild, moderate or severe with a separate category of carcinoma in situ (CIS). The term cervical intraepithelial neoplasia (CIN) was presented to classify the cervical lesions into 3 stages; CIN-1 = mild dysplasia, CIN-2 = moderate dysplasia, and CIN-3 = severe dysplasia. The classical method of screening for these lesions is based on the cytological evaluation of smears.[11]

Another widely used method of classification is The Bethesda System (TBS) which evolved from 1991 till 2001 with the inclusion of HPV testing as a mandatory part of reporting.[12] In 2006-12, management guidelines for atypical cervical cytology were repeatedly upgraded by including high-risk HPV genotyping for triage and follow-up. In the latest 2014 TBS, further additions were made which include reporting of adequacy guidelines for special situations, inclusion of immunocytochemistry procedures for HPV detection, whereas in locales where HPV testing is not available, regular Papanicolaou (Pap) testing was declared as the primary screening method.[13] There is reasonable amount of data on Pap smear testing in Pakistan available, but literature on the updated (2014) TBS and its related data in the local population is hard to find in the recommended search engines.

Sexually Transmitted Infections (STIs)

The WHO defines STIs as Infections that "spread mainly by sexual contact, including vaginal anal and oral sex". More than 30 different bacteria, viruses and parasites have been reported to be transmitted through sexual contact; eight of these are related to a high incidence of STIs. Out of these eight, four are curable, including Trichomonas (T.) vaginalis, C. trachomatis, Treponema (Tr.) palladium and, Neisseria (N.) gonorrhoea, while four are incurable, including HIV, HSV-1/2, HPV, and Hepatitis B virus (HBV) and Hepatitis C virus (HCV). STIs rank among the top five diseases for which people seek clinical care all over the world and is a major cause of morbidity.[14] The WHO estimates that 1 million STIs are reported every day worldwide, with an increase in the number of aetiological agents, thus enhancing the severity of the disease. Approximately 357 million new cases of infectious diseases per annum occur globally and STIs comprise 1 in 4 of these infections, including chlamydia, gonorrhoea, syphilis and trichomoniasis. Up to 500 million females are estimated to have HSV infection and nearly 290 million females are concomitantly HPV-positive.[15] C. trachomatis and other viral STIs in combination, including various HPV genotypes, HIV and HSV-2 have been reported to play an aggressive role in causing cervical cancer.[16]

Human Papillomavirus (HPV)

HPV is an extremely prevalent sexually transmitted virus. This virus has 40 different genotypes that infect the genital mucosa; some of which are considered carcinogenic (high risk), including types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82.[17] Local studies from Pakistan have reported increased frequency of cervical cancer associated with the persistence of high-risk HPV infection.[18] The complete cycle of HPV carcinogenesis ranges from initial infection to persistent infection with a cellular transformation to precancerous lesions and then to invasive cancer, taking decades in most cases with a minimal latency period of about seven years.[19] Epidemiological studies over the years have concluded that there is a strong biological relationship between high-risk HPV and HSV-2 in the genesis of cervical cancer.

Herpes Simplex Virus (HSV)

HSV belongs to the herpes viridae family which includes HSV-1, HSV-2, Varicella (V.) zoster, cytomegalovirus, and Epstein Bar virus (EBV) etc. About 60-95% of mature humans are either carriers of herpes viruses or are affected by the related diseases which present in the host as latent infections and manifest depending upon the port of entry, condition of host's immune

system, and frequency of entries.[20] According to the latest WHO statistics, approximately 3.7 billion people aged <50 (67%) are infected by HSV-1 worldwide, and almost 417 million people aged 15-49 (11%) globally have HSV-2 infection. Around 70% of these oro-genital herpetic infections are asymptomatic. HSV-1 is usually related to orofacial diseases, while HSV-2 is by tradition associated with genital diseases.[1] Lesion location, however, is not necessarily indicative of the viral type, as HSV-1 is associated with genital infections more often than HSV-2 in some unique subpopulations.[21]

HSV epidemiology seems to be progressing in Asia, hence, there is a need for extended seroprevalence monitoring and aetiological surveillance of genitourinary diseases, especially genital herpes.[22] HSV-1 is a ruling cause of genital herpes in developed areas, specifically in females who are aged <25 years, and is reported during childhood in societies with low socioeconomic status. The incidence of positive HSV-2 deoxyribonucleic acid (DNA) serology, and increased viral load causes progression of cervicitis to CIN or frank cervical malignancy.[23]

Irrespective of the serotype of HSV, the association of an increased risk of cervical carcinoma in women with antibodies against HSV-2 has been suggested by several studies. The mechanism of action of HSV-2 in causing CIN/cancer is the "Hit and Run" hypothesis which states that HSV-2 plays role in some phase of cervical carcinogenesis and is not involved in the retention of HSV viral genes, therefore HSV-2 is not detected constantly in the cervical biopsies of CIN/cancer, suggesting that HSV is essential for the early transformation of cells and not for its progression. Other theories postulate HSV-2 as a beginner for cervical cancer and HPV continues its way to carcinogenesis.[24]

Human Immunodeficiency Virus (HIV)

With each passing decade, a 10-fold increase in HIV burden is seen in Pakistan, including it among 12 countries in the Asia-Pacific region where more than 10% of people living with HIV are expected by 2030.[1] Individuals infected with HIV have shown a dramatic increase in mortality due to HIV-associated malignancies, thus causing an increasing number of overall deaths among persons with HIV infection.[25] A local report from Pakistan reveals HIV prevalence as 0.6% among female sex workers and <0.1% in females >15 years of age.[18] The reported data may represent the tip of the iceberg as HIV testing and registration is extremely below par in Pakistan. Prathima et al. showed abnormal cervical cytology in 30% of HIV-positive women, out of which 10% had high-grade squamous intraepithelial lesions (HSILs), 15% had low-grade squamous intraepithelial lesions (LSILs) and 5% had atypical squamous cells of undetermined significance (ASCUS). Also, HPV infection was detected in all women who had HSIL.[26] Similar results were seen in an African study which showed increased HSIL (34%) in HIV-positive females.[27]

Concomitant HIV-HPV-HSV Co-infections and Cervical Neoplasia

Women who are infected with HIV have been reported to have the highest occurrence and persistence of HPV infection and have a greater risk for abnormal Pap smears as well as cervical cancer.[28]

Furthermore, genital HSV infection has traditionally been identified as a risk factor in HIV acquisition. It is postulated that HSV-2 shedding in genital tract infection gives rise to increased risk of HIV acquisition.[29] Increased susceptibility is because of increased ulceration and inflammation present in the skin and mucosa of persons who are HSV-2-infected. These ulcerations are linked with the increased entry of cluster of differentiation-4 (CD4)-bearing lymphocytes, therefore a huge amount of target cells for HIV attachment and entry are present in the genital tract of persons infected with HSV-2 infection. Migration of activated lymphocytes to the lesions of genital herpes results in an increased local HIV replication on mucosal surfaces.[30] Previously it was thought that HSV-2 infections might induce mutations and oncogenesis in HPV-infected cervical cells, therefore it seems difficult to understand from previous research whether HSV-2 is a true causative factor or if the relationship between HSV-2 antibodies and invasive cervical carcinoma is due to the residual effect of HPV infection or other STIs.[31] According to sero-epidemiological studies, HSV2 infection along with HPV has a strong association with CIN and cervical cancer compared to the healthy women.[32,33]

Data related to the prevalence of cervical carcinoma in HIV-positive females is hard to find in literature from Pakistan. There are ample reports related to HPV and cervical carcinogenesis, but no study has yet tried to relate to the isolated HSV infection or concomitant HIV-HPV-HSV infections and their association with the abnormal Pap testing in Pakistani females. The current review was planned to ascertain the carcinogenic potential of cervicovaginal viral co-infections in Pakistani women, and to explore and overcome the challenges related to screening practices in this part of the world.

Materials and Methods

Study protocol: The scoping review-based analysis was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[34]

Search strategy: A search of published works was done using PubMed, Scopus, Web of Science, and Cochrane Library databases for relevant publications from January 1989 to July 2021. The medical subject headings (MeSH) key words used in the search were "Cervical cancer", "STIs (sexually transmitted infections)", "HPV (Human papillomavirus)", "HIV (Human immunodeficiency virus)", "HSV (Herpes simplex virus)", "Screening" and "Cytology". The reference lists of the articles were also searched to identify missed studies. No restriction was applied in terms of the time of publication or language. To facilitate the screening process of studies from online databases, all search results were downloaded into EndNote X8.

Inclusion and exclusion criteria: Full-text hospital- and clinic-based studies, as well as review articles, were considered where the cytological analysis was carried out by pathologists between January 1989 and July 2021. Studies considering women of age group 18-45 years presenting at least 2 days after the menstrual cycle with vaginal discharge were included. Pregnant women, females using any type of contraceptives, or diagnosed cases of any type of genital tract carcinoma, especially cervical carcinoma, were excluded.

Data extraction: Information was extracted from the shortlisted studies, such as first author's name, year of publication, the geographical region in which the study was carried out, duration of the study, sample size, gender and age of the studied sample, the prevalence rate of cervical cancer, sampling method, laboratory techniques used, any statistically significant results found and conclusions drawn by the authors regarding the efficacy of different laboratory techniques in the early diagnosis of cervical carcinoma.

STI Burden in Pakistan

In Pakistan, STIs are evolving as a foremost health problem. A study in 2008 showed a prevalence of 4.4% of one of the 5 STIs in the general population of 6 main cities of Pakistan. The incidence rate of STIs is higher as majority of the people with STIs do not present to physicians due to social, moral, cultural or educational restraints.[35] There is currently no appropriate STI reporting system in Pakistan and, hence, there is a scarcity of epidemiological data available that can be accessed through institutional and regional registries, which may not be true representative of the burden. According to the Ministry of Health, Islamabad, the provision for STIs in Pakistan is burdened with mistreatment and death from mal-practised strategies, thus effective counselling, follow-up, and testing for asymptomatic infections should be done. Only 2.6% of women actually take benefit of Pap screening services and that too, once in life. There is a deep concern that in Pakistan, each young adolescent girl is at risk of acquiring viral STIs along with carcinoma of the cervix, depicting the dark future and bad health of this generation.[36] Also, drug resistance for this cancer is becoming a grave health concern for decades, proving to be the leading cause of female mortality in Pakistan. Females infected with HIV have been reported to have the highest incidence and persistence of HPV infection and have a high risk for abnormal Pap smears as well as cervical cancer.[37]

According to the National Health and Nutrition Examination Survey (NHANES), HSV prevalence was found to be increased in females having any type of cancer. In the same way, a higher risk of positivity of HSV-2 infection has been discovered in females with cervical dysplasia and carcinoma in situ.[25] It has been reported by several studies that an increased risk of cervical cancer was found in the female population who had antibodies against HSV-2. A Latin American case-control study on 766 histologically diagnosed cases of cervical carcinoma revealed that females with positive HSV-2 have a 60% risk of cervical carcinoma compared to females with seronegative HSV-2. A study from Nepal reported HSV-2 in 11% cases of CIN I, 33% cases of CIN III and 40% cases of carcinoma cervix with a subtle increasing level of antibody.[38] In India, the detection of HSV was higher than HPV in cervical smears and was strongly associated with squamous intraepithelial lesion and carcinoma.[39] In contrast, studies from China[40] and Jamaica[41] reported no such relation between concomitant HSV-HPV infection and cervical neoplasia. These variabilities in data reporting may be attributed to the differences in the diagnostic methods employed and the presence or absence of symptomatic cervical infections in females for sampling purpose. The US Federal Drug Agency (FDA) recommends type-specific antibody testing during the latent or earliest period of infection, followed by a molecular analysis, including nucleic acid amplification tests (NAATs). Polymerase chain reaction (PCR) tests are now FDA-cleared for testing of anogenital specimens for HSV-1 and HSV-2.[42] Pakistan, on the other hand, completely lacks even basic HSV testing services on serology for routine cases with cervical infections and/or neoplasia. This has led to scant or underreported data regarding a potential link between HSV and cervical neoplasia in the local population.

A recent French study reported higher prevalence of high-risk HPV types in HIV-positive females compared to HIV-negative women (77% vs 55%, p=0.014). In addition, high-risk HPV infections were found to be more prevalent in HIV-positive women (55% vs 33%, p=0.03).[43] A study from lower middle income country (LMIC) Nigeria in 2014 revealed HSV-2 prevalence 73% among women aged 15-60

years, and among these women 54% presented with cervical inflammation, 10.5% with squamous intraepithelial lesions (SILs) and 50% of them were HIV-positive, thus concluding that HSV-2 infection markedly increased the risk of HIV and HPV infections by causing severe inflammation of the cervix.[44] Another recent Nigerian study reported increased prevalence of HSV-2 infection in HIV-positive women (75% vs 45%) and more SIL in HIV patients (15% vs 7%) compared to HIV-negative women. Moreover, higher incidence of SIL (54%) was seen in triple positive (HPV+, HSV-2+, EBV+) HIV patients.[45] A study determined the association between HPV and abnormal cytological findings in HIV-positive females, and showed high-grade dysplasia (most commonly CIN II/III and invasive squamous cell carcinoma [SCC]) in 97% of the cases. Moreover, significant association was found between high-risk HPV and cervical precancerous lesions ($p<0.001$).[46]

No study has yet been reported from Pakistan on the association between cervical cytological findings and the concomitant viral burden in the local female population. This scarcity reflects lack of focus and priority of the health sector and the healthcare professionals, especially the gynaecologists and infectious diseases personnel, in considering the burden of cervical neoplasia in relation to the dual or triple viral testing in females.

As far as the evolution in practice of cervical screening is concerned, Women's Interagency HIV Study (WIHS) explained that Pap smear screening test should be done after every 6 months in case of abnormal cytology results and invasive cervical carcinoma in HIV-positive cases. During their 5-year follow-up results, almost 73% of HIV-positive females had at least one abnormal Pap smear compared to 42% in HIV-negative females.[47]

Similarly, the New York State Department of Health (NYSDOH) AIDS Institute Medical Care Criteria Committee updated its guidelines regarding cervical screening for dysplasia and cancer in patients with HIV by incorporating current, evidence-based recommendations for HPV vaccination, cervical cytological screening, and follow-up of abnormal test results. These comprehensive guidelines also address the ongoing need for diligence in the early identification and treatment of precancerous and cancerous lesions.[48]

Despite many awareness and prevention programmes launched in Pakistan over the years, the incidence of HIV- and HPV-induced cervical cancer is still rising day by day.[18] Policy guidelines need to be updated and implemented. HPV-16 and 18 are considered the two vaccine-preventable types, and contribute to 70% of all cervical cancer cases. Vaccination of young women before marriage could be the most effective preventive measure against cervical cancer in Pakistan. The WHO Cervical Cancer Elimination Modelling Consortium (CCEMC) recommends that if 90% coverage of HPV vaccination of girls by age 15 could be carried out, along with 70% coverage of screening, followed by 90% application of treatment, then cervical malignancy could be eradicated globally by 2030. Therefore, multiple and synchronised policies should be made to increase the HPV vaccination status from 15% to 90% in order to reach this target by 2030.[49] For the primary prevention against HPV, cervarix and gardasil are the available vaccines in Pakistan.[50] However, the utility of this vaccination is reported to be negligible as no formal HPV vaccination and immunisation programme exists in Pakistan.

Pakistan is a Muslim country where basic knowledge about STIs is minimal. Surveillance plans are limited and commonly ignored, thus resulting in lack of knowledge regarding authentic incidence of STIs. Latest diagnostic techniques are not usually implemented, and there is insufficient standardisation of medical measures. A major challenge observed is the difficulty in attaining STI prevalence facts from women. Majority of Pakistani women consult family elders, local 'hakeems', quacks or 'daies' instead of gynaecologists and professional healthcare providers because of proximity and cost-effectiveness. Family and spousal pressures and strong society opinion halt their access to male physicians. They are frequently busy in domestic tasks and are fully dependent on men with restricted decisive control in their sexual relationships. Moreover, religious and social beliefs oppose open discussion of sexual matters. The low socio-economic status of females restricts their economic choices, which may result in substitute sex for money or other forms of financial support. Inadequate healthcare services stop the adequate prevention and management of STIs. Long-lasting misunderstandings contribute to the nationwide negligence of STI treatment and prevention.[51,52] Therefore, the variations in STI prevalence may be credited to the dispute in setups, social beliefs and level of awareness that build the strong bases for a persistent and progressive course of cervico-vaginal infections, leading to dysplasia and preceding malignancy.

Recommendations and Conclusion

Health systems around the globe are striving to achieve 2030 Sustainable Development Goals (SDGs) stating, "By 2030, the universal approach will be developed for sexual and reproductive healthcare services, including family planning, information and education and the incorporation of reproductive health into national plans

and projects". Pakistan is one of the countries with the highest maternal and neonatal mortality rates, thus calling for expeditious strategic planning to improve women's health especially in underprivileged sectors.

The elements that regulate the health activities in Pakistan can be seen in numerous physical, socioeconomic, educational, and political circumstances. Therefore, robust health education and awareness regarding viral STIs screening and their timely diagnosis should be emphasised for control of the transmission. There is an intense need to encourage safe sexual practices and STI-associated counselling without a fear of social taboos. Many women at the time of HIV detection are older and others already have an infection with HPV or cervical carcinoma, therefore in these cases expanding of the plans should be carried out to accelerate quick diagnosis and to engage patients with repeated cervical testing. In addition, regular and mandatory counselling and educational interventions in STI clinics for vulnerable groups must be ensured in public as well as all private health sectors in Pakistan.

Regular screening by Pap test for females with HIV and implementation of vaccination for HPV should be included as an interpretative part of prevention. Licensing of HPV vaccine, robust relevant health awareness campaigns and inclusion in the national immunisation programmes is the dire need of the time. The efficacy of vaccination is directly associated with the whole coverage of the community due to herd immunity, and the number of doses given, like two or three doses in accordance with age. Therefore, the extensive vaccine efficacy against cervical carcinoma among females vaccinated at age <20 years should be encouraged. Thus, vaccination combined with screening potentially eliminates the incidence of cervical cancer.

Also, serological and molecular categorisation of different viral agents causing STIs may be carried out in routine for prospective registries. In other words, the ultimate factual, scientific and compassionate outcome is to introduce an improved way for early diagnosis and more effective management of STIs that will eventually help to minimise the healthcare burden related to the disease.

Disclaimer: None.

Conflict of Interest: None.

Source of Funding: None.

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