

## LIQUID BASED CYTOLOGY OR CONVENTIONAL CYTOLOGY?

**Christine Bergeron**

Laboratoire Pasteur-Cerba, Cergy Pontoise Cedex 9, France

---

The liquid based cytology (LBC) corresponds to a sampling where cells are put in suspension in a conversation liquid. For the clinician, the sample is made the same manner as that of the conventional smear by using a plastic brush, which can take the squamo-columnar junction and the endocervix, or by combining the use of a spatula and an endocervical brush. The taken material is then immediately rinsed in the bottle, which contains a fixative allowing transport to the laboratory. A part of the sizable brush can be left in the bottle. The clinician does not have to deal with any spreading, which is done at the laboratory. Currently, two technical methods, which use automats, were validated by Food and Drug Administration (FDA) and are used frequently. One is proceeding by filtration and collecting cells vacuum-packed on a membrane with transferring cells on a glass (ThinPrep®, Cytoc®). The other is proceeding by centrifugation and sedimentation through a gradient of density (Surepath®, Tripath Imaging®). Cytoscreen System® (SEROA®), Turbitec® (Labonord®), CellSlide® (Menarini®) and Papsin® (Shandon®) technics are centrifugation and sedimentation manual techniques, which do not use automate and do not require a FDA agreement. They become established in Europe since 2003 (1,2).

Spreading out in thin layer which results from these techniques eliminates a great part of the inflammatory cells, necroses and of red blood cells, outcome to "a cleaning" of spreading out. The LBC makes it possible to avoid the majority of the artefacts of superposition of the conventional smear but the dispersion of the cellular material removes also usual visual reference marks. The cytologists are used to reading smears fixed in a liquid for the urines, the serosa or the ovaries. It imposes an analysis element by element and a training at least 6 months to readjust the morphological criteria. The cells are not flattened on the support but deposited and the pictorial aspects are some modified. The nuclei are not hyper chromatic any more but take a vesicular aspect. The cytoplasm are important to differentiate the cellular origin.

The performances were evaluated by several national agencies whose conclusions are convergent as for the improvement of the quality of the smear. The unsatisfactory smears or limited by the presence of inflammation and red blood cells are statistically less important with LBC than with the conventional method. The absence of cellular material due to a sampling of bad quality remains as frequent in LBC as in conventional smear. The presence of endocervical cells was evaluated of various manners. In the studies where the sampling was divided into a conventional spreading out and where the residual material was rinsed in the bottle (split-samples), the endocervical cells are fewer in LBC. In the studies where all the sampling was rinsed in the flask and results

compared retrospectively to those in which smearing was made in a conventional way, the absence of endocervical cells is the same in the two methods. Scotland was the first European country to integrate LBC in an organized screening program (3). This decision was made on the results of a study of 70 000 smears concerning 3 centers. Cost-efficiency calculation was for the benefit of LBC because the rate of inadequate smears passed from 7 % with the conventional smear to 1 % with the smear in liquid medium. The definition of an inadequate smear in Scotland and England includes the smears deprived of endocervical cells. This definition explains the high percentage of inadequate cells. In the pilot study made in England, the rate of definite inadequate smear according to criteria's of the National Health System Cervical Screening Programs (NHSCSP) is from 9.1 % with the conventional smear to 1.6 % with LBC (4).

In the framework of the preparation of the new European Guidelines for Quality Assurance in Cervical Cancer Screening, a meta-analysis on test characteristics of LBC and conventional cytology (CP) was also prepared (5). Low-level and progressively higher-level inclusion criteria were considered on separated studies with concomitant testing and two-cohort studies. At the first level, studies that documented rates of cytological abnormality were accepted; at the second level, studies with colposcopic and histological verification of cytological positives were considered, and finally, at the third level, studies where all women were submitted to colposcopy and histology if colposcopic suspicion of lesions were selected. For all levels, ratios of test positivity (LBC/CP) have been computed, in addition for the second and third level ratios of positive predictive values, and for the third level only, relative sensitivity and specificity. Results were compiled according to cytological cut-off ASC-US, LSIL and HSIL and histological outcome threshold CIN categories. Also, the ratios of the proportion of unsatisfactory preparations and the duration of interpretation were analyzed. A series of test and study quality characteristics was established for multi-variate analysis. 103 reports were retrieved from 93 studies matching selection criteria. Nevertheless, only six studies could be included in the third level meta-analysis (6-11). Results pooled from studies with concomitant testing showed nearly equal detection rates of HSIL and positive predictive value for CIN2+ in CP and LBC. However, in two-cohort studies, detection rates of HSIL were substantially and statistically significantly higher in LBC: pooled ratio of 1.58 (95 % [CI]: 1.39-1.79) including all systems; 1.63 (95 %: 1.38-1.93) and 1.46 (CI: 1.18-1.81) for studies with ThinPrep and AutoCyte/SurePath respectively. The sensitivity and specificity of LBC at ASC-US+ and LSIL+ for CIN2+ pooled from studies of the third level never was significantly different from CP. In two-cohort studies, 34 % (ratio: 0.66, CI: 0.42-1.02) and 83 % (ratio: 0.17, CI: 0.10-0.32) less unsatisfactory smears were found in ThinPrep and AutoCyte/SurePath smears, respectively. Overall, interpretation of LBC required 30 % less time to interpret than CP. These conclusions are partially in agreement with the metanalysis published by Davey et al. (12). Nevertheless, several flaws in the meta-analysis of the Australian colleagues were observed. Only 56 studies that matched selection criteria were found. The categorization of studies in 3 quality groups did not allow revealing substantial differences in cytological abnormality rates and quality judgment observed in two-cohort studies. Cytology and histology outcomes were mixed. Moreover the subdivision in quality groups is not reproducible. However, it was agreed with Davey *et al* that quality of literature on LBC is poor and that well-designed large randomized studies are needed. Finally, a large randomized trial comparing conventional cytology with liquid based cytology and HPV testing has been performed in Italy and shows no difference between the two techniques of cytology independently of the age (13-14).

It was concluded that no evidence is available to claim higher accuracy of LBC to predict histologically confirmed CIN2+, but recognized that LBC improves the quality and speed of interpretation, and offers the possibility of additional molecular testing. Therefore both CP and LBC for screening in Europe are recommended. Preferences should be determined depending on local economical considerations.

## References

1. Bergeron C, Fagnani F. Performance of a new, liquid-based cervical screening technique in the clinical setting of a large french laboratory. *Acta Cytol* 2003, 47:753-761.
2. Weynand B, Berlière M, Haumont E, Massart F, Pourvoyeur A, Bernard P, Donnez J, Galant C. A new, liquid-based cytology technique. *Acta Cytol* 2003, 47:149-153
3. Scottish Cervical Screening Programme : Steering group report on the feasibility of introducing liquid-based cytology, January 2002 . <http://www.show.scot.nhs.uk>
4. National Institute for Clinical Excellence (NICE). Guidance on the use of liquid-based cytology for cervical screening. October 2003. <http://www.nice.org.uk>
5. Arbyn M, Bergeron C, Bulten H, Klinkhamer P; Liquid based cytology: is it really better than conventional cytology, an attempt to answer through a comprehensive meta-analysis. International Federation for cervical pathology and colposcopy, Cancun June 8, 2005.
6. Coste J, Cochand-Priollet B, de Cremoux P et al. Cross sectional study of conventional cervical smear, monolayer cytology, and human papillomavirus DNA testing for cervical cancer screening. *BMJ* 2003 ; 326:733-6.
7. Ferenczy A, Robitaille J, Franco EL, Arseneau J, Richart RM, Wright TC. Conventional cervical cytologic smears vs. ThinPrep smears. A paired comparison study on cervical cytology. *Acta Cytol* 1996;40:1136-42.
8. Bergeron C, Bishop J, Lemarie A et al. Accuracy of thin-layer cytology in patients undergoing cervical cone biopsy. *Acta Cytol* 2001;45:519-24.
9. Confortini M, Bulgaresi P, Cariaggi MP et al. Comparing conventional and liquid-based smears from a consecutive series of 297 subjects referred to colposcopy assessment. *Cytopathology* 2004;15:168-70.
10. Longatto Filho A, Pereira SM, Di Loreto C et al. DCS liquid-based system is more effective than conventional smears to diagnosis of cervical lesions: study in high-risk population with biopsy-based confirmation. *Gynecol Oncol* 2005;97:497-500
11. Taylor S, Kuhn L, Dupree W, Denny L, De Souza M, Wright TC, Jr. Direct comparison of liquid-based and conventional cytology in a South African screening trial. *Int J Cancer* 2006;118:957-62.
12. Davey E, Barratt A, Irwig L et al. Effect of study design and quality on unsatisfactory rates, cytology classifications, and accuracy in liquid-based versus conventional cervical cytology: a systematic review. *Lancet* 2006;367:122-32.
13. Ronco G, Segnan N, Giorgi-Rossi P, Zappa M, Casadei GP, Carozzi F et al. Human papillomavirus testing and liquid based cytology: results at recruitment from the New Technologies for Cervical Cancer Randomized Controlled Trial. *J Natl Cancer Inst* 2006, 98: 765-74.
14. Ronco G, Giorgi-Rossi N, Carozzi P, Dalla Palma P, Del Mistro A, De Marco et al. Human papillomavirus testing and liquid-based cytology in primary screening of women younger than 35 years: results at recruitment from a randomized controlled trial. *Lancet Oncol* 2006, 7 :547-55.