



Is liquid-based cervical cytology test more effective than conventional pap smear?

İlknur Alkan Kuşabbi¹, Hüseyin Aydoğmuş¹, Hatice Işık², Ali Seven³, Beril Yüksel³, Gülenay Gençosmanoğlu Türkmen^{1,4}, Deniz Karçaaltıncaba^{1,5}, Yusuf Ergün¹, Muzaffer Çaydere⁶, Sertaç Batioğlu¹

ABSTRACT

Objective: To evaluate and compare the efficiencies of cytologic test methods conventional Pap smear (CVS) versus Thin Prep liquid-based cytology technique (TPT) in the histologic diagnosis of the precancerous lesions of the cervix and cervical cancer.

Materials and Methods: We selected randomly 1203 non-gravid women who were admitted to gynecology and menopause out-patient clinics of our hospital in the study. The cervical smear tests of all women were evaluated both using the conventional Pap smear and the TPT. Cytological examinations were compared according to their adequacy for evaluation. The evaluation of samples were performed and compared according to The Bethesda System.

Results: The two screening methods were statistically compatible for evaluating the samples ($\kappa=0,379$ and $p<0,001$). The diagnosis interpreted by CPS and TPT methods were synchronous and this was also statistically significant ($\kappa=0,829$ ve $p<0,001$).

Conclusion: Our cytohistologic diagnoses and samples' adequacy interpreted with CVS and TPT were statistically significantly synchronous.

Keywords: cervical cancer, high risk human papilloma virus, cervical cancer screening, cervical precancerous lesions

INTRODUCTION

Precancerous cervical lesions and cervical cancer are important public health problems especially in the developing countries. According to current statistical data; cervical cancer is the third most common cancer and fourth leading cause of cancer death in women population all over the world (1). More than 85 % of the cancer cases and cancer related deaths occur in developing countries especially eastern, western and Southern regions of Africa (1). The disproportionally high burden of cancer in developing countries is largely due to lack or absence of cervical cancer screening programs (2,3). There are well structured tests to screen cervical cancer in developed countries; but the healthcare infrastructure in the developing countries frequently does not support cervical cancer screening tests. Fortunately the general health insurance in Turkey covers the screening tests.

The most commonly used and the most cost-effective screening tests are cytology and DNA testing for human papillomavirus (HPV) in cervical cell samples. The clinical trials showed that these tests significantly decreased the morbidity and mortality in cervical cancer (4).

Here in, we tried to compare two different cytologic cervical cancer screening tests; conventional PAP smear test (CVS) and the Thin Prep liquid-based cytology technique. Thin Prep test is highly effective but more expensive when compared to conventional PAP test. Our aim in this study was to compare the accuracy and efficacy of CVS and TPT in screening cervical cytologic abnormalities.

MATERIALS AND METHODS

Between January 2011 to the end of June 2011; 1203 women who were admitted to gynecology and menopause out-patient clinics of Ankara Educational and Research Hospital Gynecology and Obstetrics Department were included in the perspective study. The ethical approval of the study was taken from local ethics comitee of the hospital. All of the participants were local residents, married and non-gravid with a mean age of 43.1 ± 12.7 (range 17-87 years).

Each patient was examined on the examination table, with the aid of speculum the cervix was exposed. A specially designed plastic endocervical brush (Plasti-med®, İstanbul, Turkey) which can pick up cells from both ecto- and endocervix was placed on the external ostium of the cervix and was rotated 360 degrees two or three times clockwise. Both sides of the brush were placed on the slide. A preservative (hair spray containing alcohol, Green World®) was applied immediately to prevent air drying, which might compromise the interpretation. Then the same brush used in the pap smear test was placed in a liquid-based medium for TPT. After closing the tap of the container, which the specimen was placed, it was shaken to diffuse the cells in the fixative solution. The conventional PAP smears were fixed and stained with papanicolau stain by an experienced pathologist. The prepared TPT liquid-based tests were sent to pathology for cytologic examination. The test samples were placed in ThinPrep 2000 machine and according to the manufacturer's instructions; sample collection, section preparation and staining were performed. The samples were examined by the same experienced pathologist. The two tests

¹ Ankara Education and Research Hospital, Department of Obstetrics and Gynecology, Ankara, Turkey

² Ankara, Turkey

³ Kütahya Dumlupınar University, Department of Obstetrics and Gynecology, Kütahya, Turkey

⁴ Zekai Tahir Burak Education and Research Hospital, Department of Obstetrics and Gynecology, Ankara, Turkey

⁵ Gazi University Faculty of Medicine, Department of Obstetrics and Gynecology, Ankara, Turkey

⁶ Ankara Education and Research Hospital, Department of Pathology, Turkey

Correspondence: Hatice Işık
Ankara, Turkey

E-mail: k.hgonbe@gmail.com

Table 1: The frequencies of the diagnoses of the samples by conventional and Liquid-based methods. The numbers in parentheses are percentages

	Normal	Inflammation	Specific	Atrophy	Unsatisfactory	Abnormal	Total
Conventional	288(23,9)	610(50,7)	83(6,9)	165(13,7)	30(2,5)	27(2,2)	1203
Liquid-based	327(27,2)	593(49,3)	71(5,9)	162(13,5)	1(1,7)	29(2,5)	1203

Table 2: The frequency table of the abnormal results interpreted by the two screening methods

		CONVENTIONAL		
		Benign	Abnormal cytology	Total
Liquid-Based	Benign	1125 (%96,8)	8 (%0,7)	1133 (%97,5)
	Abnormal cytology	11 (%1,0)	18 (%1,5)	29 (%2,5)
	Total	1136 (%97,8)	26 (%2,2)	1162 (%100)

were funded by Ankara Education and Research Hospital foundation.

Cytological examinations were compared according to their adequacy for evaluation. The criteria accepted for a specimen to be satisfactory for evaluation were determined as; squamous epithelial cells should cover at least 10% of the slide surface, endocervical transformation zone should be present and the factors that would compromise the interpretation like blood, contamination or artifacts due to drying in the air should not be present more than 75% of the slide. The samples that were confirmed as satisfactory were evaluated for the cytological results (5).

The evaluation of samples were performed according to The Bethesda System and were classified as; within normal limit (WNL); atypical squamous cells of undetermined significance (ASCUS); atypical glandular cells of undetermined significance (AGUS); low grade squamous intraepithelial lesion (LSIL); high grade squamous intraepithelial lesion (HSIL); squamous cell carcinoma (SCC) (6).

Statistical Analysis

SPSS for Windows 11.5 program was used for the statistical analysis of our prospective study. For the continuous variables; mean \pm standard deviation and for the categorized variables number of cases and percentiles (%) were used. Kappa coefficient was calculated whether the CPS and TPT were compatible. Also, McNemar test was used to test the statistical significance of the prevalence of the diagnosis made between the two test methods, $p < 0,05$ was accepted statistically significant.

RESULTS

Totally 1203 female patients were evaluated. The mean age of the patients was 43.1 ± 12.7 years (17-87 years), the mean number of the gravida was $3,32 \pm 2,09$ (0-9), the mean number of parity was $2,55 \pm 1,71$ (0-8).

The smear samples prepared by CVS and TPT method were evaluated for the adequacy. Respectively, 1173 (97,5%) and 1182 (98,3%) of the samples were evaluated as satisfactory by CPS and TPT method. The two screening methods were statistically compatible for the satisfaction of the samples ($\kappa=0,379$ and $p < 0,001$). The diagnosis interpreted by CPS and TPT methods were synchronous and this was also statistically significant (Table 1) ($\kappa=0,829$ and $p < 0,001$)

The benign results were classified as normal, inflammation, specific infection and atrophy. A normal benign findings of CVS is figured in Figure 1. Trichomonas vaginalis, bacterial vaginosis and candidiasis infestations were evaluated as specific infection. The inflammation and specific infection results were synchronously interpreted by the two smear methods which were significantly compatible for the evaluation of inflammation ($\kappa=0,815$, $p < 0,001$) and specific infection ($\kappa=0,764$ ve $p < 0,001$). The prevalence of inflammation and specific infection results of the samples were compatible in both CPS and TPT method, $p=0,128$ and $p=0,058$ respectively. Also the two sampling methods synchronously interpreted the atrophy ($\kappa=0,968$, $p < 0,001$) and no statistically difference was

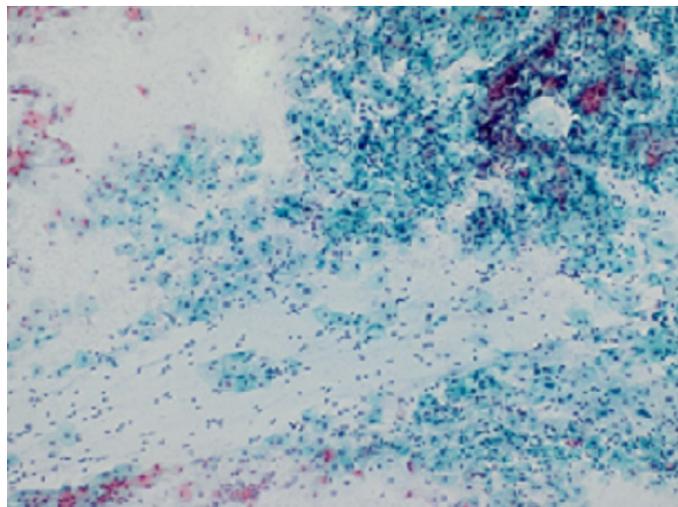


Figure 1: Normal conventional Pap smear test

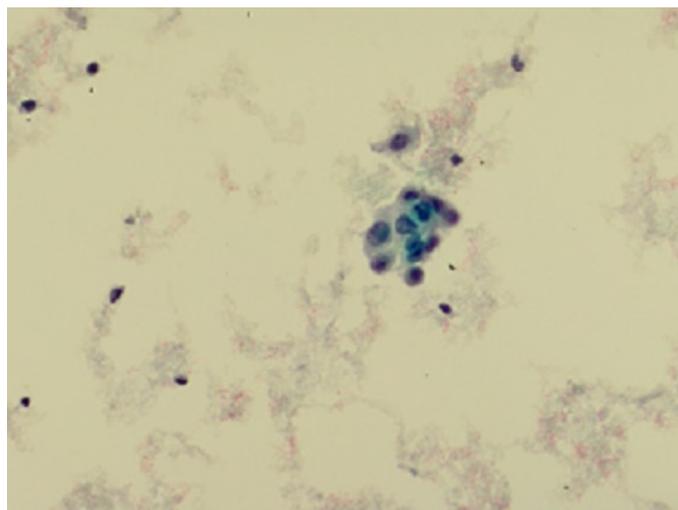


Figure 2: Overall survival time by stage

present in the prevalence of the atrophic signs of the two methods ($p=0,508$).

The abnormal cytologic results were classified as atypical squamous cells of undetermined significance (ASC-US), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), atypical glandular cells (AGC), malignant cells. Of the 1162 specimens evaluated as satisfactory; the rate of specimens interpreted as abnormal with CVS was 2,2% and 2,5% with TPT (Table-2). These rates were synchronous in the two screening tests which was statistically significant ($\kappa=0,646$, $p < 0,001$). The prevalence of the abnormal cytologic findings were statistically similar ($p=0,648$). A HSIL finding of thin-prep test is shown in Figure 2.

The diagnosis of ASCUS was 11(0.91%) with both screening methods. But, 5(0.41%) ASCUS diagnosis given with TPT were interpreted as normal with CVS, whereas 5(0.41%) ASCUS diagnosis given with CVS were interpreted as normal with TPT. The frequencies of specimens diagnosed as ASCUS were similar

Table 3: The cases of abnormal test results for conventional and liquid-based cytology screening methods

		CONVENTIONAL						Total
		Other	ASCUS	LSIL	HSIL	AGUS	Malignant	
Liquid-Based	Other		5	3	0	1	0	9
	ASCUS	5	11	0	0	0	0	16
	LSIL	5	0	5	0	0	0	10
	HSIL	1	0	0	0	0	0	1
	AGUS	0	0	0	0	1	0	1
	Malignant	0	0	0	0	0	1	1
	Total	11	16	8	0	2	1	38

Table 4: The frequency table of the abnormal results interpreted by the conventional and Thin prep test methods

	Conventional Smear(CVS)			Thin Prep test(TPT)			P value
	Only CVS	CVS+TPT	Total	Only TPT	CVS+TPT	Total	
ASCUS	5	11	16	5	11	16	1,000
LSIL	3	5	8	5	5	10	0,727
HSIL	0	0	0	1	0	1	1,000
AGUS	1	1	2	0	1	1	1,000
Malignant	0	1	1	0	1	1	1,000
Total	9	18	27	11	18	29	0,824

with CVS and TPT ($p=1,000$). The frequencies of LSIL were statistically same with CVS and TPT ($p=0.727$). Five (0.41%) specimens interpreted as LSIL with TPT were diagnosed as normal with CVS, whereas 3 (0.25%) specimens interpreted as LSIL with CVS were diagnosed as normal with TPT. One (0.083%) specimen interpreted as HSIL with TPT was diagnosed as benign with CVS. One (0.083%) specimen was interpreted as AGUS and one (0.083%) specimen was interpreted as malign with both TPT and CVS (Table 3 and Table 4).

DISCUSSION

Cytological examination of cervix is one of the most valuable successes in modern medicine. Even though, the conventional cervical cytology has been used for a very long time, in many countries the Thin Prep test is taking its place in routine practice. Numerous meta-analysis and clinical research showed that Thin Prep test is decreasing the rate of unsatisfactory and satisfactory and more sensitive in detecting cervical cell abnormalities (7,8).

In 1996, Thin Prep (Cytoc, Borxborough, MA) test and in 2003 SurePath or with its previous name AutoCyte PREP (TriPath Imaging, Inc., Burlington, NC) was approved by FDA. The research that led to FDA approval for Thin Prep was carried out by Lee et al. in 1997. The clinical data for this research was collected from 7360 patients from -three screening centers and three hospitals. For the lesions of ASCUS or higher 43% of diagnosis were made with Thin Prep. For the three screening centers, 65% more diagnoses of low-grade squamous intraepithelial lesions and higher were made on the ThinPrep slides. There was no statistical significance in detecting the benign cytologic diagnosis. Moreover the test increased the rate of satisfactory specimens by 11% (9). With this valuable research, Thin Prep test came into practice in clinics.

In 1999, Hutchinson et al. performed a population-based study over 8000 women residing in a Costa Rican province with a high incidence of cervical carcinoma and compared it with a "gold standard" final case diagnosis for each patient, that reflected an integrated interpretation of all available data, including cytology, histology, and cervico-graphy. ASCUS was accepted as the threshold for additional colposcopic evaluation. The number of patients that were referred to colposcopy according to this threshold was significantly more with the Thin Prep slide. Thin Prep slides detected 92.9% of cases with high grade squamous intraepithelial lesions (HSIL) and 100% of carcinoma cases. In conclusion the test was found to be significantly more sensitive in the detection of HSIL and cancer (10).

In 2009, Beerman et al. reported the rate of unsatisfactory slides to be significantly lower with liquid-based cytology in their study, comparing 51154 conventional cytologies with 35315 liquid based specimens (% 89.01- % 86.17, $p<0.0001$) (11). But in our study, there were no statistical differences between two methods in terms of unsatisfactory specimens.

On the diagnosis of ASCUS there are controversial studies. In a study in 2006, the detection of ASCUS was reported to be significantly higher with Thin Prep test when compared to conventional pap test (6.52%-4.09%) (12). In a split-sample, prospective study over 1,024 women in 2002, Luthra et al. reported a significant decrease in the diagnoses of ASCUS and AGUS which was evaluated as an advantage for leading to a more definitive diagnoses in atypical cases (%1.3-%2.8) (13). In our study we found similar rates of ASCUS diagnosis in two tests.

In a study by Park et al. in 2007, 26178 liquid based specimens were compared with 218548 pap smear tests. The sensitivity of liquid based technique was found to be more sensitive in detecting cervical cytologic abnormalities like HSIL, LSIL and ASCUS. Unsatisfactory specimen rate was also found lower in liquid based technique (14).

In our study, two patients had the diagnosis of AGUS with conventional Pap test. One of these patients had the diagnosis of AGUS and one patient was reported to have benign cytological findings with liquid based system.

In our study, we had similar rates of LSIL in both tests. But in literature there were different results regarding this diagnosis. In 2007, Lozano found a significant increase in detection of LSIL in liquid based system in his study with 87267 conventional and 39717 thin prep specimen (%1.57- %2.29) (15). The main view leading to the higher sensitivity of liquid based system is based on the idea of increased diagnosis of LSIL. But, the beneficial effect of it for patients is controversial, when the high possibility of reversal of these lesions is taken into account (16).

In our study; with Thin prep test, only one patient had the diagnosis of HSIL which was evaluated as benign in conventional pap smear. There was only one patient who had the diagnosis of malignancy with both tests.

There are also different results from the studies comparing these two tests regarding the diagnosis of high grade lesions. In 2007, Davey et al conducted a split-sample study with 55164 cases which resulted in 71 more cases of high grade histology with Thin Prep test than did conventional cytology. The authors concluded that Thin prep test detected 1.29 more cases of histological high grade squamous disease per 1000 women screened than conventional cytology (17). But in 2003, Cheung et al. found similar detection rates of HSIL, cervical squamous cell carcinomas, and adenocarcinomas (18).

In our study, conventional pap test and Thin prep test was found to be similar in terms of benign results. In addition, when all results are taken into account, the distribution of diagnostic results was also similar. Our results concur well with the literature. In 2004, Ferraz et al. compared the results of pap smear test with liquid-based cytology over 800 women. They reported the sensitivity and specificity of liquid based system for detection of cervical intraepithelial lesions and cancer were 75.3% and 86.4%, respectively, not statistically different from the 81.8% and 85.2% seen with the conventional method (19).

Although, liquid based systems are routinely used in many countries, the cost of the technique limits its utility in developing countries. But even though the cost of screening seems to be high, it was reported to be cost effective when its superiority in diagnosing the cervical cytologic abnormalities was taken into account (18). In a recent study, Bekker et al. reported that screening with liquid based systems can be cost-effective if it is less than (euro) 3.2 more costly per test than PAP test, if the sensitivity of it is at least 3-5 % points higher

than PAP test, if the quality of life for women in triage follow-up is only 0.39, or if the rate of inadequate PAP smears is at least 16.2 % (19). In our country Thin prep test is 4 euro more costly than conventional one and in our study 97.5% of conventional smears were adequate. For this reason we cannot suggest Thin prep test as cost-effective in our study according to Bekker criteria.

In conclusion, our cytohistologic diagnoses and adequacy interpreted with CVS and TPT were statistically significantly

synchronous. But we believe further research is needed to establish whether liquid based cervical screening systems will be more favorable with regard to its sensitivity and cost-effectiveness.

DISCLOSURE

No financial support was taken for this study.

REFERENCES

1. Jemal A, Bray F, Center MM, et al. Global cancer statistics. *CA Cancer J Clin.* 2011;61:69-90.
2. Parkin DM, Almonte M, Bruni L, et al. Burden and trends of type-specific human papillomavirus infections and related diseases in the latin america and Caribbean region. *Vaccine.* 2008;26:L1-L15.
3. Mathew A, George PS. Trends in incidence and mortality rates of squamous cell carcinoma and adenocarcinoma of cervix worldwide. *Asian Pac J Cancer Prev.* 2009;10:645-50.
4. Comprehensive Cervical Cancer Control: A Guide to Essential Practice. Switzerland: World Health Organization; 2006.
5. Gilson M, Desai A, Cardoza-Favarato G, Vroman P, Thornton JA. Does gel affect cytology or comfort in the screening papanicolaou smear? *J Am Board Fam Med.* 2006;19(4):340-4.
6. Mody DR, Nayar R, Thrall M. 2001 Bethesda System classification of glandular lesions on cervical cytology. *Monogr Clin Cytol.* 2011;20:5-14.
7. Canda MT, Demir N, Sezer O, Doganay L, Ortac R. Clinical results of the liquid-based cervical cytology tool, Liqui-PREP, in comparison with conventional smears for detection of squamous cell abnormalities. *Asian Pac J Cancer Prev.* 2009;10:399-402.
8. Chen C, Yang Z, Li Z, Li L. Accuracy of several cervical screening strategies for early detection of cervical cancer: a meta-analysis. *Int J Gynecol Cancer.* 2012;22:908-21.
9. Lee KR, Ashfaq R, Birdsong GG, Corkill ME, Mcintoch K, Inhorn SL. Comparison of conventional Papanicolaou smears and a fluid-based, Thin- Layer system for cervical cancer screening. *Obstet Gynecol.* 1997;90:278-284.
10. Hutchinson ML, Zahniser DJ, Sherman ME, Herrero R, Alfaro M, Bratti MC, Hildesheim A, Lorincz AT, Greenberg MD, Morales J, Sciffman M. Utility of liquid based cytology for cervical carcinoma screening, results of a population based study conducted in a region of Costa Rica with a high incidence of cervical carcinom. *Cancer.* 1999;87:48-55.
11. Beerman H, van Dorst EB, Kuenen-Boumeester V, Hogendoorn PC. Superior performance of liquid-based versus conventional cytology in a population-based cervical cancer screening program. *Gynecol Oncol.* 2009 Mar;112(3):572-576.
12. Lozano R. Comparison of computer-assisted and manual screening of cervical cytology. *Gynecologic Oncology.* 2007;104,134-138.
13. Luthra UK, Chisti M, Deyt P, Jolly SV, Abdulla M, Das DK, Sugathan TN, Ajrawi MT, George SS, George J, Aziz AA, Al-Juwaiser A, Karim FA, Mallik MK, Sheikh ZA, Khan S. Performance of monolayered cervical smears in gynecology outpatient setting in Kuwait. *Acta Cytol.* 2002;46:303-310.
14. Park J, Jung EH, Kim C, Choi YH. Direct-to-vial comparison of a new liquid-based cytology system, liqui-PREP versus the conventional pap smear. *Diagn Cytopathol.* 2007;35(8):488-492.
15. Davey E, d'Assuncao J, Irwig L, Macaskill P, Chan SF, Richards A, Farnsworth A. Accuracy of reading liquid based cytology slides using the ThinPrep Imager compared with conventional cytology: prospective study. *BMJ.* 2007;335(7609):31.
16. Cheung ANY, Szeto E, Leung BSY, Khoo U, Ng AWY. Liquid-Based Cytology and Conventional Cervical Smears. A Comparison Study in an Asian Screening Population Cancer (*Cancer Cytopathol*) 2003;99:331-335.
17. Mattosinho de Castro Ferraz MG, Nikolau SM, Stavale JN, Focchi J, Castelo A, Lorincz A, Rodrigues G. Cervical biopsy-based comparison of a new liquid-based thin-layer preparation with conventional pap smears. *Diag Cytopathol.* 2004;30:220-226.
18. Neville AM, Quinn MA. An alternative cost effectiveness analysis of ThinPrep in the Australian setting. *Aust N Z J Obstet Gynaecol.* 2005;45:289-294.
19. de Bekker-Grob EW, de Kok IM, Bulten J, van Rosmalen J, Vedder JE, Arbyn M, Klinkhamer PJ, Siebers AG, van Ballegooijen M. Liquid-based cervical cytology using ThinPrep technology: weighing the pros and cons in a cost-effectiveness analysis. *Cancer Causes Control.* 2012;23:1323-1331.



<http://www.ejgm.org>