

# Diagnostic Role of Papanicolaou Smear, Hemoglobin, Blood Group, and Other Clinical Symptoms in Detecting Endometrial Carcinoma: A Clinicopathological Study of 175 Iranian Women with Endometrial Carcinoma

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## Abstract

**Objectives:** Endometrial carcinoma (EC) is a common gynecologic malignancy in the female genital tract, especially in postmenopausal women. The current study aimed to analyze Papanicolaou (Pap) smear in patients with EC to assess the relationship between EC and abnormal cells in Pap smear, ABO blood group, and hemoglobin anemia.

**Materials and Methods:** A retrospective study was conducted on 175 patients with EC in Imam Hossein Hospital, Tehran, Iran, during the period from 2013 to 2019. The histology information of cases was extracted from the hospital database, and Pap smear slides were taken from pathological archives. The acquired information and slides were then reviewed by an expert pathologist in the hospital. The data were analyzed in SPSS (version 18) by the Chi-square test, Fisher's exact test, and independent-samples *t*-test.  $P < 0.05$  was assigned as significant.

**Results:** The mean age of patients was  $54.47 \pm 11.34$ , ranging from 32 to 85 years, and 31.4% of the patients were premenopausal women. Grade III, invasion  $\geq 50\%$  of myometrial, and advanced stage (III and IV) were diagnosed in 30%, 7.4%, and 22.86% of the patients, respectively. The most common histological types of EC were endometrioid (66.9%), papillary (10.3%), and malignant mixed Mullerian tumor (5.7%). The abnormal Pap smear was achieved only in 37 EC patients (21.1%). Endometrial cells, atypical squamous cells of undetermined significance, and atypical glandular cells were observed in 56.8%, 29.7%, and 13.5% of the patients  $> 40$  years of age with abnormal Pap smears, respectively. In patients with normal Pap smears, the most common results were inflammation in 75.1% and atrophy in 14.6% of the patients. Abnormal uterine bleeding was the most important problem observed in patients with EC.

**Conclusion:** The efficacy of Pap smear in detecting EC is limited. Therefore, women with EC,  $>40$  years of age, with heavy bleeding, anemia, O blood group, inflammation, and atrophy in Pap smear in the past 3 years need to be precisely checked up for EC. These items can be added as new criteria for EC screening procedures.

**Keywords:** Endometrial cancer, myometrial invasion, Papanicolaou smear, postmenopausal women

## INTRODUCTION

Endometrial carcinoma (EC) is one of the most common gynecologic malignancies<sup>[1]</sup> in the female genital tract in developed countries.<sup>[2,3]</sup> More than 80% of ECs occur in postmenopausal women,<sup>[1,4]</sup> and endometrioid histology is the

most common type of endometrial cancer.<sup>[2]</sup> However, there are biological and morphological varieties in endometrial neoplasm that cause different types of tumors, pathogenesis,

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prognosis, and histopathologic classifications.<sup>[2]</sup> The adjusted incidence rate of EC in Iran has been reported to range from 1.7% to 2.29% in 2004–2008.<sup>[5]</sup> The lifetime incidence of endometrial cancer is 1.1%, and its mortality rate is 0.4%, suggesting a good prognosis of the disease with early diagnosis.<sup>[6]</sup> Therefore, the early detection of EC results in an excellent survival rate<sup>[2]</sup> and a decrease in EC-related mortalities.

Papanicolaou (Pap) test is an essential screening test for the early detection of cervical cancer.<sup>[7,8]</sup> Nevertheless, the literature generally maintains that Pap smear is not a very precise, sensitive test for the detection of endometrial pathology.<sup>[9]</sup> To date, there is no standard screening test for the early detection of EC.<sup>[10]</sup> The Bethesda system recommends reporting of benign endometrial cells in all women over 40 years of age regardless of menopause; in 2014, the Bethesda system increased the reporting age to 45 years.<sup>[11,12]</sup>

Some studies have assessed the association of ABO blood groups with the hemoglobin (Hb) level on the prognosis of EC.<sup>[13,14]</sup> Moreover, there has been a misinterpretation about the role of Pap smear in the diagnosis of EC; hence, the effectiveness of this test in the diagnosis process of EC is uncertain. Based on the previous literature and as stated in many guidelines, the first diagnostic pathway for detecting women with EC is the measurement of endometrial thickness by transvaginal sonography.<sup>[6,15]</sup> Yet, no valid evidence has been presented for the predictive role of Pap smear in detecting EC. Therefore, the current study aimed to analyze Pap smear in patients with EC regarding the normal or atypical endometrial cells and to assess the relationship between atypical endometrial cells in Pap smear, ABO blood groups, Hb anemia, and clinically significant parameters such as grade, histopathological stage, and invasion.

## MATERIALS AND METHODS

A retrospective study was performed in the Oncology Department of Imam Hussein Hospital, Tehran, Iran, on 175 cases of EC over a 5-year period (2013–2018). The hospital database was used to extract information on cases with the histologic diagnosis of EC during these years.

All Pap smear slides of patients with EC, approved by biopsy, were taken from the pathological archives. Clinical data and demographic characteristics including menopausal status, patient age, ABO blood groups, tumor subgroup histology, grade and the stage of tumor based on the International Federation of Obstetrics and Gynecology, tumor diameter (cm), the depth of myometrial invasion ( $\geq 50\%$  and  $< 50\%$ ), myometrial invasion depth, lymphovascular invasion, surgical stage, treatment method, cervical, lymph

nodes, and lower uterine segment involvement were all extracted from patients' medical records. In addition, the Hb level of all patients with EC measured 1 day before the surgery was extracted from medical dossiers and recorded in checklists.<sup>[16]</sup>

The Pap smear slides were reviewed by an expert pathologist in the hospital for the presence of endometrial cells, and the results of reviews were reported using the 2014 Bethesda System. All results of Pap smear slides and time intervals (month) between Pap smear and cancer diagnosis were recorded. Only those EC patients were included in the analysis who had taken the Pap smear test 3 years before the EC diagnosis. Thus, patients with unknown Pap smear results, patients without Pap smear rests, or patients with a time interval of more than 3 years between Pap smear and EC diagnosis were excluded from the study.

## Ethical statements

The data of medical records and Pap smear slides of patients were used in this study. However, according to the ethics statements, informed consent was obtained from all the participating patients in the study. Besides, the Ethical Committee of Shahid Beheshti University of Medical Sciences approved the study protocol by IR.SBMU.REC.1398.693 code on January 26, 2020.

## Statistical analysis

The data were entered into SPSS version 20 (SPSS Inc., Chicago, IL, USA) and analyzed by descriptive statistics including mean, standard deviation, and frequency. Moreover, the associations among Pap smear results and demographic, clinical, and histologic data including subtype of cancer, stage, and grade were assessed by the Chi-square and Fisher's exact tests. Moreover, the mean of age, body mass index (BMI), tumor diameter, Hb, and blood group was compared between patients with abnormal and normal Pap smear by independent-samples *t*-test. Besides, the clinical outcomes including histological type, myometrium invasion depth, lymphovascular invasion, cervical involvement, lymph node involvement, lower uterine segment involvement, nuclear grade, and surgical stage were compared between EC patients with/without anemia and ABO blood groups by the Chi-square test.  $P < 0.05$  was considered statistically significant.

## RESULTS

While conducting this study, 260 patients were diagnosed with EC, but only 175 of them had Pap smear results 1 year before cancer diagnosis in the archive. Of 175 patients whose Pap smear results were assessed, 138 cases (78.9%) had normal (normal Pap smear) and 37 cases (21.1%) had atypical (abnormal Pap smear) results. One hundred

and fifty-eight patients (90.3%) were housekeepers and 143 patients (83.1%) lived in urban areas. Based on these results, the mean age of patients was  $54.47 \pm 11.34$  years, ranging from 32 to 85 years of age, and 13.4% of the patients were younger than 40 years old, while 68.6% were  $\geq 50$  years of age. The mean BMI was  $29.09 \pm 8.36$ , and according to the WHO classification, 77 patients (47.8%) were overweight and 47 patients (29.2%) were obese. The mean of Hb was  $11.30 \pm 1.66$  g/dL.

Table 1 depicts the demographic characteristics of patients, and Table 2 shows that 10 patients (6.8%) were never married and 119 patients (68.8%) were postmenopausal. The majority of the patients (92.6%, 162 cases <50%) had invasion myometrial in hysterectomy. Nuclear grade showed that 82 patients (48.2%) were Grade I, 37 patients (21.8%) were Grade II, and 51 patients (30%) were Grade III. Surgical stagings including early stages (I and II) and advanced stages (III and IV) were diagnosed in 135 patients (77.1%) and 40 patients (22.9%), respectively. The treatment of patients is shown in Table 2; as observed in Table 2, nine patients (5.15%) underwent surgery with adjuvant therapy. Of 166 patients (94.85%), 36 patients (21.68%) received chemotherapy, 49 patients (28%) received radiotherapy, and 81 patients (48.81%) received both radiotherapy and chemotherapy.

Endometrioid was the most common histological type in the studied patients found in 117 patients (66.9%). Papillary serous was observed in 18 patients (10.3%), malignant mixed Mullerian tumor (MMMT) was observed in 10 patients (5.7%), and clear cells were observed in nine patients (5.1%). Abnormal uterine bleeding and postmenopausal bleeding (PMB) were the most important problems of women with EC with 65.1% and 28% incidence rates, respectively. Menorrhagia was the most frequent symptom (17.4%) in women <40 years of age, and abdominal pain (0.8%) and calf edema (0.8%) occurred only in two postmenopausal patients. Furthermore, five postmenopausal patients (13.5%) with positive Pap smear results referred to the center for follow-up checkups.

Of all patients, 37 patients (21.1%) had abnormal and 138 patients (78.9%) had normal Pap smears. The endometrial cell was observed in 21 patients (56.8%) >40 years of age and was the most common type of result in patients with abnormal Pap smear. In addition, atypical squamous cells of undetermined significance (ASCUS) were found in 11 patients (29.7%) and atypical glandular cells (AGCs) were seen in five patients (13.5%) with abnormal Pap smear. Inflammation was the most common result in patients with normal Pap smear including severe inflammation in 15 patients (31.3%), mild inflammation in 21 patients (43.8%),

**Table 1: The frequency and relative percentage of demographic characteristics of patients with endometrial carcinoma**

Variables	n (%)
Age group	
<40 years	23 (13.4)
40-49 years	32 (18.3)
$\geq 50$ years	120 (68.6)
Marital status	
Never married	10 (6.8)
Married with spouse	115 (77.7)
Married without spouse (divorced/died)	23 (15.5)
BMI	
Underweight	3 (1.9)
Normal	34 (21.1)
Overweight	77 (47.8)
Obesity	47 (29.2)
Menopausal status	
Postmenopausal	119 (68.8)
Pre-menopausal	54 (31.2)
Residency place	
Urban	143 (83.1)
Rural	29 (16.9)
Job	
Housekeeper	158 (91.8)
Staff/worker	14 (8.2)
Education	
Lower diploma	93 (55.7)
Diploma	63 (37.7)
BS and higher	11 (6.6)
Blood group	
A	64 (37.0)
B	36 (20.8)
AB	21 (12.1)
O	52 (30.1)
Anemia	
Hb <12	109 (62.3)
Hb $\geq 12$	66 (37.7)
Blood pressure history	
Yes	66 (38.6)
Diabetes history	
Yes	36 (21.2)
Smoking history	
Yes	9 (5.3)
Hookah history	
Yes	12 (7.6)
History of using OCP	
Yes	29 (19.9)
Family history of cancer	
Yes	31 (21.4)
Myometrial invasion (%)	
<50	162 (92.6)
$\geq 50$	13 (7.4)
Nuclear grade	
1	82 (48.2)
2	37 (21.8)

*Contd...*

**Table 1: Contd...**

Variables	n (%)
3	51 (30.0)
Stage	
1	118 (67.4)
2	17 (9.7)
3	34 (19.4)
4	6 (3.4)
Histological type	
Endometrioid	117 (66.9)
Papillary	18 (10.3)
Clear cell	9 (5.1)
MMMT	10 (5.7)
Undifferentiated	2 (1.1)
Malignant mixed tumor	7 (4.0)
Unknown	12 (6.9)
Lymphovascular invasion	
Yes	54 (32.9)
Cervical involvement	
Yes	23 (14)
Lymph node involvement	
Yes	26 (16.8)
Lower uterine segment involvement	
Yes	17 (11.2)
Treatment method	
Surgery without adjuvant therapy	9 (5.15)
Surgery with adjuvant therapy	166 (94.85)
Adjuvant therapy	
Chemotherapy	36 (21.68)
EBNT	11 (6.62)
Bradycardia	21 (12.65)
Bradycardia and EBNT	17 (10.24)
Radiotherapy and chemotherapy	81 (48.81)
Surgery type	
TAH + BSO + LND + biopsy omentum	80 (48.5)
TAH + BSO	41 (24.8)
TAH + BSO + biopsy omentum	7 (4.2)
TAH + BSO + LND	37 (22.4)

MMMT: Malignant mixed Mullerian tumor, BMI: Body mass index, Hb: Hemoglobin, OCP: Oral contraceptive pill, EBNT: External Beam Radiotherapy, TAH: Total abdominal hysterectomy, BSO: Bilateral salpingo-oophorectomy, LND: Lymph node dissection

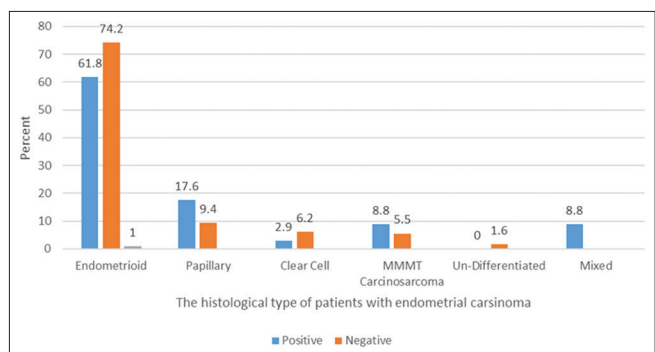
and atrophy in seven patients (14.6%); 23 patients (47.9%) were normal. Among all patients, however, 16 patients with normal Pap smears and two patients with abnormal Pap smears were unsatisfied with the results of the treatment.

Figure 1 shows that endometrioid was the most common histological type in both patients with abnormal (61.8%) and normal (74.2%) Pap smears. The papillary serous histological type was in the second rank and involved 17.6% and 9.4% of the patients with abnormal and normal Pap smears, respectively. According to the results shown in Table 2, the mean age in patients with abnormal Pap smear was higher than the mean age in normal patients (57.94 ± 12.22 vs. 53.53 ± 11.01, P = 0.038).

**Table 2: The relationship between demographic characteristics of patients based on the Papanicolaou smear results in patients with endometrial carcinoma**

Demographic characteristics	Pap smear		P
	Abnormal	Normal	
Age, mean±SD	57.94±12.22	53.53±11.01	0.038†
Age at marriage, mean±SD	18.72±3.76	21.56±19.72	0.443†
Age at first birth, mean±SD	20.11±5.35	21.17±7.41	0.404†
Age at menopause, mean±SD	48.75±5.06	48.75±4.51	0.998†
Weight, mean±SD	77.89±17.09	72.75±15.52	0.083†
Parity, mean±SD	3.90±2.31	3.44±2.16	0.303†
Interval time between Pap smear and cancer diagnosis, mean±SD	3.33±2.61	4.02±3.80	0.405†
Hb, mean±SD	10.78±1.66	11.45±1.63	0.035†
BMI, n (%)			
Normal	4 (12.5)	33 (25.6)	0.013‡
Overweight	12 (37.5)	65 (50.4)	
Obesity	16 (50)	31 (24)	
Education, n (%)			
Lower diploma	25 (67.6)	68 (49.3)	0.048‡
Diploma and higher	12 (32.4)	70 (50.7)	
Residency place, n (%)			
Urban	31 (86.1)	111 (82.2)	0.581‡
Rural	5 (13.9)	24 (17.8)	
Job, n (%)			
Housekeeper	34 (91.9)	124 (89.9)	0.497‡
Staff	3 (8.1)	14 (10.1)	
OCP use, n (%)			
Yes	8 (27.6)	20 (17.2)	0.158†
No	21 (72.4)	96 (82.8)	
Family history of cancer, n (%)			
Yes	8 (27.6)	23 (20)	0.257‡
No	21 (72.4)	92 (80)	

†t-test, ‡Chi-square test. Pap: Papanicolaou, BMI: Body mass index, Hb: Hemoglobin, OCP: Oral contraceptive pill, SD: Standard deviation



**Figure 1:** The histological type of abnormal and normal Papanicolaou smears in endometrial carcinoma

Obesity was observed in 16 patients (50%) with abnormal Pap smear and 31 patients (24%) in another group (P = 0.013). In addition, patients with abnormal Pap smear were significantly lower educated than patients with normal Pap smear (67% vs. 49.3% with lower education). However,

patients with EC were not statistically significant based on the Pap smear results in mean age at marriage, age at first birth, age at menopause, weight, and parity. Residency place, job, income level, oral contraceptive pill use, and family history of cancer were not related to the results of Pap smear. Moreover, marital status ( $P = 0.644$ ), history of blood pressure ( $P = 0.495$ ), cigarette smoking ( $P = 0.395$ ), and hookah smoking ( $P = 0.216$ ) were not significant in patients with abnormal and normal Pap smears.

As shown in Table 3, menopausal status, invasion depth, cervical, lymph node and lower uterine segment involvement, grade, and stage were significantly different in patients based on the Pap smear results ( $P < 0.05$ ). Accordingly, postmenopausal status (81.1% vs. 65.4%) and some clinicopathological finding were higher in patients with abnormal Pap smear including invasion depth  $\geq 50\%$  (21.6% vs. 3.6%), cervical involvement (30.3% vs. 10%), involvement of lymph nodes (30.3% vs. 13.2%), lower uterine segment involvement (24.2% vs. 7.6%), Grade 3 (54.3% vs. 23.7%), and advanced stage (56.8% vs. 13.8%), respectively. Nevertheless, there was no significant relationship between Pap smear results and adjuvant therapy, histological type, lymphovascular invasion, and surgery treatment ( $P > 0.05$ ). Moreover, the mean of tumor diameter was  $4.07 \pm 1.25$  cm and varied from 0.45 to 6.5 cm; the mean of tumor diameter was not statistically significant in patients with abnormal and normal Pap smears ( $P = 0.290$ ).

The mean Hb level was  $11.22 \pm 1.66$  g/dL before the surgery, and 66 patients (37.7%) had normal Hb and 109 patients (62.3%) had anemia. Patients with anemia had a higher rate of nonendometrioid histology ( $P = 0.016$ ) and advanced stages ( $P = 0.042$ ) than the other group with normal Hb [Table 4]. The rate of the advanced stage was higher in patients who had Hb  $< 12$  g/dL compared with patients with Hb  $\geq 12$  g/dL (15.2% vs. 27.5%,  $P = 0.045$ ). Besides, nonendometrioid histology type was 39.4% in patients with anemia and 22.7% in normal patients regarding Hb. Nevertheless, there was no significant relationship between anemia and other clinical outcomes of EC including myometrium invasion depth, lymphovascular invasion, cervical involvement, lymph node involvement, lower uterine segment involvement, and nuclear grade ( $P > 0.05$ ).

The frequencies of ABO blood groups are shown in Table 1. Different blood groups were observed in the patients: A (37%), B (20.8%), AB (12.1%), and O (30.1%), A blood group was the most common blood group in EC patients. Therefore, the frequencies of ABO blood groups of non-O and O were 69.9% and 30.1%, respectively. Furthermore, the association of clinical outcomes of EC with ABO blood groups revealed a significant association with the grade

**Table 3: The association between clinical outcomes of endometrial carcinoma in patients based on the Papanicolaou smear results**

Clinical outcomes	Pap smear		P <sup>†</sup>
	Abnormal (n=37), n (%)	Normal (n=138), n (%)	
Menopausal status			
Postmenopausal	30 (81.1)	89 (65.4)	0.049
Premenopausal	7 (18.7)	47 (34.6)	
Histological type			
Endometrioid	21 (56.8)	96 (69.6)	0.103
Other types	16 (43.2)	42 (30.4)	
Myometrial invasion depth (%)			
<50	29 (78.4)	133 (96.4)	0.001
$\geq 50$	8 (21.6)	5 (3.6)	
Lymphovascular invasion			
Yes	13 (37.1)	41 (32)	0.569
No	22 (62.9)	87 (68)	
Cervical involvement			
Yes	10 (30.3)	13 (10)	0.003
No	23 (69.7)	117 (90)	
Lymph node involvement			
Yes	10 (30.3)	16 (13.2)	0.020
No	23 (69.7)	105 (86.8)	
Lower uterine segment involvement			
Yes	8 (24.2)	9 (7.6)	0.008
No	25 (75.8)	109 (92.4)	
Nuclear grade			
1	6 (17.1)	76 (56.3)	<0.001
2	10 (28.6)	27 (20)	
3	19 (54.3)	32 (23.7)	
Surgical stage			
Early stage (I and II)	16 (43.2)	119 (86.2)	<0.001
Advanced stage (III and IV)	21 (56.8)	19 (13.8)	
Treatment method			
Surgery	2 (5.41)	7 (5.07)	0.989 <sup>‡</sup>
Adjuvant therapy	35 (94.6)	133 (96.4)	0.765 <sup>‡</sup>

<sup>†</sup>Chi-square test, <sup>‡</sup>Fisher's exact test. Pap: Papanicolaou

of cancer ( $P = 0.039$ ). The Grade III of EC was 42% in O blood group and 26.6% in non-O blood groups. However, the associations among ABO blood groups and other clinical outcomes of EC were not significant ( $P > 0.05$ ) [Table 5].

## DISCUSSION

A total of 175 patients with EC were investigated in this study, and their Pap smear results were reviewed. In 85.4% of the EC cases, the Pap smear screening was conducted 5 months before the EC diagnosis. Totally, endometrial cell, ASCUS, and AGC were the most common results in patients with abnormal Pap smear by 56.8%, 29.7%, and 13.5%, respectively. This may be because low-grade tumors

**Table 4: The association between clinical outcomes of endometrial carcinoma in patients with anemia**

Clinical outcomes	Anemia		P†
	Hb >12 (n=109), n (%)	Hb ≤12 (n=66), n (%)	
Histological type			
Endometrioid	66 (60.6)	51 (77.3)	0.023
Other types	43 (39.4)	15 (22.7)	
Myometrium invasion depth (%)			
<50	101 (92.7)	61 (92.4)	0.954
≥50	8 (7.3)	5 (7.6)	
Lymphovascular invasion			
Yes	37 (36.3)	17 (27.4)	0.242
No	65 (63.7)	45 (72.6)	
Cervical involvement			
Yes	12 (11.8)	11 (17.7)	0.285
No	90 (88.2)	51 (82.3)	
Lymph node involvement			
Yes	17 (17.5)	9 (15.5)	0.746
No	80 (82.5)	49 (84.5)	
Lower uterine segment involvement			
Yes	12 (12.5)	5 (8.9)	0.500
No	84 (87.5)	51 (91.1)	
Nuclear grade			
1	47 (44.3)	35 (54.7)	0.424
2	24 (22.6)	12 (18.8)	
3	35 (33)	17 (26.6)	
Surgical stage			
Early stage (I and II)	79 (72.5)	56 (84.8)	0.042
Advanced stage (III and IV)	30 (27.5)	10 (15.2)	

†Chi-square test. Hb: Hemoglobin

show mild atypia, hence difficult to be distinguished from benign endometrial cells. Lai *et al.*'s study<sup>[17]</sup> revealed that among 95 patients with EC conducting Pap smear test, 21% were diagnosed with adenocarcinoma, 13% with AGCs, 4% with endometrial cells, and 62% were negative. Similar to the results of Serdy *et al.*'s study,<sup>[18]</sup> it was observed in this study that among abnormal Pap smears, AGC type was more common in nonendometrioid histological types which are more aggressive.

The Bethesda system recommends reporting the benign endometrial cells in all women over the age of 40 regardless of menopausal status<sup>[11]</sup> because normal endometrial cells may not be shed in the second half of the menstrual cycle or in the postmenopausal phase, which is physiological natural.<sup>[19]</sup> Endometrioid was the most common histological type of cancer in this study and included 66.9% of all the EC patients: 74.2% in patients with normal and 61.8% in patients with abnormal Pap smears. In Nadaf *et al.*'s study, endometrioid carcinoma was

**Table 5: The association between clinical outcomes of endometrial carcinoma in patients with ABO blood groups**

Clinical outcomes	ABO blood groups		P†
	Non-O (n=122), n (%)	O (n=52), n (%)	
Histological type			
Endometrioid	84 (69.4)	32 (61.5)	0.312
Other types	37 (30.6)	20 (38.5)	
Myometrium invasion depth (%)			
<50	111 (91.7)	50 (96.2)	0.294
≥50	10 (8.3)	2 (3.8)	
Lymphovascular invasion			
Yes	35 (30.7)	19 (38.8)	0.315
No	79 (69.3)	30 (61.2)	
Cervical involvement			
Yes	16 (13.9)	7 (14.6)	0.911
No	99 (86.1)	41 (85.4)	
Lymph node involvement			
Yes	17 (15.6)	9 (20)	0.189
No	92 (84.4)	36 (80)	
Lower uterine segment involvement			
Yes	13 (11.9)	4 (9.5)	0.676
No	96 (88.1)	38 (90.5)	
Nuclear grade			
1	65 (54.2)	16 (32)	0.039
2	23 (19.2)	13 (26)	
3	31 (26.6)	21 (42)	
Surgical stage			
Early stage (I and II)	94 (77.7)	40 (76.9)	0.912
Advanced stage (III and IV)	27 (22.3)	12 (23.1)	

†Chi-square test

the most common histologic type and involved 84% of the EC cases.<sup>[3]</sup> Another study in the north of Iran showed that 77.2% of the patients with EC had endometrioid type histology.<sup>[20]</sup> Moreover, inflammation was reported in 75.1% of the patients with normal Pap smear, and severe inflammation was the most common result in normal Pap smears of EC patients with advanced stages and in Grade III. High-grade smears of carcinoma are characterized by inflammation, necrotic material, and blood along with leukocytes and macrophages. Malignant cells are likely to be lost unless carefully examined; therefore, it is challenging to identify well-differentiated tumor cells in small visible sizes and nuclei. These results show that gynecologists need to pay more attention to follow up patients with inflammation in their Pap smears.

The findings of the study also revealed that anemia was related to lower endometrioid histological type and the higher rate of the advanced stage in patients who had already been diagnosed with EC. Likewise, another study has demonstrated that Hb <12 g/dL is related to poor prognostic factors in

patients with EC.<sup>[13]</sup> Moreover, lower Hb level in advanced stages and higher grades leads to more bleeding. Therefore, an appropriate clinical approach in women >40 years of age with PMB is an efficient evaluation process for the diagnosis of EC.<sup>[21]</sup> In this study, O blood group was associated with higher grades, while another study in Saudi Arabia revealed no statistically significant correlations between ABO blood groups and clinicopathological factors.<sup>[14]</sup>

According to the results, postmenopausal, invasion depth  $\geq 50\%$ , the involvement of lymph nodes, lower uterine segment involvement, adjuvant therapy, higher grade (III), and advanced stage were higher in patients with abnormal Pap smear. Lai *et al.*'s study revealed that abnormal cells are more common in patients with cervical involvement, in a higher grade, and in an advanced stage.<sup>[17]</sup> Moreover, Chang's study demonstrated that the presence of endometrial glandular cells in Pap smears is a strong predictor of endometrial diseases. The results of another similar study conducted by Serdy *et al.*<sup>[18]</sup> showed that cervical involvement, lymphovascular invasion, invasion depth  $>50\%$ , and tumor type are significantly related to abnormal Pap smear results.<sup>[18]</sup> Similarly, Nadaf *et al.* found that postmenopausal status and higher nuclear grades are significant factors of abnormal Pap smear.<sup>[3]</sup> Thus, it seems that a higher grade and an advanced stage with lower uterine involvement and progress to the cervix are the causes of observing endometrial cells in Pap smear. However, the findings of this study showed that histological type, lymphovascular invasion, and surgery treatment and tumor diameter were not different in patients with abnormal and normal Pap smear.

The results showed that only 21.1% of the patients with EC had abnormal Pap smear. The overall efficacy of Pap smear to detect EC was 38% in Lai *et al.*'s study<sup>[17]</sup> and 44% in Serdy *et al.*'s study.<sup>[18]</sup> Nevertheless, recent studies have revealed that the efficacy of Pap smear to detect EC has increased in the last decade from 30% up to 38%.<sup>[17,22]</sup> Moreover, this detection rate has been reported to be 55% in Gu *et al.*'s study<sup>[23]</sup> and 71.2% in Nadaf *et al.*'s study.<sup>[3]</sup> The lower efficacy in this study might be due to the insufficient precision in reading lams and the overcrowding of our study setting. Finally, this study showed that Pap smear is not an effective method for the detection of EC except in a higher stage and grade in line with Gu *et al.*'s report<sup>[23]</sup> in which they maintained that abnormal Pap smears occur more significantly in EC patients with a high grade of tumor and Stages III–IV. The results of this study are also in agreement with some other studies,<sup>[3,23]</sup> stating that Pap smear is not sensitive enough for the detection of EC, and more than 75% of all the patients with EC have negative Pap smears in the current study.

Limitations of our study include small sample size and conventional Pap smear availability without fluid-based cytology. Hence, future studies with larger samples are necessary to assess the association of severe inflammation in normal Pap smear despite the fact that a relationship was observed between inflammation and EC diagnosis in different grades and stages in this study.

## CONCLUSION

Pap smear is not an effective method for the detection of EC except in higher stages, higher grades, myometrial invasion depth  $\geq 50\%$ , cervical and lymph node involvement, and lower uterine segment involvement. Therefore, it is suggested that women with EC in their Pap smears diagnosed in the past 3 years aged >40 years; women with heavy bleeding, anemia, obesity, and O blood group; and women with severe inflammation in their Pap smears need to follow-up and check for EC. Furthermore, endometrial sampling is a necessary screening procedure for all women with abnormal endometrial cells in their Pap smears.

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## Conflicts of interest

There are no conflicts of interest.

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