Original Article

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Prevalence of Human Papilloma Virus Infection in Young Primiparous Women During Postpartum Period: Study from a Tertiary Care Center in Northern India

Obstetrics and Gynaecology Section

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ABSTRACT

Introduction: Assessment of high-risk Human Papilloma Virus (HPV) prevalence is important for monitoring long-term decrease in cervical cancer after implementation of the prophylactic HPV vaccination.

Aim: To determine the prevalence of high-risk HPV infection and cytological abnormalities in young primiparous women in the age group of 16-26 years.

Materials and Methods: In this cross-sectional study, 214 primiparous women aged 16-26 years were recruited from a public tertiary health care center postpartum clinic between June 2013 and May 2014. Cytological analysis was performed by Pap smear test and patients underwent sampling with cervical brushes for HPV-DNA detection and typing by a PCR-based assay for HPV types 16, 18, 33 and 45.

Results: High-risk HPV was detected in 41 (19.2%) women. HPV 16 was found to be most prevalent with 17 (7.9%) samples testing positive, followed by HPV 18 in nine (4.2%), HPV 45 in six (2.8%) and HPV 31 in four (1.8%) women. Five women tested positive for more than one HPV types. There were no cases of intraepithelial lesions or cervical cancer. One patient who had Atypical Cells of Undetermined Significance (ASCUS) on cytology tested negative for all four HPV genotypes.

Conclusion: This study provides a geographic baseline data of high-risk HPV prevalence in young Indian women before implementation of a vaccination program. The results are important for comparison with other global regions and monitoring the effect of HPV vaccination.

Keywords: Cervical cancer, Epidemiology, Papanicolaou smear cytology, Polymerase chain reaction

INTRODUCTION

Cervical cancer is the fourth most common cancer among women globally, with an estimated 527,624 new cases and 265,672 deaths in 2012 [1]. Eighty four percent of these new cases are diagnosed in women living in less developed regions and 85% of deaths due to cervical cancer are reported in low- and middle-income countries. Nearly all cases of cervical cancer are associated with infection by one of the 13 oncogenic types of high-risk Human Papilloma Virus (HPV) [2]. Worldwide, HPV 16 and 18, contribute to over 70% of all cervical cancer cases after HPV 16 and 18, the six most common HPV types are the same in all world regions, namely 31, 33, 35, 45, 52, 58; and account for an additional 20% of cervical cancers [3]. In addition, there is growing evidence linking HPV infection with cancers of anus, vulva, vagina and penis [1].

Prophylactic HPV vaccines have become available over the past decade and have been considered a key element in the comprehensive cervical cancer control strategy. HPV 16 and 18 are included in both bivalent and quadrivalent vaccines. Recently 9-valent HPV vaccine was approved, which protects against five additional HPV types; HPV 31, 33, 45, 52 and 58 [4]. The primary target population for vaccination in developing countries is adolescent girls within the age range of 9-13 years [5]. By the end of 2012, 45 countries had successfully implemented the HPV vaccination [2].

Prevalence data from different socioeconomic groups and geographic locations is vital to understand the disease burden and the impact of HPV vaccine on the same. The baseline high-risk HPV status of women is important in order to follow observational studies over time and study for any decrease in cervical cancer decades from now. Previous studies from India have shown a HPV prevalence of 7%-36.8% in women with gynaecological concerns other than cervical cancer [6-13]. The prevalence has been reported to vary widely in different regions of the Indian subcontinent; Northern and Central India {Delhi (7%), Chandigarh (36.8%) and Varanasi (9.9%)}, Western and South India {Mumbai (8.1%) and Dindigul (16.9%)} [6,7,9,11,12]. When women with high-risk factors such as HIV are studied the prevalence is reportedly increased [14]. There is ample data on prevalence of HPV in women with cervical cancer; however, there is paucity of data regarding HPV prevalence in women with clinically normal cervix. A few studies have reported a prevalence of 7%-16.6% of high-risk HPV in healthy young women [8,9]. None of the previous studies have focused on young postpartum women. Young women, even in low resource settings, are increasingly utilizing the health care facilities for prenatal and postpartum care. This provides an excellent opportunity for providing counseling and vaccination to these women.

Age-related patterns of infection and the prevalence of HPV infection in younger women in India will also assist in formulating public policy and securing finances for implementation of HPV vaccination. The aim of this study was to determine the prevalence of high-risk HPV infection and cytological abnormalities in young women in the age group of 16-26 years and to evaluate if there was any association/contingency between demographic factors and HPV infection.

MATERIALS AND METHODS

This cross-sectional study included 232 primiparous women, 16-26 year-old, who attended postpartum clinic at Post Graduate Institute of Medical Education and Research, Chandigarh, India at 6-12

weeks after vaginal delivery or caesarean section during the period of June 2013 till May 2014. Women with immunocompromised status (HIV positive or on immunosuppressants etc.) and post caesarean hysterectomy status were excluded. Eligible women received full information about the study procedures and enrolled after informed consent. The study was approved by institutional ethical committee letter number NK/1105/MD/11488-489. Eligible women were interviewed in an appropriate setting ensuring privacy, using a structured epidemiological questionnaire that included information about demographic characteristics, sexual behaviour, reproductive history, contraceptive practice and smoking habits. After the interview, a conventional Pap smear was obtained with Ayer's spatula, which was immediately smeared onto a slide and dipped in 95% ethanol. The slide was stained by standard procedure and Bethesda system of reporting and classification was followed [15]. An endocervical cytobrush (Medscand, Trumbull, CT06611, USA) was gently inserted in the endocervical canal and slowly rotated 180°. The cytobrush was dipped in a self-standing 50ml centrifuge tube containing 5 ml phosphate buffered saline and immediately transported to the laboratory. The tube was centrifuged and the centrifuged deposits obtained were utilized for DNA extraction.

DNA was extracted with a commercially available extraction kit (Qiagen, Hilden, Germany) as per manufacturer's instructions. The quantity of the DNA was estimated by a spectrophotometer. The quality of DNA was confirmed by performing PCR for beta–actin, a housekeeping gene.

PCR technique was used to identify HPV 16, 18, 31 and 45 separately. The four HPV types were studied based on institutional availability of primers and resource limitation. Briefly, the PCR was performed in 20µl of reaction mixture containing 2µl 10X Taqbuffer, 2.5mm Magnesium chloride, 250µM of deoxynucleotide mix, 5pmol each of the sense and antisense primers, 5µl of template DNA and 2.0 units Taq DNA polymerase (MBI, Fermentas) by a 35 cycle protocol (denaturation for 10 min at 94°C, followed by 1 min each of denaturation at 94°C, annealing at 54°C and extension at 72°C for 33 cycles and final extension for 10 min at 72°C). Samples were tested for HPV 16, 18, 31 and 45 using type specific primers [Table/Fig-1] [16-18]. The plasmid DNA for HPV 16, 18, 31 and 45 were used as positive control in the reaction.

STATISTICAL ANALYSIS

The statistical analysis was performed by SPSS version 17.0 (Statistical Packages for the Social Sciences, Chicago, IL). The association/contingency between demographic factors and HPV infection was statistically calculated by using the chi-square test of significance. Detection of HPV infection using PCR was described as percentage.

RESULTS

Of the 232 women enrolled in the study, eight women were excluded due to vaginal bleeding. Ten samples were excluded due to DNA of unacceptable quality so 214 samples were finally analysed. The mean age of women in our study was 24.1 ± 1.8 years (range: 20-26) and the mean age at the time of marriage was 21.8± 2.0 years. Most of the women had primary education or more (92%) and lived in an urban area (66.3%). Majority of women were post vaginal delivery (78.5%), were not using any contraception (94.9%) and did not have vaginal discharge (85.5%) [Table/Fig-2]. None of the participants gave history of smoking, early sexual debut and sexual promiscuity.

HPV* TYPE	PRIMER SET
HPV 16	F 5'ATTAGTGAGTATAGACATTA-3' R 5'GGCTTTTGACAGTTAATACA-3'
HPV 18	F 5'ACTATGGCGGCGCTTTGAGGA3' R 5'GGTTTCTGGCACCGCAGGCA-3'
HPV 31	F 5'AGACAATTACCCGACAGCTCAGAT-3' R 5'GTAGAACAGTTGGGGCACACGA-3'
HPV 45	F 5' GACCTGTTGTGTTACGAGCAATT-3' R 5'TGCACACCACGGACACAAAG-3'

[Table/Fig-1]: Oligonucleotide sequences used as primers for detection of HPV and its different types.
*HPV – Human Papilloma Virus

Out of 214 women, 41 women (19.2%) tested positive for HPV DNA, 36 (16.8%) women were positive for single HPV type 16, 18, 31 or 45, whereas five (2.3%) women were positive for two HPV types. Overall HPV 16 was the most prevalent genotype which was positive in 17 (7.9%) women, followed by HPV 18 in nine (4.2%), HPV 45 in six (2.8%) and HPV 31 in four (1.8%) women. Out of five women who had co-infection with two HPV genotypes, two women (0.9%) tested positive for HPV 16 and 18, two women (0.9%) tested positive for both HPV 31 and 45 and one woman (0.46%) tested positive for both HPV 18 and 45. None of the women was positive for three or all four HPV types.

[Table/Fig-2] shows the comparative distribution of study variables in women who tested positive and negative for HPV. No statistically significant difference was found between the two groups in terms of parameters like age, literacy, residence, coital frequency, mode of delivery, contraception, vaginal discharge.

The cytological examination of cervical smears revealed 12(5.6%) smears unsatisfactory for interpretation. Out of 202 women with satisfactory smears, 201 (93.9%) smears were normal; only 1 woman (0.46%) had Pap smear suggestive of Atypical Cells of Undetermined Significance (ASCUS) for which repeat smear and colposcopy were found to be normal.

Baseline characteristics (n=214)	HPV positive n=41 (19.2%)	HPV negative n=173 (80.8%)	p-value
Age (Years)			
20-22 (n=43)	7 (16.3%)	36 (83.7%)	0.326
23-24 (n=68)	10 (14.7%)	58 (85.3%)	
25-26 (n=103)	24 (23.3%)	79 (76.7%)	
Mean Age (Years) ± S.D.	24.3±1.8	24.0±1.8	0.312
Age at Marriage (Years) ± S.D.	22.2 ± 2.2	21.7±2.0	0.158
Literacy Status			
Illiterate (n=17)	2 (11.8%)	15 (88.2%)	0.093
Primary Education (n=104)	15 (14.4%)	89 (85.6%)	
Graduate (n=93)	24 (25.8 %)	69 (74.2%)	
Residence			
Rural (n=72)	11 (15.3%)	61 (84.7%)	0.304
Urban (n=142)	30 (21.2%)	112 (78.8%)	
Mean Coital Frequency (times / week) ± S.D.	2.6±1.3	2.4±1.0	0.514
Delivery			
Caesarean Section (n=46)	9 (19.5%)	37 (80.4%)	0.937
Vaginal delivery (n=168)	32 (19.1%)	136 (80.9%)	
Contraception			
Barrier (n=11)	3 (27.2%)	8 (72.8%)	0.483
None (n=203)	38 (18.7%)	165 (81.3%)	
Vaginal discharge			
Present (n=31)	7 (22.6%)	24 (77.4%)	0.601
Absent (n=183)	34 (18.6%)	149 (81.4%)	

[Table/Fig-2]: Socio-demographic profile & comparative distribution of study variables in HPV (16, 18, 31 and 45) positive and negative women.
p-value <0.05 is significant

DISCUSSION

Prevalence of data on high-risk HPV and its type distribution in India is limited and highly inconsistent due to study participants having

a wide age range and socioeconomic status, inclusion of women with cervical cancer and disparity due to rural or urban residence of the patients. This makes interpretation and comparison of findings difficult [19]. It is worth noting that our study population comprised of young reportedly monogamous women who were sampled after the birth of their first child. The factors for HPV infection like smoking, sexual promiscuity, HIV positivity (one of the exclusion criteria) were also reportedly absent.

In this cross-sectional study, PCR testing revealed the prevalence of high-risk HPV to be 19.2%. A previous study from our center that looked at the prevalence in a wider age range (19-75 years), reported a higher prevalence of 36.8% [6]. Overall, the prevalence rates are higher than those previously reported (7 to 16.9%) from other centers in India [7-13]. One possible explanation for the high prevalence in the studies from our center could be that this tertiary care center caters to a large referral population from many neighboring states with a high incidence of cervical cancer [20].

Worldwide, HPV prevalence has been shown to vary from 10.4% to 68.4% [21-25]. For example, the HPV prevalence in primiparous Brazilian women aged 15-24 years was 58.5% when 28 HPV genotypes were studied [24]. The prevalence reported in our study was lower compared to these global statistics [22-25]. This difference may be attributed to different population and sexual behaviour characteristics such as early age at first sexual intercourse, long duration of sexual activity, multiple sexual partners and smoking in contrast to that seen in our population. Nonetheless, one of the studies done in Italian women of age group 18-26 years reported a prevalence of 19% which was similar to our study [26].

HPV 16 behaves as a more virulent virus causing greater proportion of cervical disease, causing disease earlier and being more likely to persist than other high-risk oncogenic types. Therefore HPV 16 is included in all HPV vaccines - bivalent, quadrivalent and 9-valent HPV vaccine. Consistent with previous studies, we found that HPV 16 was the most prevalent HPV type (8.9%). This is comparable to previous studies in India varying from 8.4% to 10% [8,10,13]. Worldwide, prevalence of HPV 16 is higher ranging from 12%-17.3% [24,25]. Only 0.9% of participants in our study had evidence of concomitant infections by high-risk HPV types 16 and 18, similar to that reported by Rama et al., [24]. None of the participants had simultaneously three or all four HPV types being studied, whereas high rate of concomitant infection with multiple HPV genotypes has been reported by many other studies [7,9,11,22,26]. HPV 16 was the most common genotype detected in multiple infections, followed by HPV 31 and 18. Younger women were significantly more likely to harbor multiple high-risk HPV infections, reflecting common sexual transmission of multiple high-risk HPV [27].

None of the women in this study had any low grade or high-grade intraepithelial cervical lesions. One patient had ASCUS. Prevalence of premalignant lesions is low in young women and frequency of abnormal cytological lesions increased significantly with increasing age of women after 25 years [7,10].

HPV vaccination represents an important opportunity to significantly reduce the burden of cervical cancer. In resource-strained settings, young adolescent girls who are less likely to be infected with HPV, remain the primary target for vaccination [5]. Catch up vaccination is recommended for females aged 13-26 years who have not been previously vaccinated against HPV or who have not completed full series [28]. For most developing countries like India, the acceptance and uptake of this new vaccination continues to be a challenge. The cost of the vaccine and its delivery is higher than that for routinely recommended vaccines [29]. Besides affordability, lack of awareness, concerns from parents and providers vaccination against a sexually transmitted disease may promote sexual promiscuity, mistrust of the government health policies ('vaccine may impact fertility'), cultural barriers targeting vaccination in general, operational and logistic challenges in vaccine delivery including competing health priorities are some of the obstacles in HPV vaccination [30,31].

Young women in India and other developing nations, especially in rural areas, represent a population with high school dropout rates and hence are unlikely to benefit from potential school vaccination programs. In such regions, community based efforts to reach girls outside schools is an alternative. In addition, increasing awareness and adopting a comprehensive approach by using one system to deliver multiple interventions can prove not only cost effective but can increase vaccine coverage [32]. One such strategy is to utilize the postpartum visit as an opportunity for catch up HPV vaccination through an already existing infrastructure for family planning services.

The findings of this study add to our knowledge of HPV prevalence in women seeking care at a tertiary care center catering to three Northern Indian states (Punjab, Haryana and Himachal Pradesh) and the suburban population of Chandigarh and adjoining areas. This information can be employed not only for proper utilization of the present prophylactic HPV vaccines but also can be used for the generation of a new specific vaccine against the HPV types prevalent in this population. This is one of the first studies to report the prevalence of HPV in young Indian women, with low risk factors, during postnatal period. It presents a valuable baseline data on prevalence and type distribution of HPV and adds unique geographical data to our knowledge of HPV, which may be sufficiently important to prioritize an intervention in future. Since the HPV prevalence in this group of women is high (19.2%), it represents a target population for comprehensive cervical cancer prevention programs.

LIMITATION

Due to the sample size and cross-sectional design of the study, we were limited in our ability to correlate HPV infection with behavioural and socio-demographic factors. Due to the social and cultural bounds of the study population, there is a possibility of underestimation of sensitive parameters like age at first sexual intercourse and promiscuity. The results of the study were also dependent on inclusion of four high-risk genotypes with inability to study other HPV types. Future studies on a large population of women from this region and inclusion of other high-risk genotypes will add to this data.

CONCLUSION

There was a significant prevalence of high-risk HPV types in women in northern India. Strategies such as cervical cancer screening with combination of cytology, visual inspection methods and prophylactic vaccination programs should be focused towards this population to reduce disease burden due to oncogenic HPV infection and cervical cancer.

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ABBREVIATIONS

ASCUS	Atypical squamous cells of undetermined Significance
FDA	Food and Drug Administration
HPV	Human Papilloma Virus
HIV	Human Immunodeficiency Virus
ICMR	Indian Council of Medical Research
PCR	Polymerase chain reaction
Pap	Papanicolaou smear

SPSS	Statistical Packages for the Social Sciences
WHO	World Health Organization

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