Original Article

Colposcopy Value in Young Child-bearing Women: Is New Recommendations Necessary?

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Abstract

Background: Cervical cancer is a common malignancy in women and HPV infection is directly linked to it and can be considerably prevented through routine screenings. Despite the belief about the persistence of HPV infection in older than 30-year-old women, high-grade lesions might be detected in younger ages; therefore, the purpose of the current study is to determine the worth of HPV infection screening in younger than 30-year-old women.

Materials and Methods: This cross-sectional study has been executed on 100 under 30-year-old women who have undergone genotyping. Fourteen HPV subtypes including HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 were defined as high risk and the patients were categorized in HPV 16/18 or other high-risk groups. Pap smear and colposcopy were performed for both groups and interpreted as normal, low-risk and high-risk lesions and compared between the groups.

Results: In terms of demographic, clinical, and sexual behavioral characteristics, the present study exhibited similarity (P value > 0.05). Pap smear (P value = 0.100) and colposcopy (P value = 0.711) grading did not differ between those with HPV 16/18 versus other high-risk HPV patients. Pap smear and colposcopic findings were weekly in agreement ($\kappa < 0.5$, P value < 0.001).

Conclusion: Early cytological plus genotyping assessment in women at early child-bearing ages seems logical, as the cervical premalignant lesions have a slow progressing nature and can be easily treated in early stages.

Keywords: Colposcopy, Papanicolaou test, papillomavirus infection, uterine cervical neoplasm

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Introduction

Cervical cancer is the second most common prevalent cancer in women accounting for approximately 500,000 new and 275,000 deaths annually. The association of high-risk human papillomavirus (HPV) infection in developing cervical cancer is significant.[1]

About 100 genotypes of HPV with the capability to invade anogenital epithelium have been extracted among which 14 types were potentially carcinogenic. Accordingly, infection with high-risk HPVs through sexually transmission route can lead to carcinogenesis and subsequently, cervical cancer development.[2] HPV 16 and 18 are responsible for 55–60%

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and 10–15% of the cervical cancers, respectively. The other high-risk HPV genotypes include HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. Epidemiological studies on cervical cancer have revealed that over 90% of patients with cervical cancer had positive tests for genital HPV infection.[3]

Accordingly, public health officials have recommended screening programs by which a dramatic decrease in cervical cancer has been achieved. These strategies include age-appropriate screenings including cervical cytology alone for ≥21-year-old women or after the first sexual intercourse every three years, and cotest (cervical cytology and HPV genotyping) performed for ≥30-year-old women every five years. There are controversies in terms of cervical cancer screening in different guidelines. In the recent guideline provided by the American Food and Drug Administration (FDA), high-risk HPV genotyping for HPV 16/18 along with the other 12 genotypes has been recommended for any age above 25 years old.[4-6] Nevertheless, most of the studies in the literature have considered the significance of cotest screening for over 30-year-old cases. However, an increasing body of evidence has shown that HPV infection rises the risk of pathological manifestations even in younger ages than late days of the third decade of life.[7-9] Given that, the current study aims to investigate cytology assessments along with genotyping in high-risk patients referring with or without genitalia lesions. In our study, all high-risk subtypes of HPVs are included and various demographic variables are investigated which is the novelty of our study as in the others only HPV 16 and 18 types were considered and variety of demographic data are not like ours.

Materials and Methods

Study population

This cross-sectional study has been elucidated on 100 under-30-year-old women who have undergone genotyping. The studied population referred to the outpatient clinics of Obstetrics and Gynecology Clinics affiliated with Isfahan University of Medical Sciences from January 2021 to March 2022.

The study protocol in line with the Helsinki Declaration was approved via the Ethics Committee of Isfahan University of Medical Sciences (code number IR.MUI.MED.REC.1400.275). The included patients were reassured about their personal data confidentiality and signed written consent.

Child-bearing under-30-year-old women who have undergone HPV genotyping and had high-risk genotypes were included. Fourteen HPV subtypes including HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 were defined as high risk.[10] The patients who did not accept to perform Pap smear/colposcopy study had immunosuppression with or without use of immune-suppressive therapy or with a history of cervical dysplasia were excluded and were the other exclusion criteria. Accordingly, the total population of 107 patients entered the study among who seven ones were excluded due to inability to perform vaginal examination or Pap smear.

The study population entered the study through convenience sampling.

Data collection

The gathered baseline data included demographic characteristics (age, marital status, occupation, educational level, race, and economical level) and habitual behaviors (smoking, alcohol consumption, and psychotropic substances).

Besides, the sexual activity information including age at the first sexual intercourse and at the first giving birth, the number of gravidities with or without live births, and the number of sexual partners, cesarean history, contraception method (withdrawal, barrier, hormone therapy, and intra-uterine device), the history of unprotected sexual intercourse, and history of Pap smear screening were recruited.

Unprotected sexual intercourse was defined as intermittent or irregular use of a barrier. In other words, permanent barrier use during sexual intercourse was determined as protection with barrier. Based on type I error rate (α) = 0.05, power ($1-\beta$) = 0.8 and expected population standard deviation (SD) = 2 total sample size were calculated as 110 patients.

Pap smear evaluation

Any type of cervical cell sampling including conventional or liquid-base preparations (Thin Prep Pap test, Cytyc Corporation, Boxborough, MA, USA), after rechecking by an expert pathologist in the field of gynecologic malignancies, were accepted. The results were reported using the Bethesda system.[11] The Pap smear reports were categorized as normal (normal, cervicitis, inflammation, and metaplasia), low risk for malignancy (atypical squamous cells of undetermined significance and low-grade squamous intraepithelial lesion [LSIL]) and high risk for malignancy (atypical glandular cells of undetermined significance, high-grade squamous intraepithelial lesion [HSIL], high-grade squamous intra-epithelial lesion, carcinoma, and adenocarcinoma).

HPV genotyping

The accepted method was Hybrid Capture2 (Qiagen) kit for HPV-DNA scans and CLART kit (Genomica) or Cobas® HPV kit (Roche).[10] HPV genotypes were categorized as 16 and 18 (high-risk HPV) and the other high-risk including 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68.

Colposcopy

In the case without abnormal colposcopic finding, biopsies were performed randomly. The biopsied tissues were interpreted as normal (normal or cervicitis), low-grade (LSIL or cervical intra-epithelia neoplasia-1 [CIN-1]), and high-grade lesions (CIN-2, CIN-3, HSIL carcinoma, and adenocarcinoma).[12]

Statistical analysis

The extracted data were analyzed by the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 24.

Descriptive data were calculated in mean, SD, percentages, and absolute numbers. Chi-square test or Fisher's exact test was administered to compare the categorical data. An independent *t*-test was applied for the comparison of continuous variables. The agreement of Pap smear and colposcopic outcomes was assessed using κ coefficient test. Kappa coefficient was considered weak, moderate, and powerful if <0.5, 0.5–0.7, and ≥0.7. The level of significance considered as a *P* value of less than 0.05.

Results

In the current study, data of 100 under-30-year-old women were recruited and assessed regarding the association of HPV infection with the risk of developing malignant cervical lesions. The mean age of the studied population was 26.78 ± 3.18 years old.

The genotyping of the HPV revealed that 58 ones (58%) was infected by HPV 16/18, while the others (42%) were in the other high-risk HPV group. Among the first group, 43, 10, and five ones were infected with HPV 16 only, 18 only and both, respectively. The patients in the two groups did not differ in terms of demographic characteristics including age (*P* value = 0.870), marital status (*P* value = 0.630), occupation (*P* value = 0.207), educational level (*P* value = 0.245), race (*P* value = 0.99), and economical level (*P* value = 0.827). Besides, they were similar in terms of habitual behaviors such as smoking (*P* value = 0.269), alcohol consumption (*P* value = 0.512), and psychotropic substance use (*P* value = 0.99). Detailed information is demonstrated in Table 1.

The mean age of the patients at the time of their first sexual intercourse and giving a child-birth (*P* value = 0.383), the number of pregnancies (*P* value = 0.460), the number of birth(s) (*P* value = 0.455), and the number of sexual partners (*P* value = 0.273) were similar between the groups. Most of the cases presented withdrawal protection as their contraception method; however, using other contraception methods did not differ between two groups (*P* value = 0.887). Unprotected sexual intercourses were presented in all the patients of the two groups (*P* value = 0.99) [Table 2]. The history of Pap smear screening was not statistically different between the groups (*P* value = 0.581).

The association of high-risk lesions, both in Pap smear (*P* value = 0.07) and colposcopy, was not significant with high-risk HPV infection (*P* value = 0.44) [Table 3].

The association of Pap smear with colposcopy reports considering the age of the patients has been assessed in

Table 1: Demographic and habitual characteristics of the studied population

Variables	HPV 16/18	Other high-risk HPV	*P*
Demographic characteristics			
Age (years), mean±standard deviation	26.52±3.47	26.38±4.84	0.870*
Marital status, *n* (%)			
Single	14 (24.1)	7 (16.7)	0.630#
Married	40 (69)	33 (78.6)	
Divorced	4 (6.9)	2 (4.8)	
Occupation, *n* (%)			
Household	30 (57.1)	29 (69)	0.207#
University student	11 (19)	5 (11.9)	
Employee	8 (13.8)	6 (14.3)	
Self-employed	9 (15.5)	2 (4.8)	
Educational level, *n* (%)			
Diploma and less	24 (41.4)	11 (26.2)	0.245**
Bachelor of Science/Art	32 (55.2)	30 (71.4)	
Master of Science/Art and more	2 (3.4)	1 (2.4)	
Race, *n* (%)			
Iranian	57 (98.3)	41 (97.6)	0.99**
Other	1 (1.7)	1 (2.4)	
Economical level, *n* (%)			
<4 million	2 (3.4)	0 (0)	0.827**
4–8 million	15 (25.9)	11 (26.2)	
8–16 million	38 (65.5)	28 (66.7)	
≥16 million	3 (5.2)	3 (7.1)	
Habitual behaviors (yes), *n* (%)			
Smoking	19 (32.8)	9 (22.5)	0.269#
Alcohol consumption	2 (3.4)	0 (0)	0.512**
Addiction	0 (0)	0 (0)	–
Psychotropic substance use	1 (3)	0 (0)	0.999**

*Independent *t*-test. **Fisher's exact test. #Chi-square

Table 2: Sexual activity–related variables

Variables	HPV 16/18	Other high-risk HPV	*P*
Age at the first sexual intercourse (years), mean±standard deviation	22.17±3.08	22.72±2.84	0.383*
Age at the first giving birth (years), mean±standard deviation	23.40±2.67	22.92±2.31	0.654*
Number of pregnancies, *n* (%)			
None	45 (77.6)	28 (66.7)	0.460**
One	9 (15.5)	10 (23.8)	
Two and more	4 (6.5)	4 (9.5)	
Number of giving birth(s), *n* (%)			
None	46 (79.3)	29 (69)	0.455**
One	8 (13.8)	10 (23.8)	
Two and more	4 (6.9)	3 (7.1)	
Number of sexual partners, *n* (%)			
One	43 (74.1)	35 (83.3)	0.273#
>1	15 (25.9)	7 (16.7)	
Cesarean history, *n* (%)			
0	49 (84.5)	35 (83.3)	0.999**
1	7 (12.1)	5 (11.9)	
2	2 (3.4)	2 (4.8)	
Contraception method, *n* (%)			
Withdrawal	50 (86.2)	35 (83.3)	0.887**
Barrier	0 (0)	0 (0)	
Hormone therapy	7 (12.06)	6 (14.3)	
Intra-uterine device	1 (1.7)	1 (2.4)	
History of unprotected sexual intercourse, *n* (%)	58 (100)	42 (100)	0.99#
History of Pap smear, *n* (%)	26 (49.1)	22 (54.8)	0.581#

*Independent *t*-test. **Fisher's exact. #Chi-square test

Table 3: The association of Pap smear and colposcopic biopsies with HPV genotype

Variables	HPV 16/18	Other high-risk HPV	*P*	*P**
Pap-smear, *n* (%)				
Normal	37 (63.8)	27 (64.3)	>0.99	0.100
Low risk	13 (22.4)	14 (33.3)	0.25	
High risk	8 (13.8)	1 (2.4)	0.07	
Colposcopy, *n* (%)				
Normal	17 (29.3)	13 (31)	>0.99	0.711
Low risk	29 (50)	23 (54.8)	0.68	
High risk	12 (20.7)	6 (14.3)	0.44	

*Chi-square test

Table 4. Neither the younger than 25-year-old patients nor the latter group differed regarding their Pap smear or colposcopic findings (P value > 0.05).

Table 5 shows the consistency of Pap smear with colposcopy results which revealed significant correlations (P value < 0.001); however, the κ coefficients were not low ($\kappa < 0.5$).

Discussion

The current study has been conducted with some main goals, evaluating the value of genotyping in early child-bearing ages rather than only over 30 years old and investigating the value of cotest versus Pap smear alone in under-30-year-old women. Accordingly, we divided our patients into two groups of HPV infection with 16/18 or other high-risk genotypes. The diverse demographic, habitual, and sexual behavioral aspects were similar between both groups; accordingly, all the findings would be attributed to the genotypes only. The studied population was predominantly infected with high-risk HPV 16 and 18; however, despite the higher prevalence of high-risk lesions in both Pap smear and colposcopic assessments in this group rather than the latter. The stages of their lesions were not statistically different between the groups.

A study in Turkey with a similar design but on over 30-year-old women presented that the rate of infected women with other high-risk HPVs was more than that of 16/18 as the most significant carcinogen ones; but cytological studies by both Pap smear and colposcopy revealed statistically higher rate of precancerous and cancerous lesions among those with HPV 16/18. Considering the age group of the patients might reflect the persistence of infection among them comparing with younger ages assessed in our study.[10]

Karimi-Zarchi and her colleagues conducted another study in Iran in which they found other high-risk HPVs more prevalent than 16/18 alone, in combination with other types or concurrent 16 and 18. Nevertheless, in line with our findings, they presented a higher probability of high-grade lesions in the infection with genotypes 16/18 through both colposcopy and Pap smear. Eventually, they preferred colposcopy rather than Pap smear for its higher specificity and lower rate of false negatives.[13]

Table 4: The association of Pap smear and colposcopic biopsies with HPV genotype

Variables	<25 years old (*n*=24)		25–30 years old (*n*=76)		*P**	*P*** (comparison between the groups <25 years old)	*P*** (comparison between the groups 25–30 years old)
	HPV 16/18 (*n*=15)	Other high-risk HPV (*n*=9)	HPV 16/18 (*n*=43)	Other high-risk HPV (*n*=34)			
Pap-smear, *n* (%)							
Normal	11 (73.33)	5 (62.5)	26 (60.46)	22 (64.70)	0.502	0.513	0.263
Low risk	2 (13.33)	3 (37.5)	11 (25.58)	11 (33.33)	0.99		
High risk	2 (13.33)	0 (0)	6 (13.95)	1 (3.03)	0.99		
Colposcopy, *n* (%)							
Normal	5 (33.3)	2 (20)	12 (27.90)	11 (32.35)	0.29	0.292	0.670
Low risk	6 (40)	6 (80)	23 (53.48)	17 (50)	0.31		
High risk	4 (26.67)	0 (0)	8 (18.60)	6 (17.64)	0.61		

*Chi-square test. **Fisher's exact test

Table 5: The consistency of Pap smear with colposcopy

	Pap smear								
	Total (*n*=100)			HPV 16/18 (*n*=58)			Other high-risk HPV (*n*=42)		
	Normal	Low risk	High risk	Normal	Low risk	High risk	Normal	Low risk	High risk
Colposcopy									
HPV 16/18 (*n*=58)									
Normal	–	–	–	15 (25.86)	2 (3.44)	0 (0)	–	–	–
Low risk	–	–	–	18 (31.08)	10 (17.24)	1 (1.72)	–	–	–
High risk	–	–	–	4 (6.89)	1 (1.72)	7 (12.06)	–	–	–
Other high-risk HPV (*n*=42)									
Normal	–	–	–	–	–	–	12 (28.57)	1 (2.38)	0 (0)
Low risk	–	–	–	–	–	–	13 (30.95)	10 (23.80)	0 (0)
High risk	–	–	–	–	–	–	2 (4.76)	3 (7.14)	1 (2.38)
Total (*n*=100)									
Normal	27 (27)	3 (3)	0 (0)	–	–	–	–	–	–
Low risk	31 (31)	20 (20)	1 (1)	–	–	–	–	–	–
High risk	6 (6)	4 (4)	8 (8)	–	–	–	–	–	–
	P<0.001, κ=0.325			*P*<0.001, κ=0.308			*P*<0.001, κ=0.342		

The other study has been conducted by Monsonego *et al*.[14] on a large population of American women. They included over 25-year-old females and evaluated HPV genotypes in them. HPV 16, 52, 31, and 18 were the most prevalent genotypes among the studied population. HPV 16 played a key role in the cervical pathologies ≥CIN3. Besides, HPV 18 was responsible for 50% of the lesions compatible for adenocarcinoma *in situ*. They concluded that genotyping for HPV 16 and 18 is necessary; however, other high-risk genotypes should be risk stratified.

Hooi and colleagues assessed genotypes among the women with advanced cervical lesions and represented that genotype 16/18 was the most common ones found in the cytologies representing precancerous lesions including invasive cervical cancers and CIN grades 1, 2, and 3.[1] This study has included CIN I in the high-risk group that is different to ours.

Kasraei *et al*.[15] were the other group of researchers who performed their study on 394 over 35-year-old women with negative Pap smears, but positive HPV infection and found that HPV 16/18 was less prevalent than other high risks; however, they opposed us regarding the association of high-grade lesions with HPV genotypes.

It is well documented that the risk of cervical preinvasive lesions and cancer development increases when HPV infection persists and time passes, while the guidelines currently suggest cotest follow-up among over 30-year-old women.[16] Besides, the guidelines recommend HPV vaccination in advance to any HPV-infection exposure.[17] Moreover, the annual screening has been recommended for those with non-16/18 high-risk HPV whose cytology are negative.[18] We found high-grade lesions in colposcopic assessment of those who had normal or low-grade Pap smears, primarily clarifying the value of cotest rather than Pap smear alone and secondarily the significance of early screenings. Severe epithelial changes could be the result of a delayed diagnosis and advanced lesions. Furthermore, it should be notified that false-negative rate of Pap smear accounted for 15–65% in the previous investigations representing the value of early genotyping and colposcopy;[19] however, we found no association between colposcopic interpretations and HPV genotyping. In confirmation, a study

revealed higher rates of false low-grade cytomorphology in Pap smears of cases infected with other high-risk HPVs than 16/18.[20] Therefore, early genotyping seems logical considering a significant Pap smear alone underdiagnosing rate.

The other confirmatory theory regarding cotest screening in early child-bearing ages refers to slow progression of low-grade lesions to develop invasive ones. Accordingly, as the majority of lesions are transient and spontaneously eliminated; they might be missed and develop high-grade lesions in the future.[21] However, we have found high-grade lesions in younger than 30-year-old females representing that not all of the lesions in ages younger than 30 years are temporary. Therefore, further studies with cohort design are strongly recommended to evaluate the persistence of HPV lesions and their development to high-grade lesions.

Another study verified this hypothesis reporting a two-fold increased rate of high-grade cervical lesions detection through primary HPV screening rather than cytology study.[22] According to the guidelines, the next step in a patient with positive high-risk HPV, particularly in other high-risk lesions, should be considered based on Pap smear results. Therefore, those with normal Pap smear mostly do not require colposcopy and biopsy. Pap smears with LSIL report require colposcopy if the patient is positive for high/other high-risk HPVs or with unknown genotyping, while those Pap smears compatible with LSIL that are negative for HPV require annual checkup.[19,20] In addition, guidelines recommend to perform Pap smear every three years for under-30-year-old women; but in this study, 10 out of 100 patients had normal or low-grade Pap smears who underwent colposcopic study due to high-risk HPV which revealed CIN $\geq$ 2 in them. Considering LSIL Pap smear reports in four ones out of these 10 patients, the necessity of colposcopy/biopsy among those with unknown HPV and LSIL Pap smear is better clarified.

In contrast, as we found high-risk lesions (CIN $\geq$ 2) in the colposcopy of the patients with normal Pap smear in both groups of the study, it is suggestible to (1) HPV screening, particularly using cotest or genotyping in under-30-year-old high-risk women; (2) routine anti-HPV vaccination and its coverage by insurances before the first sexual intercourse due to risky sexual behaviors and earlier initiation of sexual activities; and (3) improvement of education and practice regarding HPV vaccination, screening, and high-risk sexual activity in school ages and adolescence. The necessity and continuity of protection should be concisely included in the educational schedule, while it should be emphasized that none of the techniques can completely protect sexual disease transmission.[23] The most important novelty of our study is that all different subtypes of high-risk HPV are investigated in our study, and colposcopy with other confirmatory tests is documented in patients. A variety of demographic data are also documented and reported in our study.

Limitations

Despite the strong points of this study such as its novelty in the assessment of young women; it has significant limitations. The study could be more powerful and generalizable if the population was larger, conducted on different ages, and with a design to assess false-negative responses of HPV genotyping, as we found cases with normal Pap smear whose colposcopy was CIN II and worse.

Conclusion

In light of this study's findings, high-risk Pap smear and colposcopic findings were more prevalent among 16/18 HPVs than other high-risk HPVs; however, they did not significantly differ. Therefore, early cytological plus genotyping assessment in women at early child-bearing ages seems logical, as the cervical premalignant lesions have controllable progressing nature and can be easily treated in early stages.

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Conflicts of interest

There are no conflicts of interest.

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