Research Journal of Biological Sciences 3 (6): 627-630, 2008
ISSN: 1815-8846

Liqui Prep™ a New Liquid Based Cervical Cytology Method in Comparison with Conventional Pap Smear in Developing Counteries

[1]Nadereh Behtash, [1]Zeinab Nazari, [2]Mahmod Khaniki, [3]Kazem Zendedel,
[4]Fereshteh Fakor and [5]Mamak Shariat
[1]Department of Gynaecology and Oncology, Vali Asr Hospital,
[2]Department of Cytopathologist, Central Pathology Centre,
Emam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran
[3]Department of Epidemiology, University of Karolinska, Stockholm, Sweden
[4]Departmnet of Gynecology and Oncology, Gilan University of Medical Sciences, Iran
[5]Vali Asr Repruductive Health Reserch Center, Emam Khomeini Hospital, Tehran, Iran

Abstract: The aim of the study was to compare, the screening performance of a new liquid-based cytology method, Liquiprep™,with conventional Pap in a low risk population, using colposcopy followed histology as "gold standard". Methods: This prospective study was performed in a general gynecology clinic in ValiAsr University Hospital, Tehran, Iran from February 2004 to March 2005. The split-sample method was used for preparing conventional and liquid-based cytology. A new technique of liquid-based cytology; Liqui-prep™ was used in this study. All positive result of smears and 10% of negative results in each group were submitted to colposcopy and a biopsy taken when any atypical transformation zone was seen. Sensitivity, specificity, positive and negative predictive values and overall accuracy of both conventional and Liquiprep™ methods were computed in relation to histology. A total of 506 patients were analyzed by two cytology methods and in 65 (12.84%) of cases histologic diagnosis was performed. There were more adequate samples with Liquiprep™ (94.7%) than with conventional (92.1%) smears. There was not any LSIL and HSIL report in two groups. ASCUS was diagnosed significantly more with conventional than with Liquiprep™ smear (1.56 vs. 0.79%). Pathologically 50% of ASCUS in Liquiprep™ and 12.5% in CP had squamous abnormality. Liquiprep™ had a significantly higher sensitivity (66 vs. 83%) and specificity (86 vs. 98%) than the conventional Pap smear to detect ASCUS+ at histology. This study confirms the superiority of the Liquiprep™ method to detect cervical lesions.

Key words: Cervical carcinoma, screening, conventional smear, liquid based smear

INTRODUCTION

Cervical cancer is one of the three most common malignant tumours in terms of incidence and mortality in women, worldwide (Parkin *et al*., 1985). Objective of cervical cancer screening is to reduce cervical cancer incidence and mortality by detecting and treating precancerous lesions. Cervical cytology has been in use now for more than 50 years and has proven itself to be the main weapon defense against this disease (Koss, 1989). Although organized and high-level opportunistic, frequently repeated cytology screening has resulted in a large reduction in the cervical cancer burden in developed countries, incidence rates in developed countries continue to be unabated for want of effective screening programs.

However, in order to effectively protect the population from cervical cancer, two keys element must be in place- the maximum number of adult women must be reached with the screening test and the quality and effectiveness of test itself must be unquestionable.

Since the introduction of cervical cytology screening by Dr. Papanicolaou in 1943, much has been written about the sensitivity of the Papanicolaou smear as a method of detecting cervical lesions, with reported estimates of false-negative rates ranging from 6-50% (Coppleson and Brown, 1974; Rubio, 1977; Vooijs *et al*., 1986; Dehner, 1993). Possible sources of error include variability among

Corresponding Author: Zeinab Nazari, Department of Gynaecology and Oncology, Vali Asr Hospital,
Tehran University of Medical Sciences, Tehran, Iran

sample takers, cell collection techniques employed, inadequate screening and errors in interpretation. If one focuses on sampling and slide preparation methods, several studies have shown that the majority of the cellular sample remains on the collecting device(s) and is discarded after a conventional smear is made (Gay *et al*., 1985; Goodman and Hutchinson, 1996). Smear adequacy is also a contributory factor in rendering an accurate diagnosis (Hutchinson *et al*., 1994).

Two liquid based cervical cytology methods; Thin Prep (Cytyc Corporation, Boxborough,MA) and AutoCyte prep (TriPath Imaging, Burlington, NC) was approved by U.S. Food and Drug Administration (FDA).Numerous recently published split-sample studies have compared conventional smears to TP(Thin Prep) (Hutchinson *et al*., 1999; Lee *et al*., 1997; Monsonego *et al*., 2001; Park *et al*., 2001; Tezuka *et al*., 1996; Wang *et al*., 1999) as well as to Auto Cyte prep (Bishop *et al*., 1998; Hesling *et al*., 2001; Minge *et al*., 2000), generally indicating increased detection of Squamous Intraepithelial Lesions (SIL) with the liquid-based methods. These liquid based technologies are not available in Iran. We decided initiate to evaluate other modified liquid based cytology which would not need such expensive equipments.

The goal of this investigation was to compare, in a split-sample protocol, the screening performance of conventional smears with the new liquid-based cytology method, Liquiprep™, in a low risk population, using colposcopy followed histology as "gold standard".

MATERIALS AND METHODS

The study was performed in Vali-Asr University Hospital gynecology clinic, Tehran, Iran from February 2005 to March 2006. After approval by hospital and university ethic committee, 506 split samples were evaluated. All women singed an informed consent. Samples were received only from our hospital and prepared by a trained midwife using a Cervex broom-like brush. A conventional smear was prepared with one side of the brush and then the residual material on the Cervex brush was rinsed in the vial of Liqui-prep™ Preservative Solution (LGM International, Inc., Fort Lauderdale, FL). Both specimens were sent blindly to central pathology laboratory of EmamKhomeini hospital.

In cytology laboratory the solution was mixed with a vortex and then was added onto 4 mL of Liqui-prep™ Cleaning Solution in centrifuge tube. Centrifuge was done with a swinging bucket instrument in 1,000 g (+/-100g) speed. After addition of Liqui-prep™ Cellular Base solution, 50 uL of homogeneous sample was taking with pipette and used for preparation slid. After drying, all cervical smears were stained with a modified Papanicolaou technique and then screened and reported according to the Bethesda 2001 system. All smears both conventional and Liqui-prep was evaluated and reported by one expert cytologist. The cytologist was blind for matched conventional Pap test.

Positive Pap result in each method was defined as ASC-US and higher according to Bethesda (2001). Women with positive results were referred for colposcopy and positive results of colposcopy including; CIN1, CIN2, CIN3, cervical carcinoma, endometrial carcinoma and atypical endometrial hyperplasia were considered for the determination of sensitivity and specificity. We also performed colposcopy in 10% of negative results in each method for obtaining false negative rate. Women with no abnormality at the colposcopy were recorded as negative histology.

All data entered into computer by SPSS 11 software and analyzed with T student test, Chi square test and MC Nemar test. p value <0.05 considered significant.

RESULTS

A total number of 506 paired samples were screened. The mean age was 39 years (range 19-79), mean gravity 4 (range 0-14) and mean parity 3 (range 0-14).

There were more adequate samples with LiquiPrep (94.7%) than with conventional (92.1%) smears but this difference was not statistically significant. Sever inflammatory infiltration observed in 26.1% of CP and only in 19% of LiquiPrep smears. (MC Nemar value=0.007) Presence of tissue fragments in slides was13.4% in CP and 3% in Liquiprep. (MC Nemar p value = 0.005).

The screening prevalence of ASCUS and squamous intraepithelial lesions according to Liquiprep and conventional Pap are listed in Table 1 and 2.

There was not any LSIL and HSIL report in two groups. ASCUS was diagnosed significantly more with conventional than with Liquiprep smear (1.56 vs. 0.79%). Pathologically 50% of ASCUS in Liquiprep and 12.5% in CP had squamous abnormality.

Prevalence of ASC-H was 0.39% in both group and all of them had epithelial abnormality in histology. There were two reports of Atypical Glandular Cells (AGC) in CP and one report in Liquiprep. Positive pathologic finding was found in 50% of CP and 100% of Liquiprep smears with AGC report.

Agreement between the two cytologic methods in terms of reporting diagnosis is shown in Table 3.

Table 1: Cytology results (Liquiprep) compared to colposcopy followed by histology findings

	Normal	CINI	CC	Polyp	EH	T
Negative	31	1	25	1	0	58
ASCUS	2	2	0	0	0	4
ASC-H	0	2	0	0	0	2
AGC	0	0	0	0	1	1
Total	33	5	25	1	1	65

Table 2: Cytology results (conventional) compared to colposcopy followed by histology findings

	Normal	CINI	CC	Polyp	EH	T
Negative	30	2	21	0	0	53
Ascus	3	1	4	0	0	8
ASC-H	0	2	0	0	0	2
AGC	0	0	0	1	1	2
	33	5	25	1	1	65

Table 3: Comparison between Liquiprep and Conventional Pap smear diagnosis

Conventional / Liquiprep	Negative	ASCUS	ASC-H	AGC	Total
Negative	491	7	0	1	499
ASCUS	3	1	0	0	4
ASC-H	0	0	2	0	2
AGC	0	0	0	1	1
Total	494	8	2	2	506

Table 4: Sensitivity, specificity, positive (+PV) and negative (-PV) predictive values of Liquiprep and conventional Pap for any histological alterations

	Liquiprep	Conventional	p value
Sensitivity	83%	66%	<0.05
Specificity	98%	86%	NS
+ PV	83%	33%	<0.05
-PV	96%	96%	NS

Table 4 summarizes the diagnostic parameters of conventional and Liquiprep preparations. Liquiprep had a significantly higher sensitivity (66 vs. 83%) and specificity (86 vs. 98%) than the conventional Pap smear to detect ASCUS+ at histology.

DISCUSSION

A screening test, as opposed to a diagnostic procedure, should have a low threshold to detect disease, i.e., should have high sensitivity. A case screened positive warrants further diagnostic investigation to confirm or rule out disease. Cervical cytology is no exception. Conventional cytology has long been known for its low sensitivity, attributed to inadequate sample collection and interpretation difficulties (Baandrup *et al*., 2000). Higher sensitivity of liquid-based cytology has been well documented (Bastin *et al*., 1999; Weintraub and Morabia, 2000; Malle *et al*., 2003). Liqui-prep, a novel liquid-based system, has similar cell morphology as Thinprep and Autocyte (Geyer and Marino, 2004a). Although, clinical studies with large size of samples did not performed for evaluation of this method, some available data affirm its superiority to conventional smears (Geyer and Marino, 2004b; Vassilkos *et al*., 2000). In the study, of James *et al*., Liqui-prep was compared with SurePath and conventional Pap test, with a detection rate 5.08% for ASCUS+ in Liqui-prep, 6.41% in SurePath and 3.49% in conventional method. In our study this rate was 1.4% in Liqui-prep and 2.37% in CP. The reason for this difference may be due to sampling population. In James study the population which samples obtained is not clear. The result of our study is comparable with Hutchinson´s study for Thin-prep method (Hutchinson *et al*., 1999).

As per this study protocol, Liqui-prep slides used residual cells. Despite favoring the conventional method, Liqui-prep proved to be a superior screening test, as demonstrated by its much higher sensitivity and positive predictive value to detect epithelial abnormality at histology. A direct-to-vial protocol could yield even better results, as reported by Vassilakos *et al*. (2000).

CONCLUSION

Liqui-prep™ a screening method that can be easily implemented in clinical practice is associated with fewer unsatisfactory samples and a significantly higher sensitivity when compared to conventional cytology. In addition, Liqui-prep™ has the advantage of collecting material for HPV-DNA Hybrid capture test, when deemed necessary.

REFERENCES

Baandrup, U., J.W. Bishop and T.A. Bonfiglio *et al*., 2000. Sampling, sampling errors and specimen preparation. Acta. Cytol., 44: 944-948.

Bastin, L., S. Datta and V. Hasselblad *et al*., 1999. Evidence report: Evaluation of cervical cytology. AHCPR publication 99-E010, Available at:htpp:// hstat. nlm.nih.gov.

Bishop, J.W., S.H. Bigner and T.J. Colgan *et al*., 1998. Multicenter masked evaluation of AutoCyte prep thin layers with mached conventional smears: Including initial biopsy results. Acta Cytol., 42: 189-197.

Coppleson, L.W. and B. Brown, 1974. Estimation of screening error rate from the observed detection rates in repeated cervical cytology. Am. J. Obstet. Gynecol., 119: 953-958.

Dehner, L.P., 1993. Cervicovaginal cytology, false negative results and standards of practice. Am. J. Clin. Pathol., 99: 45-47.

Gay, J.D., L.D. Donaldson and J.R. Goelner, 1985. False negative results in cervical cytologic studies. Acta Cytol., 29: 1043-1046.

Geyer, J. and J. Marino, 2004. Evaluation of Liquid-prep™ encapsulation method for Liquid-Based cytology: Cell loss estimates during processing. Abstract Number 176, XV International Congress of Cytology, Santiago, Chile.

Geyer, J. and J. Marino, 2004. Evaluation of Liquid-prep™ encapsulation system by comparison with the Surpath™ prep. Abstract Number 175, XV International Congress of Cytology, Santiago, Chile.

Goodman, A. and M. Hutchinson, 1996. Cell surplus on sampling devices after routine cervical cytologic smears. A study of residual cell populations. J. Reprod. Med., 41: 239-275.

Hesling, J.J., D.S. Raso, B. Schiffer, J. Callicott, M. Husain and D. Taylor, 2001. Effectivenes of thin-layer preparations vs, conventional Pap smears in a blinded, split-sample study: Extended cytologic evaluation. J. Reprod. Med., 46: 880-886.

Hutchinson, M.L., D.J. Zahniser and M.E. Sherman *et al*., 1999. Utility of liquid-based cytology for cervical for cervical carcinoma screening results of a population-based study conducted in a region of Costa Rica with a high incidence of cervical carcinoma. Cancer Cytopathol., 87: 48-55.

Hutchinson, M.L., L.M. Isenstein and A. Goodman *et al*., 1994. Homogeneous sampling accounts for increased diagnostic accuracy using the Thin-Prep processor. Am. J. Clin. Pathol., 101: 215-219.

Koss, L.G., 1989. The Papanicolaou test for cervical cancer detection: A triumph and tragedy. JAMA., 261: 737-743.

Lee, K.R., R. Ashfaq, G.G. Birdsong, M.E. Corkill, K.M. McIntosh and S.L. Inhorn, 1997. Comparison of conventional Papanicolaou smears and a fluid-based. thin-lyer system for cervical cancer screening. Obstet. Gynecol., 90: 278-284.

Malle, D., P. Pateinakis, E. Chakka and C. Destouni, 2003. Experience with a thin-layer, liquid-based cervical cytologic screening method. Acta Cytol., 47: 129-134.

Minge, L., M. Fleming, T. VanGeem and J.W. Bishop, 2000. AutoCyte prep system vs, conventional cervical cytology: Comparison based on 2,156 cases. J. Reprod. Med., 45: 179-184.

Monsonego, J. and C. Autillo-Touati and Bergeron *et al*., 2001. Liquid-based cytology for primary cervical cancer screening: A multi-center study. Br. J. Cancer, 84: 360-366.

Park, I.A., S.N. Lee, S.W. Chae, K.H. Park, J.W. Kim and H.P. Lee, 2001. Comparing the accuracy of ThinPrep Pap tests and conventional Papanicolaou smears on the basis of histologic diagnosis: A clinical study of women with cervical abnormalities. Acta Cytol., 45: 525-531.

Parkin, D.M., P. Pisani and J. Ferlay, 1993. Estimates of worldwide incidence of eighteen major cancers in 1985. Int. J. Cancer, 54: 594-606.

Rubio Ca, 1977. The false negative smear: II. The trapping effect of collecting instruments. Obstet. Gynecol., 49: 576-580.

Tezuka, F., H. Oikawa, H. Shuki and H. Higgashiiwai, 1996. Diagnostic efficacy and validity of the Thinprep method in cervical cytology. Acta Cytol., 40: 513-518.

Vassilakos, P., D. Schwartz and F. Marval *et al*., 2000. Biopsy-based comparison of liquid-based, thin layer preparation to conventional Pap smears. J. Reprod. Med., 45: 11-16.

Vooijs, G.P., A. Elias and Y. VanDer Graaf *et al*., 1986. The influence of sample taker on the cellular composition of cervical smears. Acta Cytol., 30: 251-257.

Wang, T.Y., H.S. Chen and M.C. Tsou, 1999. Comparison of fluid-based, thin-layer processing and conventional Papanicolaou methods for uterine cervical cytology. J. Formos Med. Assoc., 98: 500-505.

Weintraub, J. and A. Morabia, 2000. Efficacy of a liquid-based thin layer method for cervical cancer screening in a population with a low incidence of cervical cancer. Diagn. Cytopathol., 22: 52-59.