

# The Value of Cervical Smears Collected with The ThinPrep Technique in The Detection of Endometrial Cancer

Cem BATUKAN<sup>1</sup>, M.Tuncay ÖZGÜN<sup>1</sup>, Çağdaş TÜRKYILMAZ<sup>1</sup>, Bülent ÖZÇELİK<sup>2</sup>, Işın SOYUER<sup>2</sup>, İ.Serdar SERİN<sup>1</sup>  
Kayseri-Turkey

**OBJECTIVE:** As liquid-based cervical cytology show promise for detecting endometrial adenocarcinoma, the aim of this study was to evaluate the cytological findings in liquid-based cytology of women in with endometrial cancer. Pap smear findings were correlated with histological grade and stage of the tumor to determine whether the presence of atypical cells have any prognostic value.

**STUDY DESIGN:** This prospective study comprises 51 women with endometrial cancer from which a pre-operative cervical Thinprep Pap smear was available. In all cases endometrial thickness was measured transvaginally. The Bethesda nomenclature system for cervico-vaginal cytology was used to define atypical glandular cells (AGCs), atypical squamous cells (ASCs) and endometrial adenocarcinoma cells (EACs). Statistical analysis was done with the independent T test and  $\chi^2$  test.

**RESULTS:** Cytological atypia was present in a total 26 (51%) cases. AGCs or EACs were present in Pap smears of 19 (37%) women. The rate of FIGO grade 2-3 tumor in patients with and without AGCs/EACs was 36.8% (7/19) and 12.5% (4/32), respectively ( $p=0.09$ ). Figures for endometrial thickness were  $14.8 \pm 5.6$ mm and  $16.8 \pm 6.6$ mm, respectively ( $p=0.3$ ). Thirty-two percent (6/19) of patients with AGCs/EACs were FIGO stage 1C or more, whereas the rate for patients with normal cytology was 20% (5/25) ( $p=0.59$ ).

**CONCLUSION:** The sensitivity of the ThinPrep Pap smear in detecting endometrial cancer is low. AGCs/EACs on Pap smear do not correlate with tumor grade or stage and there is no association between endometrial thickness and incidence of AGCs/EACs on Pap smear.  
(*Gynecol Obstet Reprod Med 2007;13:1 58-62*)

**Key Words:** Cervical smear, Liquid-based cytology, Atypical glandular cells, ThinPrep, Endometrial adenocarcinoma

Endometrial cancer is the most common malignancy of the female genital tract. It is predominantly a disease of affluent, obese, postmenopausal women of low parity, although an increasing proportion of younger patients with endometrial cancer have been reported. All risk factors for endometrial cancer are linked to a theoretic, if not apparent, increase in estrogen stimulation of the endometrial cavity.

About 90% of women with endometrial carcinoma have vaginal bleeding or discharge as their only presenting complaint. Less than 5% of women diagnosed with endometrial cancer are asymptomatic. In the absence of symptoms, endometrial cancer may be detected as the result of investigation of abnormal Pap test results or discovered during evaluation for an unrelated reason.

<sup>1</sup>Erciyes University, School of Medicine, Department of Obstetrics and Gynecology

<sup>2</sup>Department of Pathology, Kayseri, Turkey

Address of Correspondence Cem Batukan  
Erciyes University, School of Medicine,  
Department of Obstetrics and  
Gynecology  
Gevher Nesibe Hospital,  
38039 Kayseri, Turkey

Submitted for Publication: 16.01.2007

Accepted for Publication: 12.02.2007

Although the continuity of the endocervix with the other components of the primary mullerian system initially raised hopes, endometrial cancer continues to lack a screening modality comparable with the efficacy of the Pap test for cervical cancer screening.<sup>1,2</sup> Even in patients with advanced disease, the conventional Pap test alone will detect endometrial cancer in only 25-67% of patients.<sup>3-6</sup> Possible explanation for the low sensitivity include a low shedding rate for endometrial carcinomas, cervical stenosis and its association with endometrial cancer, exfoliated degenerated malignant cells that are not infrequently obscured by blood and/or inflammation, and, at times, the shedding of well-differentiated morphologically unremarkable malignant cells.<sup>7</sup> Additionally, the performance of the conventional Pap smear is hampered by inadequate sampling, preparation, and interpretation of the specimen.

Although low sensitivity and poor predictive value have caused the conventional Pap test to fall into disfavor as a primary screening modality for endometrial cancer, recent studies on liquid-based preparations (one of which is the ThinPrep) show promise with increased detection rates.<sup>8,9</sup> The ThinPrep is a new technique of collection and preparation of cervical material, overcoming some of the limitations posed with the conventional Pap test. It results in a uniform thin layer of cells in a clean background, which makes the slide

more suitable for screening and diagnostic review.<sup>10</sup>

The aim of this study was to evaluate the cytological findings in liquid-based cytology of women in with endometrial cancer and to determine the sensitivity of this method for the diagnosis of this tumor. Additionally Pap smear findings were correlated with histological grade and stage of the tumor to determine whether the presence of atypical cells has any prognostic value.

## Material and Methods

Patients with endometrial cancer treated between the years November 2004 and November 2006, from which a cervical cytological specimen obtained with the Thinprep (Cytoc Company, Boxborough MA) technique was available, were included in this prospective study. All specimens were collected within one month before surgery and/or diagnostic endometrial sampling. Diagnosis of endometrial cancer was based on the histopathological findings of the preoperative endometrial biopsy and/or hysterectomy specimen. Stage and grade of the tumor were classified according to the FIGO classification. Demographical data as well as information about the histological type and surgical stage of the tumor were extracted from the medical files of each individual.

Cervical smears were obtained by the attending physician at our policlinic in the dorsal lithotomy position before performing a bimanual vaginal examination. The standard cyto-brush was rotated 360° over the cervical surface to collect the material, which was subsequently transferred in a vial containing PreservCyt (Cytoc Company). The ThinPrep 2000 Automated Slide Processor (Cytoc Company) was used to transfer the cells onto glass slides.<sup>11</sup> Staining was done with the Papanicolaou method.

After material for cervical cytological evaluation had been obtained, endometrial thickness was measured using a 5 MHz transvaginal transducer. In a midsagittal section of the uterus calipers were placed beneath the anterior and posterior hypoechogenic basal layer of the myometrium, thereby measuring both endometrial linings. The measurement was taken from the fundus if the endometrial stripe was linear, whereas the thickest part was measured if the endometrial line appeared irregular. The hypoechogenic area between the anterior and posterior endometrium was extracted from the measurement if free intrauterine fluid was suspected.

For the purpose of this study, specimens of all cases with endometrial cancer were evaluated by one and the same experienced cyto-pathologist (I.S.), who was blinded to the final histopathological diagnosis (i.e. endometrial cancer). The Bethesda nomenclature system for cervico-vaginal cytology was used to define atypical glandular cells (AGCs), atypical squamous cells (ASCs) and adenocarcinoma cells (EACs).<sup>12</sup>

(Chheng et al., 2000). No attempts were made to classify AGCs according to their origin (i.e. 'endocervical' or 'endometrial').

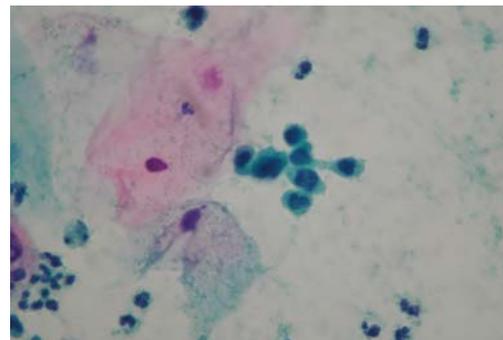
Data were expressed as mean  $\pm$  SD (min-max) and n (%). The independent T test and  $\chi^2$  test (with Yates' correction) were used when applicable. Analysis was performed with the statistical package for social science (SPSS) 13.0 version (Chicago, Illinois). Statistical significance was set at  $p < 0.05$ .

## Results

A total of 51 patients, 41 (80.4%) being postmenopausal, with a mean age of  $57.6 \pm 10$  years (36-80) were included in this study. Forty patients complained about post-menopausal bleeding at the time of presentation. In one asymptomatic postmenopausal woman endometrial sampling was performed because the endometrium appeared thick (30 mm) on transvaginal ultrasound. In 10 women of reproductive age, endometrial cancer was diagnosed during evaluation for menometrorrhagia (n=8) or primary/secondary infertility (n=2). At the time of diagnosis,<sup>9</sup> post-menopausal women had used in the past or were still on hormone replacement therapy.

The mean endometrial thickness at the time of diagnosis was  $16 \pm 6.3$  mm (5-30). The tumor was stage 1a in 4 (7.8%) cases, 1b in 34 (66.7%) cases, 1c in 8 (15.7%) cases, 2b in 2 (3.9%) cases, 3a in 1 (1.9%) case and 3c in 2 (3.9%) cases. Histopathological findings consisted of endometrioid type of endometrial adenocarcinoma (n=48), clear cell carcinoma of the endometrium (n=2) and serous papillary carcinoma (n=1). Number of patients with low (FIGO grade 1) and high (FIGO grade 2-3) histologic grade was 40 (78.4%) and 11 (21.6%), respectively.

Cytological atypia was present in a total of 26 (51%) cases. These were consistent with AGCs in 14 (27.5%) cases, EACs in 5 cases (9.8%), ASCs in 5 (9.8%) cases and one each of high (2%) and low (2%) grade intraepithelial lesion. The ThinPrep revealed clusters of cells that were easily recognized, regardless of the number of diagnostic cells, due to the good cellular preservation and relatively clean background (Figure 1). No atypical glandular or squamous cells were present in the cervico-vaginal smears of 25 (49%) patients.



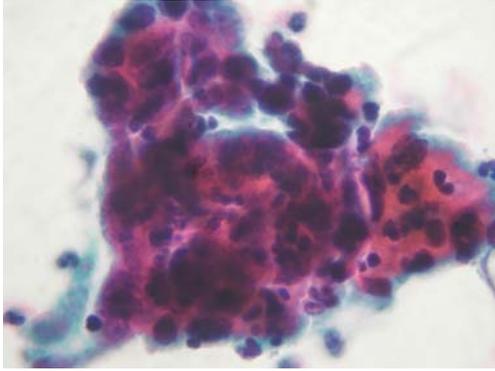


Figure 1. Cervical Pap test. a. Cluster of atypical glandular cells (Papanicolaou stain x 400). b. Poorly-differentiated adenocarcinoma of the endometrium (Papanicolaou stain x 1000)

Eighty-four percent (16 cases) of the women with AGCs or EACs and all women with ASCs were post-menopausal. The distribution of atypical cells in Pap smears of women with endometrial cancer according to the tumor stage is represented in Table 1. Thirty-two percent (6/19) of patients with AGCs/EACs were stage 1C or more, whereas the rate for patients with normal cytology was 20% (5/25) ( $p=0.59$ ). The rate of grade 2-3 tumor in patients with and without AGCs/EACs was 36.8% (7/19) and 12.5% (4/32), respectively ( $p=0.09$ ). The endometrial thickness of patients with ( $14.8 \pm 5.6\text{mm}$ ) and without ( $16.8 \pm 6.6\text{mm}$ ) AGCs/EACs were comparable ( $p=0.3$ ). The rate of AGCs/EACs in patients treated (2 of 9 patients; 22.2%) and not treated (17 of 42 patients; 40.5%) with estrogen and progesterone were also similar ( $p=0.3$ ).

Table 1. Preoperative cytological findings in ThinPrep Pap smears of women with endometrial cancer.

FIGO Stage	Total (n=51)	Normal cervical smear (n=25)	Pathological cervical smear (n=26)				
			AGC (n=14)	EAC (n=5)	ASC (n=5)	LSIL (n=1)	HSIL (n=1)
1a	4	2 (50)	-	1 (25)	-	-	1 (25)
1b	34	18 (53)	9 (26.5)	3 (8.8)	3 (8.8)	1 (2.9)	-
1c	8	4 (50)	3 (37.5)	-	1 (12.5)	-	-
2b	2	-	-	1 (50)	1 (50)	-	-
3a	1	1 (100)	-	-	-	-	-
3c	2	-	2 (100)	-	-	-	-

Data are shown as n (%).

AGC, Atypical glandular cell; ASC, Atypical squamous cell, LSIL, Low-grade intraepithelial lesion; HSIL, High-grade intraepithelial lesion

## Discussion

Although currently there is no screening method to satisfy the standard criteria (i.e. being cost effective and painless) for a good screening test in asymptomatic women, a certain Pap

smear findings may be useful in detecting endometrial cancer. Of these, atypical glandular cells are the most important.<sup>13</sup> The incidence of atypical glandular cells in the general population (consisting of both pre- and postmenopausal women) is quoted at around 0.08 to 2.1%,<sup>12,14,15</sup> most studies reporting <1%. They are defined as cells showing either endometrial or endocervical differentiation displaying nuclear atypia that exceeds obvious reactive or reparative changes but that lack unequivocal features of invasive adenocarcinoma.<sup>16</sup> While the presence of benign appearing endometrial cells in women over 40 years of age carries a very low risk of significant endometrial pathology, the risk is increased in the presence of cytological atypia.<sup>5,17</sup>

A comprehensive survey showed that ThinPrep tends to be more sensitive and specific than the conventional Pap test in detecting squamous cell lesions.<sup>18</sup> However, only a few studies have examined AGCs-diagnosis and outcome in conventional and liquid-based preparations.<sup>8,11,19-22</sup> The results are conflicting, varying from no difference to increased or decreased detection of glandular lesions on ThinPrep versus conventional smear. In this study we found that the presence of atypical glandular or adenocarcinoma cells on liquid base monolayer of cervico-vaginal smears had a 37% sensitivity of detecting endometrial cancer. This represents a much lower detection rate than that of others.<sup>8,9</sup> Schorge et al.<sup>9</sup> stated that the overall sensitivity of ThinPrep smear in detecting either cervical or endometrial adenocarcinoma was higher than the conventional Pap test (72% vs. 41.5%). The ThinPrep performed also better for endometrial than for cervical glandular

lesions. In their study the false-negative rate was significantly lower in ThinPrep than in the conventional Pap smear group. Similarly, Guido and Selvaggi<sup>8</sup> reported that with the ThinPrep technique the detection rate of endometrial adenocarcinoma increased by 60% over conventional Pap smear. These findings have been confirmed by others.<sup>20</sup> The liquid-based preparations transfers 80-90% of the cells to the liquid media, as compared with only 10-20% transferred to the glass slide with conventional cytologic testing. These findings suggest that the ThinPrep Pap test may be useful in detection of endometrial cancer in asymptomatic women.<sup>8</sup>

The reason for the low detection rate of ThinPrep Pap test found in our study is not entirely clear, but may be related to the surgical stage of the tumor.

It is known that women who are found to have malignant cells on Pap test are more likely to have a higher grade and more advanced stage of disease.<sup>4,6,23-25</sup> Our cohort consisted mainly of cases with relatively early stage endometrial cancer, with most of the cases showing <1/2 myometrial invasion (i.e. FIGO stage 1a/1b tumor). Demirkiran et al.<sup>23</sup> stated that 8% of

patients with inner 1/2 myometrial invasion had malignant cells in their smear, compared to 51% of patients with outer 1/2 myometrial invasion. Patients have twice the risk of grade 2-3 tumor or outer 1/2 myometrial invasion and three times the risk of positive peritoneal washings if their smear contains malignant cells.<sup>24</sup> (DuBeshter, 1991). We could not reproduce these results, as the stage of the tumor was comparable in both groups with and without AGCs in ThinPrep Pap smears. Moreover, although the rate of AGCs in high (i.e. FIGO grade 2-3) compared with low (i.e. FIGO grade 1) histologic grade endometrial carcinomas was high, this difference did not reach statistical significance. Again, the reason for this may be caused by a relatively small number of patients with advanced-stage tumor. We found that tumoral shedding was not related to the size (tumor burden) within the uterine cavity, which was assessed by sonographic endometrial thickness. Of note, the literature is devoid of any study, which compares the rate of atypical cells on Pap smear with endometrial thickness in cases with endometrial cancer.

The risk of harboring a high grade squamous lesion is increased in the presence of AGC on Pap smear, especially in women younger than 35 years of age. Glandular lesions become more frequent after the age of 35. One study found that the risk of endometrial cancer in women with AGC age 35-50 and over age 50 was 6% and 27%, respectively.<sup>14</sup> Therefore referral for colposcopic evaluation and endocervical curettage is indicated in all women over age 35 with AGCs on Pap smear, regardless of whether clinical symptoms are present. However, a recent survey found that only 36% of the patients with AGCs on Pap smear a receiving an appropriate and thorough evaluation.<sup>26</sup> Conization, preferably cold-knife, should be considered in cases with persisting AGCs in Pap smears.<sup>27</sup> Conversely, women with ASC-US Pap tests have a lower rate of malignancy (i.e. %0.1), and those with low risks can be followed up with a Pap test in 4-6 months.<sup>26</sup> The 2001 consensus guidelines for the management of cervical cytological abnormalities recommend that postmenopausal women with ASC-US should be treated with a course of intra-vaginal estrogen followed by a repeat cervical cytology test obtained approximately one week after completing the regimen. This option is acceptable for women who have clinical or cytological evidence of atrophy and no contraindications to intra-vaginal estrogen use.<sup>27</sup>

AGCs found in cervical smears can be of endometrial or endocervical origin. However, most studies did not specify the nature of AGCs. Approximately 5-6% of AGCs are of endometrial origin.<sup>12</sup> As in our study only cases with biopsy proven endometrial cancer were included, it can be assumed that all AGCs are of endometrial origin. Nevertheless, several studies have criticized the 2001 Bethesda system, as endometrial and endocervical glandular cells can not be easily differ-

entiated from each other, hence resulting in great inter-observer variability.<sup>28</sup>

In summary, this study found the sensitivity of the ThinPrep Pap smear in detecting endometrial cancer to be low. AGCs on Pap smear did not correlate with tumor grade or stage. Moreover, there was no association between endometrial thickness and incidence of AGCs on Pap smear.

## References

1. Smith RA, Cokkinides V, Eyre HJ; American Cancer Society. American Cancer Society guidelines for the early detection of cancer, 2004. *CA Cancer J Clin.* 2004;54:41-52.
2. American College of Obstetricians and Gynecologists. Routine cancer screening. ACOG opinion no. 185. Washington, D.C., 1997
3. Ng AB. The cellular detection of endometrial carcinoma and its precursors. *Gynecol Oncol.* 1974;2:162-79.
4. Gu M, Shi W, Barakat RR, Thaler HT, Saigo PE. Pap smears in women with endometrial carcinoma. *Acta Cytol.* 2001;45:555-560.
5. Van den Bosch T, Vandendael A, Wranz PA, Lombard CJ. Cervical cytology in menopausal women at high risk for endometrial disease. *Eur J Cancer Prev.* 1998;7:149-52.
6. Larson DM, Johnson KK, Reyes CN Jr, Broste SK. Prognostic significance of malignant cervical cytology in patients with endometrial cancer. *Obstet Gynecol.* 1994;84:399-403.
7. Vuopala S. Diagnostic accuracy and clinical applicability of cytological and histological methods for investigating endometrial carcinoma. *Acta Obstet Gynecol Scand.* 1977;70:1-72.
8. Guidos BJ, Selvaggi SM. Detection of endometrial adenocarcinoma with the ThinPrep Pap test. *Diagn Cytopathol.* 2000;23:260-5.
9. Schorge JO, Hossein Saboorian M, Hynan L, Ashfaq R. ThinPrep detection of cervical and endometrial adenocarcinoma: a retrospective cohort study. *Cancer.* 2002; 96:338-43.
10. Lee KR, Ashfaq R, Birdsong GG, Corkill ME, McIntosh KM, Inhorn SL. Comparison of conventional Papanicolaou smears and a fluid-based, thin-layer system for cervical cancer screening. *Obstet Gynecol.* 1997;90:278-84.
11. Ramsaroop R, Chu I. Accuracy of diagnosis of atypical glandular cells - Conventional and ThinPrep. *Diagn Cytopathol.* 2006;34:614-9.
12. Chhieng DC, Elgert P, Cohen JM, Cangiarella JF. Clinical significance of atypical glandular cells of undetermined significance in postmenopausal women. *Cancer.*

- 2001;93:1-7.
13. Zucker PK, Kasdon EJ, Feldstein ML. The validity of Pap smear parameters as predictors of endometrial pathology in menopausal women. *Cancer*. 1985;56:2256-63.
  14. Daniel A, Barreth D, Schepansky A, Johnson G, Capstick V, Faught W. Histologic and clinical significance of atypical glandular cells on pap smears. *Int J Gynaecol Obstet*. 2005;91:238-42.
  15. Davey DD, Neal MH, Wilbur DC, Colgan TJ, Styer PE, Mody DR. Bethesda 2001 implementation and reporting rates: 2003 practices of participants in the College of American Pathologists Interlaboratory Comparison Program in Cervicovaginal Cytology. *Arch Pathol Lab Med*. 2004;128:1224-9.
  16. Anonymous. The 1988 Bethesda system for reporting cervical/vaginal cytological diagnoses. National Cancer Institute Workshop. *JAMA*. 1989;262:931-934
  17. Kerpsack JT, Finan MA, Kline RC. Correlation between endometrial cells on Papanicolaou smear and endometrial carcinoma. *South Med J*. 1998;91:749-52.
  18. Abulafia O, Pezzullo JC, Sherer DM. Performance of ThinPrep liquid-based cervical cytology in comparison with conventionally prepared Papanicolaou smears: a quantitative survey. *Gynecol Oncol*. 2003;90:137-44.
  19. Bai H, Sung CJ, Steinhoff MM. ThinPrep Pap Test promotes detection of glandular lesions of the endocervix. *Diagn Cytopathol*. 2000;23:19-22.
  20. Ashfaq R, Gibbons D, Vela C, Saboorian MH, Iliya F. ThinPrep Pap Test. Accuracy for glandular disease. *Acta Cytol*. 1999;43:81-5.
  21. Negri G, Menia E, Egarter-Vigl E, Vittadello F, Mian C. ThinPrep versus conventional Papanicolaou smear in the cytologic follow-up of women with equivocal cervical smears. *Cancer*. 2003;99:342-5.
  22. Hecht JL, Sheets EE, Lee KR. Atypical glandular cells of undetermined significance in conventional cervical/vaginal smears and thin-layer preparations. *Cancer*. 2002;96:1-4.
  23. Demirkiran F, Arvas M, Erkun E, Kosebay D, Isiloglu H, Aktas E, Mil Z. The prognostic significance of cervico-vaginal cytology in endometrial cancer. *Eur J Gynaecol Oncol*. 1995;16:403-9.
  24. DuBeshter B, Warshal DP, Angel C, Dvoretzky PM, Lin JY, Raubertas RF. Endometrial carcinoma: the relevance of cervical cytology. *Obstet Gynecol*. 1991;77:458-62
  25. Eddy GL, Wojtowycz MA, Piraino PS, Mazur MT. Papanicolaou smears by the Bethesda system in endometrial malignancy: utility and prognostic importance. *Obstet Gynecol*. 1997;90:999-1003.
  26. Sharpless KE, Schnatz PF, Mandavilli S, Greene JF, Sorosky JI. Lack of adherence to practice guidelines for women with atypical glandular cells on cervical cytology. *Obstet Gynecol*. 2005;105:501-6.
  27. Wright TC Jr, Cox JT, Massad LS, Twiggs LB, Wilkinson EJ; 2001 ASCCP-sponsored Consensus Conference. 2001 Consensus Guidelines for the Management of Women with Cervical Cytological Abnormalities. *J Low Genit Tract Dis*. 2002;6:127-143.
  28. Simsir A, Hwang S, Cangiarella J, Elgert P, Levine P, Sheffield MV, Roberson J, Talley L, Chhieng DC. Glandular cell atypia on Papanicolaou smears: interobserver variability in the diagnosis and prediction of cell of origin. *Cancer*. 2003;99:323-30.