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Enhancing Early Detection of Cervical Cancer: The Role of HPV and STI Screening in Female Patients

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Abstract: ***Background: High - risk human papillomaviruses (HPV) infection has been the most common viral sexually transmitted infection worldwide. Moreover, it is a necessary factor for the development of cervical cancer. Several studies have been carried out that screen HPV and other sexually transmitted infections (STI) s occurring in patients at the same time. Timely screening can help early diagnosis of pre - cancerous lesions and assist in prompt treatment to reduce mortality in such patients. In many countries such as UK, primary cervical cancer screening is based on hrHPV testing, with further risk stratification to patients who may need cytology or colposcopy based on results of hrHPV testing. Objectives: The objective of the present study was to screen Indian women for the presence of high - risk HPV (hrHPV) for the early diagnosis of cervical cancer. Some women were additionally screened for STIs. We also aimed to establish an association between the presence of HPV and STI. Study design: A total of 40 women aged 20 - 67 years participated in this study. Cervical and or vaginal swabs were collected in liquid - based cytology containers. The samples were tested for fourteen HPV genotypes by USFDA - approved Cobas HPV test. Out of these 40 women 26 were also tested for STI panel. Result: All women participants were screened for hr - HPV. A total 65% of the study population underwent both the HPV test and the STI test.7.5% of total women were positive for hrHPV.30.76% of women tested positive for Ureaplasma and Gardnerella vaginalis in the STI panel. Some women also showed simultaneous presence of STI and hrHPV. Conclusions: The results of this study will help in better and early diagnosis of women at risk of cervical cancer. The detection of HPV and STI present simultaneously can further help in establishing the role of these two conditions in the development of cervical cancer. Such studies are an encouragement to the HPV elimination programme and vaccination drive that has taken an impetus in recent times in India.***

Keywords: HPV screening, cervical cancer, sexually transmitted infections, early diagnosis, vaccination drive.

1. Introduction

The Human Papilloma Virus is a small non - enveloped, double - stranded DNA virus that infects the skin and mucosal cells. It is reported to be one of the most common viral sexually transmitted viruses, whose persistent and prolonged infections may eventually lead to cervical cancer. The association of the etiology of cervical cancer with HPV has been discovered long back in the 1980s and since then several tests have been developed and evolved to identify its presence. (1) worldwide, cervical cancer is the fourth most common cancer with 6, 04, 127 new cases and 3, 41, 831 deaths reported annually. (2) In India too the prevalence of cervical cancer is very high. It is the second most common cancer in Indian women with 1, 23, 907 new cases and 77, 348 deaths reported per year. (2)

With such high prevalence, the World Health Organization (WHO) is already on its toes with multiple strategies for the screening of HPV as it sets the stone rolling for the elimination of cervical cancer to begin in 2030. Major advances in HPV testing and increased span of HPV testing implementation even in low - and - middle - income countries around the world is a big step in the elimination program. Persistent infection of the lower genital tract of women by one of about 15 high - risk HPV (hrHPV)

types, happens to be the necessary cause of cervical cancer. It is noteworthy that 80% of the women will acquire at least one of the fifteen hrHPV infections. The reason is the ease of transmission and ubiquitous nature of the virus. Only one - tenth of such infections can become persistent and may further develop lesions that may result in a pre - cancerous state. (3) Furthermore, HPV is not only associated with cervical cancer but several other cancers may arise due to HPV infection. The hrHPVs lead to cancers such as cervical, vulvar, vaginal, anal, penile, head and neck, oral cavity, and larynx. (1) HPV infection frequency differs according to the anatomical site, for example, higher prevalence is shown in the anogenital than in the oral region. (4)

In countries like India, the occurrence of cervical cancer has been reported to be common in the age group of 15 - 44 years. However, the diagnosis is at the highest rate only in women belonging to the age group of 55 to 59 years. The late diagnosis is a major reason for the increased rate of mortality in HPV infections. According to a study, only 19% of the population in low - middle income countries is targeted for HPV screening as compared to 63% in the developed countries. (5)

From Pap smear tests to the current screening methods for HPV, there has been a major transformation in the screening techniques that have been possible owing to insights into the pathogenesis of the disease and incessant research in this field. The current screening techniques include cytology evaluation, visual inspection tests, HPV testing, co - testing and the use of some protein biomarkers and next - generation sequencing (NGS) - based tests for integration of the viral genome. (2) With more than 6 lakh cases of cervical cases annually, prevention of HPV infection and early detection of the lesions are of utmost importance. HPV vaccination is another important strategy in the elimination of this cancer.

(2)

Currently around 226 HPV genotypes have been identified and more are on their way due to continuous research in this field. (6) It is important to understand that not all HPV genotypes are carcinogenic. The International Agency for Research on Cancer (IARC - WHO) has classified the genotypes concerning carcinogenicity. According to them, genotypes 6 and 11 are low - risk hrHPV and they do not cause cancer. There are three groups in hrHPV genotypes. Group 1 comprises the genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 and is denoted as high - risk carcinogenic. Group 2A consists of HPV68 and is denoted as probably carcinogenic while the HPV types 26, 30, 34, 53, 66, 67, 69, 70, 73, 82, 85, and 97 are classified as possibly carcinogenic and fall under Group 2B. (1)

Considering the high prevalence of HPV worldwide and in India, and the expensive screening strategies, we decided to carry out HPV screening in some patients at the Cama and Albless Hospital in Mumbai, Maharashtra. Our objective was to use this screening as a diagnostic tool for identifying the carcinogenic traits in the patients as a preventive measure against developing cervical cancer.

2. Methodology

Study population
The present study included female patients who visited the Cama and Albless Hospital in Mumbai, Maharashtra.40 women were included in the study as they complained about the symptoms such as cervical itching, irritation, bleeding, and frequent white discharge. Considering their symptoms, the doctors prescribed the test for HrHPV or STI panel. Doctors prescribed both tests for some patients.

The patients were selected based on the inclusion criteria that all were above 20 years of age and showed the above - mentioned signs and symptoms. Women under 20 years of age were excluded from the study. The same swab was used for both the tests HPV screening and the STI panel screening.

Sample collection:
The samples were collected from all 40 women was a cervical/vaginal swab that was immediately placed in the liquid - based cytology container and sent to AyuGen Biosciences Pvt. Ltd, Pune for testing.

Test procedure:
Detection: The HPV test for detecting the presence of hr - HPV is a UFDA - approved Cobas HPV test. The method is based on proprietary Taqman Real - Time PCR chemistry and is processed on a fully automated Roche - Cobas 4800 system. Being one of the very few tests that have received FDA approval, this test has undergone rigorous clinical validation and has more than 50 publications all over the world to its credit. The test contains primers separately for 1) hrHPV 16, 2) hrHPV 18 and 3) a combined pool to detect hrHPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. The test help in detecting clinically significant HPV infection and whether it is HPV type is 16 or 18 or the 12 other high risk types.

For the STI test, we used multiplex real - time PCR using Taqman technology where we used organism - specific primer to detect specific organisms. The STI panel covered in the test involves the following organisms: *Chlamydia trachomatis, Neisseria gonorrhoeae, Mycoplasma genitalium, Trichomonas vaginalis, Ureaplasma urealyticum/ parvum, Gardnerella vaginalis, Herpes simplex virus 1/2.*

3. Results

The age of all the women who participated in the study ranged from a minimum of 20 years to a maximum of 67. The mean age was 41.9 years.

All 40 women were prescribed by the doctors to take the HPV test, while 26 women also took the STI test. Hence, a total of 65% of the study population underwent both the HPV test and the STI test.

We noted the baseline characteristics of the 40 women considered for our study. In the HPV testing study, 40 women were tested and only three tested positive for hrHPV. Only 7.5% of total women were positive. The distribution was one woman (2.5%) tested positive for hrHPV - 18, while 5% i. e.2 women showed positive results for Other 12 hrHPV. None of them tested positive for the HPV - 16 genotype. The results are depicted in Table no.1.

From the STI panel that we used in 26 women, we got some interesting findings. The overall results in the STI panel showed that in 26 women the highest infections were reported with *Ureaplasma urealyticum/parvum*. A total of 13 women out of 26 (50%) tested positive for one or more than one microorganism in the STI panel. Further analysis shows that 8 women out of 26 (30.76%) who took the STI test tested positive for both Ureaplasma and *Gardnerella vaginalis*.4 women out of 26 (15.38%) tested positive for *Ureaplasma* only while only 1 woman among the 26 (3.84%) showed positive results only for *Trichomonas*. Out of the 8 women who tested positive for both Ureaplasma and *Gardnerella*, two women also tested positive for hrHPV (one was positive for other hrHPV and one for hrHPV - 18). The number of women testing positive for the STI panel is given in detail in Table No 2.

Table 1: Results of HPV testing

Test Particulars	Number of women	Percentage (%)
Total number of women for HPV test	40	100
Positive for hrHPV - 16	0	0
Positive for hrHPV - 18	1	2.5
Positive for other hrHPV	2	5

Table 2: Results of STI testing

Test Particulars	Number of women	Percentage (%)
Total women tested for STI panel	26	100
Positive for *Ureaplasma urealyticum/ parvum* and *Gardnerella vaginalis*	8	30.76
Positive for *Ureaplasma urealyticum/ parvum*	4	15.38
Positive for *Trichomonas vaginalis*	1	3.84

4. Discussion

Sexually transmitted diseases are very common worldwide. Many countries show a high prevalence of several STIs. At the same time, HPV infections which if occur persistently can be a gateway to cervical cancer are also highly prevalent. With the co - occurrence of HPV and other STIs in women, our study was designed to primarily detect the presence of hrHPV and in some women from this group we screened for STI after physically examining the signs and symptoms reported by the women under the study. All the women included in the current screening procedure were the patients who visited the outpatient department of Cama And Albless Hospital in Mumbai.

In the current study, the occurrence of hrHPV - 18 was reported in 2.5% of participant women, while other hrHPV was reported in 5% of the study population. This screening can be a warning for predicting the possibility of cervical cancer in these women and doctors can prescribe further investigations. ACS now (2020 guidelines) recommends cervical cancer screening with an HPV test alone every 5 years, HPV/Pap cotest every 5 years (acceptable) and Pap test every 3 years (acceptable) for everyone with a cervix from age 25 until age 65. For females above 65 years of age no screening if a series of prior tests were normal.
The coinfections of HPV and STI have been studied previously in different research groups. (7, 8) and the existence is common. Similar findings were reported in this particular study. Out of the 40 women who tested for high - risk HPV, 26 women were prescribed to take the STI panel test additionally. Our HPV genotyping was mainly focused on hrHPV - 16 and hrHPV - 18 and some other hrHPV genotypes as they are highly predictive of cancer. Similarly, the STI panel included the most common microorganisms associated with sexually transmitted diseases of non - HPV nature. Some previous studies have reported an association between hr - HPV and other STIs with cervical cancer. (9, 10) Our findings go hand in hand with the earlier studies. Out of the 8 patients who tested positive for *Ureaplasma urealyticum/parvum* and *Gardnerella vaginalis, one woman tested positive for* other hrHPV and one woman showed positive results for hrHPV - 18.

The high occurrence of *Ureaplasma urealyticum/parvum* and *Gardnerella vaginalis* is similar to the results obtained in another study of similar nature that shows around 60% prevalence of coinfection of these two species. (11) *Ureaplasma and Gardnerella* along with many other bacteria are present in the commensal flora of the genital tract. (12) Any disturbance in the vaginal ecosystem results in the replacement of the lactobacilli that are most common in the vaginal ecosystem by an abnormally high number of bacteria such as *Ureaplasma and Gardnerella*, that may eventually cause an infection. (13)

This study can be considered as a contribution to establishing an association between hrHPV and the simultaneous presence of STI as a role in developing cervical cancer in India. The mechanisms involved coinfections of hrHP and STI have been put forth by researchers. One such mechanism may be the interaction between HPV and the other microbes present at the vaginal site that may act as an enhancer of HPV replication and even speed up the development of cancer. This needs to be further investigated with larger clinical studies.

This demonstration study, though very limited in sample size, shows that a screening programme using simple sample collection techniques can be used in the public institutions like Cama and Albless Hospital with minimal requirement of manpower and training. Public institutions in India are overburdened with gynaecological patients. Performing visual inspection by acetic acid in public institutions, though very cost effective, can be challenging since it requires time and skilled manpower. The method itself has limitations of subjective variation and much lower sensitivity compared to HPV testing. But if an accurate HPV test like Cobas hrHPV test if made available and affordable to the patients in public institutions can significantly help in reducing overall cost and resources in managing such patients. If available at free of cost this can be an opportunity to screen women that are vising the public hospitals. Identifying high risk women in time can help prevent the disease development to herself and also prevent the spread of the infection to others.

5. Review of Literature

According to National Cancer Institute the dual - stain test, studied for over a decade, detects p16 and Ki - 67 proteins in cervical cells, indicating HPV infection and abnormal cell growth. In the study, 46% of women had a positive dual - stain result, while 51% had an abnormal Pap test. The test proved more predictive of cervical precancer risk over five years than the Pap test. Women with a positive dual stain result had a higher risk of developing precancer, while those with a negative result had a lower risk compared to a normal Pap test. These findings highlight the test's potential for improving early detection and risk assessment. The findings suggest that HPV - positive women with a positive dual stain test result should get a biopsy to check for cervical precancer or cancer, the study authors concluded, whereas those with a negative result can safely wait 3 years before getting screened again. On March 11, 2020, the Food and Drug Administration (FDA) approved the first dual - stain test for women who have tested positive for HPV. The test, called CINtec® PLUS Cytology, is used to help doctors decide if an HPV - positive woman should have a biopsy to look for cervical precancer or cancer.

A Swedish trial found that HPV - based cervical screening reduced invasive cervical cancer risk more effectively than cytology - based screening. Women invited to HPV screening had a 17% lower risk, while participants had a 28% lower risk over eight years. HPV - negative women had significantly reduced cancer risk compared to those with normal cytology results. Despite increased colposcopy referrals, HPV - based screening proved more effective in real - world prevention. HPV - based screening has proven to be more effective in preventing invasive cervical cancer compared to cytology - based methods. While the initial implementation led to a higher demand for colposcopy and histopathology resources, this burden is expected to decline in subsequent screening rounds as the prevalence peak subsides. Additionally, ongoing HPV vaccination programs and revised screening protocols that exclude low - risk HPV types will further reduce resource demands. Despite some study limitations,

including randomization imbalance and restricted HPV genotyping, the findings emphasize the need for updated European guidelines on managing HPV - positive cases to optimize screening effectiveness. (14)

6. Conclusion

The results of this study will help for better and early diagnosis of women for cervical cancer. The detection of HPV and STI present simultaneously can further help in establishing the role of these two conditions in the development of cervical cancer. Screening using standardized, accurate and automated HPV testing must be encouraged for the cervical cancer elimination programme being advocated in recent times in India. The recommended age limit for cervical cancer screening has been consistent across different guidelines over the years. But there are current efforts to study the age limit more because it's an area where we have less data.

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