

Comparison of Pap Smear and Colposcopy in Screening for Cervical Cancer in Patients with Secondary Immunodeficiency

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Abstract

Introduction: Cervical cancer is the second most common cancer among women worldwide. The sensitivity of conventional Pap smear in detecting cervical lesions before cervical cancer is 51%, which means the false negative value is 49%. The aim of this study was to compare two methods for screening for cervical cancer in patients with secondary immunodeficiency, i.e., the conventional Pap smear and colposcopy.

Methods: This cross-sectional study was conducted on 101 immunodeficient patients who were referred to the Gynecologic Clinic at Shahid Sadoughi Hospital in Yazd from March 2011 to August 2012. All patients underwent the Pap test, a colposcopy, and a cervical biopsy, with the latter being considered as the gold-standard test.

Results: The most frequency of immunodeficiency was noted among patients with rheumatoid arthritis (53.3%), and this was followed by patients who were undergoing chemotherapy (30.7%), patients with lupus erythematosus (12.9%), and patients with AIDS (3%). The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the Pap smear were 18.2, 98.5, 85.5, 71.3, and 72.2%, respectively. The respective values for colposcopy were 66.7, 98.94, 80, 97.9, and 97%, respectively.

Conclusion: In this study the accuracy, sensitivity, specificity, and negative predictive values of colposcopy were higher than those for the Pap smear in detecting high-grade, cervical, pre-malignant lesions (cervical intraepithelial neoplasia: CIN \geq 2). Therefore, an annual colposcopy is advised for secondary immunodeficient patients instead of a Pap smear.

Keywords: immunodeficiency, conventional Pap smear, colposcopy, cervical cancer, sensitivity, specificity

1. Introduction

Cervical cancer is the second most common cancer among women worldwide, and it is responsible for 275,000 deaths each year (1). Among all known types of cancer, the prospects for preventing or curing cervical cancer are among the best because it can be diagnosed early when it is still curable. About 80% of cervical cancer cases occur

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in developing countries, and it is the most common cause of death in women (2, 3). The Papanicolaou (Pap) test is the most common and cost-effective screening method for detecting cervical cancer, and it has been effective in reducing the prevalence of this cancer and the associated mortality rates among women (4). Since 1950, the Pap smear has decreased the rate of cervical cancer by as much as 79%, and it has decreased the mortality rate by 70% (5). However, the incidence of cervical cancer in patients who undergo frequent Pap smears is increasing (6). The sensitivity of the conventional Pap smear in detecting lesions before cervical cancer occurs is 51%, which means the false negative value of this method is 49% (7). The sensitivity and specificity of the Pap test in detecting high-grade lesions of cervical intraepithelial neoplasia (CIN II and CIN III) have been shown to be 55.4 and 96.8%, respectively (8). In a study performed in Iran, it was found that less than 2% of the patients with cervical cancer had undergone a Pap smear in the previous 10 years (9, 10). Human papilloma virus (HPV) is the main cause of cervical intraepithelial neoplasia (CIN) and cervical cancer. Some studies have shown that women infected with high-risk HPV have a higher rate of progression from CIN to cancer, with a 300-fold increase in the risk of high-grade disease (6, 11, 12). Usually, HPV infections are not persistent, but those that remain may be latent for many years. Most women who are exposed have no clinical signs, and the infection is finally suppressed or eliminated (6, 7). In other women, low-grade cervical lesions occur, but, for the most part, they regress spontaneously. In many cases, the infection will clear in 9 to 15 months (6, 13). In a limited number of women who are exposed to HPV, persistent infection occurs that may progress to CIN (6, 7). In recent years, the use of prophylactic HPV vaccination has been initiated, but such vaccinations are not used in Iran, so we do not have the benefit of its effective role in decreasing the incidence of persistent HPV infection (6). The aim of this study was to compare two methods, i.e., Pap smear and colposcopy, for screening secondary immunodeficient patients for cervical cancer. These patients were referred to the Gynecologic Clinic at Shahid Sadughi Hospital in Yazd from March 2011 to August 2012.

2. Material and Methods

This was a cross-sectional study that examined 101 immunodeficient patients who were referred to Shahid Sadughi Hospital from March 2011 to August 2012. The criteria for inclusion in the study were being married, not being pregnant, and the age of 21 or within three years of the onset of sexual activity with no previous hysterectomy or previous histories of treating cervical lesions with a compromised immune system. The term 'immunodeficient patients' refers to immunosuppressed renal transplant recipients, patients known to be infected with HIV, patients being treated with immunosuppressive drugs for more than two months, such as cyclosporine, tacrolimus, sirolimus, mycophenolate mofetil, azathioprine, cyclophosphamide, thalidomide, etanercept, or corticosteroid with a dosage of 15 mg per day for three months, and patients taking chemotherapy for non-cervical cancer for more than two months. The exclusion criteria were patients whose Pap smear was not satisfactory. At the first visit, after providing informed consent, all of the patients underwent a Pap test, colposcopy, and cervical biopsy, and all of the results were recorded. The data were analyzed using SPSS version 17 (SPSS, Inc., Chicago, Illinois, USA). By using descriptive indices, we determined the sensitivity, specificity, positive and negative predictive value, and accuracy of each method, i.e., conventional Pap smear, colposcopy, and cervical biopsy, with the latter considered as the gold-standard test. The sample size was determined by considering 5% error and 80% sensitivity for colposcopy in detecting cervical intra-epithelial lesions, and, with the least error of 10%, the minimum size of the sample was determined to be 70 patients. However, we actually enrolled 101 patients in the study who met the inclusion criteria.

3. Results

In this study of 101 immunodeficient patients, the highest incidence of immunodeficiency (53.3%) was associated with rheumatoid arthritis. This was followed by chemotherapy (30.7%), patients with lupus erythematosus (12.9%), and AIDS (3%). Tables 1 and 2 provide the results of the Pap smears, colposcopies, and cervical biopsies.

Table 1. Distribution of diagnostic results of colposcopy and biopsy cytology among the referred patients

Results of biopsy and colposcopy	Biopsy		Colposcopy	
	n	%	n	%
Normal	68	67.3	60	59.4
CIN1 ¹	28	27.7	36	35.6
CIN2	4	4	4	4
CIN3	1	1	1	1
Total	101	100	101	100

1: Cervical intraepithelial neoplasia

Table 2. Frequency of distribution of diagnostic results of cytology among the referred patients

Results of cytology	Cytology	
	n	%
LSIL ¹	5	5
ASC-H	3	3
ASCUS ²	4	4
Normal	89	88
Total	101	100

1: Low Grade Squamous Intraepithelial Lesion; 2: Atypical Squamous Cell Undetermined Significant

To achieve the results of sensitivity, specificity, positive and negative predictive value in Pap smear, once in general form and another time based on age and the type of immunodeficiency, data were analyzed (Tables 2-5). Sensitivity and specificity of colposcopy was not measurable based on age and the type of immunodeficiency because of existing one cell empty in table of sensitivity and specificity. In the 23 to 44 age group, we had three cases that had both positive colposcopy and positive biopsy. In the 45 to 78 age group, we had two cases with positive colposcopy, but no one had a positive biopsy. In the group I of immunodeficiency, we had two cases with positive colposcopy and positive biopsy, and, in the group II of immunodeficiency, we had three cases with positive colposcopy and just one with a positive biopsy.

Table 3. Comparison of the frequency distributions of diagnostic results of biopsy among the referred patients based on Pap smear test and colposcopy

Results of Pap smear and colposcopy		Biopsy results		p-value
		Positive	Negative	
Pap smear	Positive	6	1	0.002
	Negative	27	67	
	Total	33	68	
Colposcopy	Positive	4	1	0.000
	Negative	2	94	
	Total	6	95	

Table 4. Comparison of the frequency distribution of diagnostic results of biopsy and Pap smear test among the referred patients based on the type of immunodeficiency

Results of Pap smear		Biopsy results		p-value
		Negative	Positive	
Group I immunodeficiency	Positive	1	3	0.064
	Negative	44	19	
	Total	45	22	
Group II immunodeficiency	Positive	0	3	0.014
	Negative	20	8	
	Total	20	11	

Table 5. Comparison of the frequency distribution of diagnostic results of biopsy among the referred patients based on age groups and Pap smear

Results of Pap smear (grouped by age)		Biopsy results		p-value
		Positive	Negative	
23-44 year	Positive	5	0	0.001
	Negative	18	43	
	Total	23	43	
45-78 year	Positive	1	1	0.490
	Negative	9	24	
	Total	10	25	

Sensitivity and specificity 18.2% (CI: 12.6-24.6), 98.5% (CI: 92.5-100) and positive and negative predictive value of Pap test in general were 85.7 and 71.3%, respectively. The precision of the Pap smear was 72.2%. Sensitivity and specificity of colposcopy were 66.7% (CI: 60.7- 72.7) and 98.94% (CI: 92.94-100), respectively, and the positive and negative predictive values of colposcopy were 80 and 97.9%, respectively. In general, the accuracy of colposcopy was calculated as 97%. Sensitivity and specificity of Pap smear in the 23-44 age group (fertility ages) were 21.7% (CI: 15.7-27.7) and 100%, respectively, and the positive and negative predictive values were 100 and 70.5%, respectively (table 3). We divided the immunodeficient patients into two groups, as shown in Table 4. Group I consisted of patients with systemic lupus erythematosus or rheumatoid arthritis, as well as renal transplant recipients who had been treated with immunosuppressive drugs for more than two months, e.g., cyclosporine, tacrolimus, sirolimus, mycophenolate mofetil, azathioprine, cyclophosphamide, thalidomide, etanercept, and corticosteroid with dosages of 15 mg per day for three months. Group II included patients with different types of tumors, such as breast cancer or lymphoma, who had undergone chemotherapy for more than two months. Sensitivity and specificity of Pap smear in group I of immunodeficiency patients, including patients with systemic lupus erythematosus and rheumatoid arthritis as well as renal transplant recipients and those with multiple sclerosis 13.6% (CI: 7.6-19.6) and 97.8% (CI: 91.8 -100) respectively. Positive and negative predictive were 75% and 69.8%, respectively. Group II immunodeficiency patients included patients receiving chemotherapy, and the sensitivity and specificity of their Pap test were 27.3% (CI: 33.3- 21.3) and 100%, respectively, and their positive and negative predictive values were 100 and 71.4%, respectively. The accuracies of the Pap smears in groups I and II of immunodeficient patients were calculated as 70.14 and 74.19%, respectively. We had four patients who were Atypical Squamous Cell Undetermined Significant (ASCUS) in the Pap test and three of them were CIN1 in colposcopy, while only one of them was confirm by biopsy as CIN1. According to Table 6, among the 101 immunodeficient patients, the frequency distribution of HPV infection was 21.8%, and the most frequency was related to HPV16 subtype of HPV, which was 17.8%.

Table 6. Frequency distribution of HPV infection among referred patients

Result of HPV test		n	%
Negative for HPV		79	78.2
Positive cases	HPV6	2	2
	HPV16	18	17.8
	HPV18	1	1
	HPV34	1	1
Total positive cases		22	21.8

4. Discussion

In developing countries, cervical cancer, which is preventable, is one of the most common causes of death in women. Several meta-analysis studies have shown that the sensitivity and specificity of cervical cytology is relatively low, since sensitivity is 30-87% and specificity is 100 to 86% (14). In this study, sensitivity, specificity, and the positive and negative predictive values test of Pap smear were determined to be 18.2, 98.5, 85.7, and 71.3%, respectively. Sensitivity, specificity, and the positive and negative predictive values of colposcopy were calculated as 66.7, 98.94, 80, and 97.9%, respectively. An abnormal Pap smear is an indication for colposcopy, endocervical curettage, and cervical biopsy for detecting cervical cancer (15). In this study we had four patients who were ASCUS in Pap test and three of them were CIN1 in colposcopy, while only one of them was CIN1 and approved for cervical biopsy. The results of ASCUS in Pap smear were not of concern here, because they were all reported as CIN1 or normal in biopsy. There have been very few studies of the performance of the Pap test when it is used for immunocompromised women (16), but in one study conducted by Cordiner et al., high false-negative rates were found in immunosuppressed recipients of kidney transplants (17). The Cordiner et al. study, as well as similar studies conducted by other researchers, have proposed that all immunosuppressed women be tested with colposcopy to detect important changes at the cellular level (18). The sensitivity and specificity of colposcopy, when used with a general population to detect CIN and cervical lesions, ranged from 87 to 99% and 23 to 87%, respectively (19). In this study, sensitivity, specificity, and positive and negative predictive values of Pap smear in the 23-44 age group were 21.7, 100, 100, and 70.5%, respectively. In the 45-78 age group, the values were 10, 96, 50, and 72.7%, respectively. However, the sensitivity and specificity of colposcopy were 80% (CI: 74-86) and 97.7% (CI: 91.9-100), respectively, and the positive and negative predictive values of colposcopy were 66.7 and 68.9%, respectively. The false negative results in the Pap test of HIV-infected patients could have been due to other infections, such as *Neisseria gonorrhoeae* and *trichomonas vaginalis* (20). Studies have shown that even HIV patients who have a negative Pap smear should be screened every six months. The study showed that this approach can be more

beneficial than other preventive cares. This study showed that 20.3% of HIV patients had abnormal Pap smears, and 10.7% of them had abnormal colposcopy. The results of this study suggest that colposcopy should be considered as the routine screening for these patients (21). While, in this study, abnormal Pap smear was 7% and abnormal colposcopy was 5%. In the study of Maiman et al. (1998) in Colombia on 248 HIV-infected women, the sensitivity and specificity of colposcopy for all CIN grades were 80 and 29%, respectively, and, for high-grade CIN, they were 83 and 27%, respectively (22). In this study, the positive colposcopy included CIN2 and higher, and, because of the inadequate sample, we could not calculate the sensitivity and specificity in each grade of CIN separately as was done in the previous study. In Vanuatu, in a pilot study of 496 women, cytology and visual Inspection were evaluated as screening tests for detection of CIN2 or worse (CIN2+). Using Lugol's iodine for the detection of CIN2+ on biopsy, the sensitivity of Visual Inspection was 0.63. The specificity was 32%, and the positive predictive value was 0.09. Sensitivity was 0.99 and specificity was 0.77 for HSIL cytology, while the positive predictive value was 0.88. Compared to visual inspection, HSIL cytology was much more sensitive, and its positive predictive value for CIN2+ was significantly greater ($p < 0.01$) (23). A Japanese study used low-grade squamous intraepithelial lesion as the cut-off point, and there was a 94.7% sensitivity for the detection of cervical cancer (24). Due to the use of different reference tests and different target groups, various studies have reported different accuracy values for conventional cytology (8, 25). Even so, sensitivity was in the range of 50 to 80%, while specificity was in the range of 70 to 90% (26). In a cohort study, Anderson et al. examined the accuracy of the Pap test among women who had HIV infections as well as women at high risk for such infections. They concluded that, for these two groups of women, there was significant agreement between the cytologic findings and the colposcopic and histologic findings. Despite having normal cytologic findings, a few of the HIV-infected women had cervical intraepithelial neoplasia. Among these women, Pap screenings would have detected cytologic abnormalities in 95% of these women within one year. These findings do not support the routine use of colposcopy in all HIV-infected women (27). Studies in the USA have shown that women in the 29-30 age group who live in areas where the prevalence of HPV and HIV is high have a higher risk of having cervical cancer. Cervical cancer is invasive, but it also is preventable if special screening is conducted for HIV-infected women (28). The results of a review study showed that many gynecologists in health organizations consider neither special screening for cervical cancer for HIV-infected women nor the function of the immune system, such as CD4 lymphocyte (29). Canada is one of the many countries in the world in which colposcopy is used extensively for the routine screening of HIV-infected women. However, for ethical reasons and because of the high cost, this method is not routinely used to date. In Canada, routine screening is done every six months using the Pap smear and follow-up tests if the patients have HIV (30). In the USA, it is suggested that, even when the Pap smear is normal, patients should repeat the Pap smear every three months (31-33). Leibenson et al. studied 84 HIV-infected women, and their results showed that HIV-infected and immunocompromised women are more vulnerable to cervical cancer, but special programs for screening of these patients have yet to be implemented (32). It seems that the rate of persistent HPV in these patients is higher than in the general population because their immune systems are compromised, making them vulnerable to pre-malignant lesions.

5. Conclusions

In this study, colposcopy produced higher levels of accuracy, sensitivity, specificity, and negative predictive value than Pap smear in detecting high-grade, cervical, pre-malignant lesions (CIN \geq 2). Since cervical cancer is the most common gynecological cancer in developing countries and since the accuracy of the Pap smear was low in this study, there is a clear need for a method that can provide an early diagnosis of cervical cancer. For that reason, we recommend that secondary immunodeficient patients have an annual colposcopy instead of a Pap smear.

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Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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