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DECTECTION OF HBV DNA IN PATIENTS UNDERGOING CERVICAL SWAB TESTS FOR HPV DNA TESTING

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Abstract:

Background: At international level, cancer cervix has created a big health issue. In incidence & mortality, it is termed as the most commonly occurring female malignancy. Many factors are involved in cancer cervix in which persistent infection is most popular along with one of (HPV) high risk types. By early identification & frequent screening, its mortality & morbidity can be minimized. In recent years, many researches have been performed to find out better tests for screening for pre-invasive disease of cervix cancer to have better prognosis & early intervention. To give a contrast of sensitivity of PAP test & HPV DNA test for screening pre-invasive disease of the cancer cervix was the major objective of this research.

Methods: Hundred females were from those who were attending Services Hospital Lahore & Punjab Employees Social Security Institute Lahore Gynaecology Department for knowing the reasons instead of cancer cervix were taken to Pap smear. Moreover, cervical swab for HPV +ve were made to be subjected to cervical punch biopsy, VIA test & colposcopy were taken of aceto-DNA testing on the identical setting. The cases having HSIL, whitening of cervix or any other abnormality were also observed. The cases with LSIL or ASCUS were re-smeared right after a period of three to six months in case of colposcopy, persistent or progressive pathology& punch biopsy were taken from areas which were acetowhite.

Results: The cases were observed as: 21 percent i.e. twenty-one cases were found HPV +ve & 66 percent i.e. sixty-six cases were +ve for intraepithelial lesions i.e. 11 percent HSIL, 37 percent ASCUS & 18 percent LSIL along with re-smearing. The number of cases were three persistent ASCUS 8.1 percent & five LSIL cases i.e. 27.78 percent. Biopsies & colposcopy done have been taken from ten HSIL cases i.e. 90.1 percent, three ASCUS i.e. 8.1 percent, five LSIL i.e. 27.8 percent & 10 HPV +ve cases i.e. 62.5 percent. Along with important relation among HPVDNA positivity, colposcopy findings & abnormal cytology observation was made. Four were CIN II, 14 were CIN I & biopsies were 18.

Conclusions: There is a +ve link between HPV-DNA positivity & HSIL. Pap smear is also a less costly & most easy technique for screening. Moreover, as a technique for screening HPV-DNA test is less sensitive than cytology.

Keywords: *Screening of cancer cervix, Pre-invasive disease of the cervix, HPV-DNA.*

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INTRODUCTION:

Cancer cervix comprises a big health issue. Both in mortality & incidence, it has been termed now as the 4th commonly occurring female malignancy. Almost 87 percent cases in under developed countries & 80 percent in developing countries, cervical cancer deaths are occurring [1]. The possible reasons could be low socioeconomic status, long term use of contraceptives, smoking, immunosuppression, sexual partners, early sexual activity & high parity. Cervical cancer has some best chance for treatment & prevention in the pre invasive stage if it is diagnosed early in all known kinds of cancer [2].

A number of countries have implemented screening for cervical cancer & it was initiated in 1960's & it has led to minimizing of cervical cancer. The maximum screening method must diagnose the cervical cancer precursors which are supposed to grow into invasive cancers i.e. increasing the advantages of screening. It avoids the identification & unnecessary cure of transient HPV infection [3]. It can remove the identification & unnecessary cure of temporary HPV infection along with its linked benign lesions which are not supposed to be made cancerous i.e. reducing the harms associated with respect to screening. The process of screening is performed by cytology-based screening which is Pap test, colposcopy examination, visual inspection of aceto-white cervix i.e. V.I.A, HPV based screening [4].

In the years before 1980, American Cancer Society i.e. ACS, recommended a Pap smear test as a part of check-up at regular intervals. Pap smears along with cervical cytology were preferred annually for women above the age of twenty years from 1980 up to 1987. A method known as liquid-based cytology L.B.C, has been recommended first time by (FDA) American Food and Drug Administration. It is approved as a technique for cervical screening test in the year 1996. Moreover, it is allowed simultaneous HPV screening but it has an issue that it is not yet accessible in developing countries [5].

ACS i.e. American Cancer Society in the year 2002, first time guideline for early identification of cervical cancer utilized (HPV) DNA testing. During the years 1980's, HPV was observed to be more significant causative agent for cervical cancer along with almost hundred percent of cervical cancer cases which were tested +ve for HPV [6].
International Agency for Research on Cancer i.e. (IARC) divided HPV genotypes in 2 categories. The 1st group was high risk & in this group, type 68 was defined as class II carcinogens, & in class I carcinogens the following types were included: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 & 59. The 2nd group includes the low risk types which are 6, 11, 42, 43 & 44 and these are linked with hyperplastic lesions like genital warts [7]. Lots of HPV (DNA) diagnostic assays are presently thought to be clinically validated along with cervical scraping of cervical cancer screening objectives like INNO-LiPA i.e. Inn Genetics-Line Probe Assay, PCR & Hybrid Capture 2 i.e. HC2. The incidence percentage of cervical cancer out of 100.000 people is following: in upper, middle & Lower Egypt is 0.48 percent, 1.06 percent & 1.26 percent respectively. HPV is the danger factor for invasive & pre-invasive disease of cervix cancer.

METHODS:

The research was made like a cross sectional study & Hundred females were from those who were attending Services Hospital Lahore & Punjab Employees Social Security Institute Lahore Gynaecology Department. All these women were in the age group ranging from 30 to 60 years & asymptomatic women who were trying to know screening for cancer cervix. The ethics committee recommended the protocol for this study and moreover during this research, informed agreements were taken from all those under research population.
The population under study were in the process of complete general examination, history taking, TVUS & speculum examination. After that cervical swab of HPV DNA testing & Pap smear have been performed on the same setting. Then amplification, detection & HPV DNA extraction were made exactly like the manufacturer`s directives which were mentioned in a manual named as 'Sansure Biotech Inc. Changsha, China". It was made by using real-time fluorescence quantitative P.C.R based technology.

The follow-up of cases was exactly like HPV DNA results & Pap outcomes. The cases along with +HPV & HSIL were under visual inspection right after application of five percent acetic acid i.e. VIA colposcopy & colposcopy guided biopsy from the acetowhite & founded lesions areas. In case of regression nothing could be done in the cases of ASCUC & LSIL and could be re smeared after three to six months. In the case of progressive or persistent intraepithelial lesion i.e. ASCUC or LSIL, all the cases have been taken to colposcopy examination, VIA & biopsy taken from all the areas which were suspected. Punch biopsy was taken from ace to white epithelium. The biopsy sample was fixed immediately & submitted for examination named as histopathological.
The data of research was under statistical analysis. The data was entered in computer & analysed by

using the methods of IBM, SPSS software having a version of (20.0). By using the Chi-square test, the comparison among different groups with respect to categorical was carried out. The time when more than twenty percent of cells were hoped to be counted less than five, the correction for chi-square was performed by the method of Monte Carlo correction or Fisher's Exact test. In case the data was distributed in an abnormal manner, the tests used for normally distributed data were nonparametric tests. The contrastive study among 2 studied groups was performed using independent t-test but in case of data distributed abnormally, the comparison was carried out using Mann Whitney test. The importance of obtained outcomes was examined at the level of five percent.

RESULTS:

The following was the result of all cases: 79 percent were HPV -ve & 21 percent were HPV +ve, 34 percent were -ve for intraepithelial lesions i.e. 30 percent normal & 66 percent were +ve for intraepithelial lesions & 37 percent ASCUS. And 18 percent LSIL and 11 percent of HSIL. One percent inflammatory atypia and three percent squamous metaplasia.

Underlying relationship among abnormal cytology results and HPV DNA results was shown in table no.1. Moreover, it demonstrated that sixty-six cases had intraepithelial lesions of cervix and eleven cases had HSIL. From these 11 cases, three were negative for HPV & eight were positive for HPV. Eighteen cases had LSIL & from these eighteen cases, seventeen were negative & one was found to be positive. For HPV category, thirty-seven cases had ASCUS from which thirty were negative & six were found positive for HPV. A clear +ve link was found between HPV DNA positivity & HSIL. Size and configuration, nuclei are round with minimal irregular outlines and size 2-3 times of normal intermediate cell or twice the squamous metaplastic cell.

All the cases of LSIL and ASCUS have been re-smeared after a time period of three to six months. Moreover, there was a regression of abnormality found in thirty-four cases which was 91.9 percent & thirteen cases which was 72.2 percent. And there was found a persistence of abnormality in three cases i.e. 8.1 percent of ASCUS & five cases i.e. 27.8 percent in the case of LSIL. The colposcopy examination of all cases along with HSIL i.e. ten out of eleven cases were attended. The +ve HPV which was sixteen out of twenty-one cases were attended and persistent LSIL & ASCUS. The cases along with abnormal cytology were examined through VIA test and colposcopy had abnormal lesions. The biopsies were obtained & ten in sixteen cases of HPV +ve at the percentage of 62.5 have abnormal lesions by colposcopy. The biopsies have been obtained & results were fourteen cases of CIN I & four cases of CIN II as in table no.2.

The table no. 2 shows that seven in ten HPV positive cases had CIN I & three cases had CIN II. Moreover, six in ten cases with HSIL had CIN I & four cases had CIN II. Three cases of ASCUS had CIN I & five cases of LSIL.

The outcomes of this study showed that HPV DNA testing had sensitivity at 22.73 percent and specificity which was found at 82.35 percent. When compared with Pap test in table no.3, it was found that +ve predictive value i.e. PPV was 67.43 percent & -ve predictive value i.e. NPV at the rate of 35.44 & the accuracy was 43 percent.

Table 1: Relation between HPV DNA results and different types of abnormal cytology

	HPV		∟2	p			
	Negative (n = 51)		Positive (n = 15)				
	No.	%	No.	%			
Positive smears					16.229*	MCp <0.001*	
Cases with HSIL	3	5.9	8	53.3	18.791	FEp <0.001*	
Cases with LSIL	17	33.3	1	6.7	4.156*	FEp = 0.051*	
Cases with ASCUS		31	60.8	6	40.0	2.033	0.154

Table 2: Histopathological study of punch biopsies

Biopsy for results of punch biopsy	DNA positive cases (n=10)		HSIL cases attended (n=10)		LSIL cases (n=5)		ASCUS cases (n=3)	
	No.	%	No.	%	No.	%	No.	%
Mild dysplasia (CIN I)	7	70.0	6	60.0	5	100.0	3	100.0
Moderate dysplasis (CIN II)	3	30.0	4	40.0	0	0.0	0	0.0

Table 3: Relation between HPV 16, 18 DNA results and cytology results

	Cytology		C2		p	
	Normal (n = 34)		Abnormal (n = 66)			
	No.	%	No.	%		
HPV						
Negative (n = 79)	28	82.4	51	77.3	0.349	0.555
Positive (n = 21)	6	17.6	15	22.7		
Sensitivity	22.73					
Specificity	82.35					
PPV	71.43					
NPV	35.44					
Accuracy	43.00					

DISCUSSION:

The disease of cervical cancer is linked along with many factors in which hormonal contraceptive consumption, human papilloma virus infection, smoking & sexual behaviour are included [7]. The reduction in the mortality & incidence of cervical cancer can be made by using high quality cervical screening. This study shows that HPV 16 and 18 DNA test is less sensitive as compared to Pap smear in the early identification of pre-invasive diseases of the cervix & cytology is a basic in the process of HPV DNA if we use it as a screening technique [8].

According to this research, Syrjänen et al in a study of women in the number of 3175 for screening of cancer cervix by using HPV testing & routine cytology, it was observed that Pap smear cytology had identified a high-grade lesion along with sensitivity of 64 percent and specificity of 89.1 percent [9]. While 33 percent of cases were +ve for all oncogenic HPV types. On the other side, Castle et al in a research of women in the number of 797,927, HPV DNA testing & Pap smears, for thirteen carcinogenic HPV genotypes have been carried out [10]. This research concluded that possibility of testing carcinogenic HPV +ve however cytologic -ve to be just slightly more common as compare to the likelihood of testing carcinogenic HPV -ve but cytologic +ve were 3.99 percent against 2.90 percent [11].

Another named Carozzi et al, in a research showed that HPV test identified 99.2 percent which was 132 in 133 of CIN 2 cases identified during follow-up time with a median follow-up time duration of 1.6 years [12]. The danger of CIN2 in the period during 5 years with a -ve HPV test was 0.44 percent in follow-up time period. This study shows that, there has been statistically clear relation among HSIL & HPV positivity as it is 72.73 percent i.e. eight cases and of cases with HSIL were HPV +ve [13]. According to this study, Allameh et al had studied a total of 130 cases along with abnormal cytology by using DNA test. The outcomes showed that prevalence of HPV infection is greater in all the types of cervical neoplasia specifically in the precancerous lesions [14]. One more Jung An et al, showed in a study including women of number 1983, reached at a conclusion that 98.1 percent of HSIL cases were HPV +ve & observed that HPV-16 was the most prevalent kind in HSILs at the rate of 51.9 percent which was followed by HPV-58 at 15.7 percent & HPV-18 at the rate of 6.7 percent.

CONCLUSIONS:

The cases were observed as: 21 percent i.e. twenty-one cases were found HPV +ve & 66 percent i.e. sixty-six cases were +ve for intraepithelial lesions i.e. 11 percent HSIL, 37 percent ASCUS & 18 percent LSIL along with re-smearing. The number of cases were three persistent ASCUS 8.1 percent & five LSIL cases i.e. 27.78 percent. Biopsies & colposcopy done have been taken from ten HSIL cases i.e. 90.1 percent, three ASCUS i.e. 8.1 percent, five LSIL i.e. 27.8 percent & 10 HPV +ve cases i.e. 62.5 percent. Along with important relation among HPVDNA positivity, colposcopy findings & abnormal cytology observation was made. Four were CIN II, 14 were CIN I & biopsies were 18. There is a +ve link between HPV-DNA positivity & HSIL. Pap smear is also a less costly & most easy technique for screening. Moreover, as a technique for screening HPV-DNA test is less sensitive than cytology.

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