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Comparison Between Pap smear, Colposcopy and Cervical Histopathology Findings in Patients with Atypical Glandular Cells Results in Pap Smears

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ABSTRACT

Background & Objective: The objective of this study was to evaluate colposcopic, endocervical curettage (ECC) and endometrial curettage (EMC) findings in comparison with Pap smears findings.

Materials & Methods: Out of 100,000 Pap smears, a total number of 75 eligible women with atypical glandular cells (AGCs) referred to gynecology clinics in Isfahan, Iran, and seventy women were selected to undergo Pap smear test, colposcopic examination and ECC. EMC was performed in women older than 35. Pap smear test results were classified as normal, inflammation, AGCs and necrosis. Colposcopy, ECC and EMC findings were classified as normal, benign and malignant pathologic lesions.

Results: Repetitive Pap smears findings were as follows: 15.7% were normal, 77.2% had inflammation, 4% had AGC and 3.1% had necrosis. Based on colposcopy findings, 61.2%, 7.5%, and 31.3% of the samples were classified as normal, benign and malignant, respectively. ECC findings in 95.5% of women was indicative of benign lesions and malignant lesions in 4.5%. EMC findings showed that 79.7% were normal, 8.5% had benign lesions and 11.9% had malignant lesions. Pap smears with several AGCs were associated with benign lesions in 24.2% of the cases and premalignant and malignant lesions in 14.2% of the cases.

Conclusion: According to our study, due to the significant association between AGC cytology and pathologic cervical and endometrial lesions, intensive assessment is necessary in women with AGC Pap smears, especially in older and post-menopausal women, in order to reduce mortality.

Keywords: Atypical Glandular Cells, Colposcopy, Endocervical curettage, Pap smear, Endometrial curettage

Introduction

Cervical cancer is one of the leading causes of death in women worldwide **(1, 2)**. This cancer is manageable and highly curable when found and treated in early stages, using regular screening tests **(3)**. Widespread screening programs are available to diagnose pre-malignant cervical lesions, which can be an important approach to decrease cervical cancer mortality **(4, 5)**.

In the last 60 years, Pap smear, the most widely used screening test for cervical cancer, which enabled the prompt identification of morphological changes in the cervical epithelium, has led to decrease in cervical cancer incidence and mortality **(6)**. In countries with regular Pap smear screening programs, the incidence of cervical cancer has decreased from the second-most common cancers to the eighth in the last 50 years. While in most areas without screening programs, cervical cancer is still the second most common cancer in women **(7)**.

Positive Pap smear test may reveal either squamous or glandular cell abnormalities **(8)**. Atypical glandular cells (AGCs) are found less commonly and according to the literature, in 0.1% to 2.1% of cervical cytology samples **(9, 10)**. AGCs are closely associated with premalignant and malignant diseases. Therefore, Pap smear samples including AGCs are clinically important. It was previously reported that invasive carcinomas are found in 3% to 17% and cervical intraepithelial neoplasia are found in 9% to 38% of the samples with AGC **(9)**. Accordingly, additional diagnostic tests must be used to detect premalignant or malignant conditions. Cervical biopsy, colposcopic examination, endocervical curettage (ECC) and endo-metrial curettage (EMC) are among evaluations used

for women with AGCs in their Pap smear **(11, 12)**. Various findings have been reported in studies addressing the management of patients with AGCs in their Pap smear. Therefore, the present study aims to review the colposcopic, ECC and EMC findings in women with AGCs in their Pap smear.

Materials and Methods

From August 2018 to April 2019, out of 100,000 Pap smears, 75 women with AGCs in their Pap smear referred to gynecology clinics in Isfahan, Iran. Women were eligible if they did not have any history of squamous cell abnormality in Pap smear and prior history of cancer of any type. Women with previous or concurrent chemotherapy and/or radiation to the uterine corpus, cervix and vagina, or human immune-deficiency virus (HIV) infection were excluded. The study was approved by the Institutional Review Board and Ethics Committee of Isfahan University of Medical Sciences (ir.mui.rec.1397.3.376) and written informed consent was obtained from all studied women.

Firstly, all women underwent Pap smear test. All Pap smears were performed using conventional method and were classified as: normal, inflammation, AGCs and necrosis. All women received colposcopic examination and ECC. For Women older than 35 years old, EMC was also performed. The procedures were performed by a gynecologist-oncologist. Collected samples were transported to the laboratory and initially screened by a pathologist. The interpretations of colposcopy were made by a gynecologist-oncologist as normal, benign change (metaplasia or polyp) and premalignant or malignant change (acetowhite lesions, abnormal vascular patterns or cauliflower lesions). Furthermore, the interpretations of ECC and EMC findings were made by a pathologist and they were classified as normal, benign lesions (cervicitis, endocervical polyp and endometrial polyp) and premalignant or malignant lesion (in situ carcinoma, cervical adenocarcinoma, cervical squamous cell carcinoma, endometrial hyper-plasia and endometrial adenocarcinoma). Pati-ents were followed for 6 months and Pap smears test was performed again in all women expect for five patients who underwent hysterectomy and one patient who passed away.

Collected data included age, marriage age and gravidity, parity status, history of abortion, the patients' and their partners' smoking status, education level (illiterate, under diploma, diploma and higher education), socioeconomic status (SES) (low, moder-ate, high), history of sexually transmitted disea-ses (STD), menopause status and contraceptive usage.

Statistical analysis was done using SPSS 24 (SPSS, Inc., Chicago, IL, USA). Descriptive data are presented as mean±SD. Independent sample t-test, one-way ANOVA and Chi-square test were used to compare women's characteristics in regard to colposcopy, ECC and EMC findings. The level of significance was considered to be less than 0.05.

Results

From August 2018 to April 2019, 100,000 screening Pap smears were collected in Isfahan, Iran, from which, 75 Pap smears had AGCs with a prevalence rate of 0.075%. Five women were excluded from the study due to excluding criteria, leaving 70 patients.

The mean of age and marriage age in studied women were 43.1 and 18.8 years, respectively. Most of the women (81.4%) were Multiparous. In these women, 15.7% had histories of abortion and 8.6% were active or passive smokers. Menopause had occurred in 20% and 37.6% reported histories of STD.

Comparison of patients' characteristics in regard to colposcopy findings are presented in Table 1. The mean age, marriage age and gravidity were similar among women with normal, benign and malignant colposcopy (P>0.05). Parity status, history of abortion, the patients' and their partners' smoking status, history of STD and menopause status in women with normal, benign and malignant colposcopy were similar and no significant differences were noted (P>0.05). In addition, education level, SES and contraceptive usage were not significantly different among women in regard to their colposcopy findings (P>0.05).

Comparison of women's characteristics in regard to ECC findings are shown in Table 2. Women's age, marriage age and gravidity were similar in regard to benign or malignant ECC findings (P>0.05). Also, women with benign or malignant ECC findings were similar in respect to all other variables including parity status, history of abortion, smoking status, education level, SES, history of STD, menopause status and contraceptive usage (P>0.05).

Table 3 shows the comparison between women's characteristics in regard to EMC findings. Women with malignant results were significantly older than other women with normal and benign EMC findings (P=0.039). Mean marriage age and gravidity were similar among women with normal, benign and malignant EMC (P>0.05). Menopause had occurred in 71.4% of women with malignant, whereas, only 14.9% of women with normal findings had experienced menopause (P=0.003). All the other studied charact-eristics were similar among women in regard to EMC findings (P>0.05).

Repetitive Pap smear tests at baseline were normal in 15.7% of the women, 77.2% had inflammation, 4% had AGCs and 3.1% had necrosis. According to colposcopy findings, 61.2%, 7.5%, and 31.3% of pati-ents had normal, benign and premalignant or malignant findings, respectively. Our results showed the 100% sensitivity and 72.4% specificity of colposcopy for cervical pathologic lesions but only 60% sensitivity and 43% specificity of colposcopy for endometrial

pathologic lesions. ECC findings in 95.5% of women was indicative of benign lesions and malignant lesions in 4.5%. Moreover, findings of EMC in studied women were as follows: 79.7% with normal, 8.5% with benign and 11.9% with malignant lesions. Pap smears with several AGCs were associated with benign lesions in 24.2% of the cases and premalignant and malignant lesions in 14.2% of the cases.

Of these 70 patients, five patients underwent surgery because of cervical or endometrial malignant lesions. Four of them received medical therapy due to diagnosis of endometrial hyperplasia. Surgery or medical therapy was not reported in 60 patients. One patient received chemo radiation therapy because she was inappropriate candidates for surgery due to stage 2B of cervical cancer.

During the six-month follow-up period, except five women who underwent hysterectomy and one patient who passed away, 24.6% of fallow-up Pap tests were normal and 75.4% had inflammation.

Table 4 shows abnormal ECC and EMC findings in studied women with AGC Pap smears and the relative outcomes.

Table 1. Profile of studied women by colposcopy findings

	Colposcopy findings			
	Normal	Benign	Malignant	P-value
Age (year)	44.3 ± 10.9	42.0 ± 7.2	39.9 ± 8.4	0.237
Marriage age	18.4 ± 41	18.0 ± 3.4	19.7 ± 5.4	0.51
Gravidity	2.8 ± 1.8	4.0 ± 1.4	2.6 ± 1.4	0.238
Parity				
Nulligravid	3 (7.3)	0	1 (4.8)	
Primiparous	5 (12.2)	0	4 (19)	0.788
Multiparous	33 (80.5)	5 (100)	16 (76.2)	
History of abortion	7 (17.1)	1 (20)	3 (14.3)	0.937
Smoking	4 (9.8)	0	2 (9.5)	0.766
Partner smoking	11 (26.8)	1 (20)	5 (23.8)	0.928
Education status				
Illiterate	7 (17.1)	0	3 (14.3)	
Under diploma	15 (36.6)	4 (80)	10 (47.6)	0.448
Diploma and upper	19 (46.3)	1 (20)	8 (38.1)	
Socioeconomic status				
Low	9 (22)	0	8 (38.1)	
Moderate	21 (51.2)	5 (100)	7 (33.3)	0.091
High	11 (26.8)	0	6 (28.6)	
Contraceptive use	11 (26.8)	1 (20)	1 (4.8)	0.117
Menopause	9 (22)	1 (20)	2 (9.5)	0.610
History of STD	16 (39)	1 (20)	9 (42.9)	0.731

Data are mean ± SD, median [IQR] or number (%), STD: Sexually Transmitted Diseases

Table 2. Profile of studied women by Endocervical curettage findings

	Endocervical curettage findings		P-value
	Benign	Malignant	
Age (year)	42.9 ± 9.7	48.0 ± 11.3	0.376
Marriage age	18.6 ± 4.1	16.7 ± 2.9	0.426
Gravidity	2.9 ± 1.7	2.3 ± 1.1	0.537
Parity			
Nulligravid	2 (3.1)	0	
Primiparous	9 (14.1)	0	0.735
Multiparous	53 (82.8)	3 (100)	
History of abortion	11 (17.2)	0	0.432

	Endocervical curettage findings		P-value
	Benign	Malignant	
Smoking	5 (7.8)	0	0.615
Partner smoking	17 (26.60	1 (33.3)	0.796
Education status			
Illiterate	8 (12.5)	1 (33.3)	0.508
Under diploma	28 (43.8)	1 (33.3)	
Diploma and upper	28 (43.8)	1 (33.3)	
Socioeconomic status			
Low	16 925)	0	0.263
Moderate	29 (45.3)	3 (100)	
High	19 929.7)	0	
Contraceptive use	14 (21.9)	0	0.597
Menopause	11 (17.2)	2 (66.7)	0.094
History of STD	26 (40.6)	0	0.223

Data are mean ± SD, median [IQR] or number (%), STD: Sexually Transmitted Diseases

Table 3. Profile of studied women by Endometrial curettage findings

	Endometrial curettage findings			
	Normal	Benign	Malignant	P-value
Age (year)	42.3 ± 9.0	46.0 ± 4.4	51.4 ± 9.9	0.039
Marriage age	19.5 ± 4.9	16.4 ± 2.2	16.9 ± 1.9	0.153
Gravidity	2.9 ± 1.8	3.0 ± 1.2	2.8 ± 1.3	0.99.
Parity				
Nulligravid	3 (6.4)	0	0	0.918
Primiparous	6 (12.8)	0	1 (14.3)	
Multiparous	38 (80.9)	5 (100)	6 (85.7)	
History of abortion	9 (19.1)	0	0	0.270
Smoking	4 (8.5)	1 (20)	0	0.331
Partner smoking	15 (31.9)	0	1 (14.3)	0.317
Education status				
Illiterate	6 (12.8)	1 (20)	1 (14.3)	0.546
Under diploma	19 (40.4)	2 (40)	5 (71.4)	
Diploma and upper	22 (46.8)	2 (40)	1 (14.3)	
Socioeconomic status				
Low	13 (27.7)	2 (40)	1 (14.3)	0.173
Moderate	20 (42.6)	1 (20)	6 (85.7)	
High	14 (29.8)	2 (40)	0	
Contraceptive use	10 (21.3)	1 (20)	1 (14.3)	0.912
Menopause	7 (14.9)	0	5 (71.4)	0.003
History of STD	16 (34)	3 (60)	5 (71.4)	0.111

Data are mean ± SD, median [IQR] or number (%), STD: Sexually Transmitted Diseases

Table 4. Endocervical curettage (ECC) and Endometrial curettage (EMC) findings in studied women and our outcomes

Pathology	Number of cases	Mean age	Treatment
Cervical metaplasia	10(14.3%)	32	follow-up
Cervical Polyp	3(4.2%)	35	follow-up

Pathology	Number of cases	Mean age	Treatment
Endometrial Polyp	4(5.7%)	48	follow-up
SSC OF Cervix	2(2.8%)	55	Radical hysterectomy(1B2) + adjutant chemo radiotherapy chemo radiotherapy(2B)➔mortality
Adenocarcinoma of Cervix	1(1.4%)	70	Radical hysterectomy(1B2) + adjutant chemo radiotherapy
Endometrial Atypical Hyperplasia	6(8.5%)	49	4 cases: medical therapy 2 cases: hysterectomy➔ pathology: Atypical complex hyperplasia
Endometrial Adenocarcinoma	1(1.4%)	40	Hysterectomy + BSO (stage 1B-Grade1) +radiotherapy

Discussion

According to the literature, AGCs are rarely found in Pap smears (<5%) **(13, 14)**, while malignant or premalignant lesions can be found in 22% to 53% samples with AGCs **(15)**. AGCs observation rate in the present study (0.075%) was almost the same as the pervious literature. Furthermore, in our study, 38% of pathologic lesions including 24.2% benign lesion and 14.2% malignant or premalignant lesions were diagnosed in patients with AGCs in their Pap smears.

In a study by Wanq *et al.* (2016) on 3054328 Pap smears from 1980 to 2011, the prevalence of cervical cancer was 1.4% in women with AGC, which was lower than that of women with high grade squamous intraepithelial lesion (HSIL) (2.5%), but higher than that of women with low grade squamous intraepithelial lesion (LSIL) (0.2%). Cervical adenocarcinoma was the most common malignancy in patients with AGCs in this study. The incidence rate of adenocarcinoma was 61 times higher in women with normal cytology results in the first screening round after AGC, and remained nine times higher for up to 15.5 years **(16)**. In our study, histologic findings revealed cervical squamous cell carcinoma in two patients. Cervical adenocarcinoma and endometrial adenocarcinoma were separately diagnosed in two patients (4% had cervical cancer and 1.3% had endometrial cancer).

In a study by Saad RS *et al.* (2006) on 90 women with AGC Pap smears, 40% assertion with important pathologic lesions was reported, especially in patients older than 50 **(17)**. In a Kim MK *et al.* (2017) study on 435778 Pap smears, 0.17% AGC cytology was reported. In patients with malignant pathology AGC-NOS, AEM and AEC were reported in 15.3%, 59.6% and 25.1% of the cases, respectively. Prevalence of endometrial neoplasia in women over 40 years and prevalence of cervical neoplasia in women under 40 years were discovered **(18)**. In a Pradham *et al.* (2016) study on 589830 Pap smears, 0.06% AGC cytology was reported. The underling neoplasia in patients under and over 50 years were CIN2-3 and endometrial carcinoma, respectively **(19)**. We understood that endometrial pathologic lesions but not cervical lesions in older and post-menopausal women were the most common in our study.

The consistency between cytological findings and colposcopic and histopathological findings is evaluated in other studies. In a study by Akhter *et al.*, the alignment between colposcopic findings, Pap smear cytology and histopathological diagnosis in gynecology patients was assessed. They reported a significant association between colposcopic findings and histopathological diagnosis and weak consistency between cytological findings and colposcopic and histopathological findings **(20)**. Dasari *et al.* found that histopathology findings were not in agreement with cytological findings and showed high proportion of CIN, which can be found in Pap smear with persistent inflammatory **(21)**. Furthermore, other studies reported insignificant association between cytology and colposcopic findings. The consistency between cytology and histopathology was fair **(22, 23)**. In our study on Pap smears with AGCs, we realized that although colposcopy was neither specific nor sensitive for endometrial pathologic lesions in patients with AGC Pap smears indicating the necessity of endometrial biopsy for these patients, sensitivity and specificity of colposcopy for cervical pathologic lesions were 100% and 72.4%, respectively, which confirms the critical role of colposcopy in early diagnosis of pathologic cervical lesions in women with AGC Pap smears.

This study has limitations and the results should be interpreted with caution. Firstly, due to the small samples size and consequently, low percentage of women with AGC Pap tests, we were not able to analyze the colposcopy, ECC and EMC findings in women with AGC in their Pap smears by classifying them into sub categories. Secondly, women who underwent health examinations at governmental gynecology clinics were enrolled on this study; therefore, our results may not reflect the general population. Hence, further multi-center studies with lager sample sizes are warranted to compare the colposcopy, ECC and EMC findings in women with AGC Pop smears.

Conclusion

According to our study and the similar studies, Pap smear screening in asymptomatic women is very important in order to prevent mortality. Moreover, because of high association between AGC cytology and pathologic cervical and endometrial lesions, intensive assessment is necessary in women with AGC

Pap smears, especially in older and post-menopausal women in order to reduce mortality. We also conclude that colposcopy is a sensitive and specific diagnostic method for cervical pathology, but not for endometrial pathology, in women with AGC Pap smears. We are pleased to contribute to access the best diagnostic and therapeutic approach for cervical cancer in women by presenting this study and reviewing other similar studies.

Statement of Ethics

The patient had ssigned the informed consent in the aim of reporting present article.

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Conflict of Interest

The authors declared no conflicts of interest.

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