Liquid based cytology improves the positive predictive value of glandular smears compared to conventional cytology

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Summary

Purpose: To investigate whether the introduction of liquid-based cytology (LBC) in an urban setting decreases the diagnosis of glandular neoplasia (grade 6) and improves the positive predictive value (PPV) of cervical cytological screening. *Methods:* A retrospective database review was conducted identifying women with cervical cytological abnormalities including glandular neoplasia (grade 6) before and after the introduction of LBC. *Results:* Following the introduction of LBC the rate of glandular neoplasia (grade 6) referrals fell from 1.08% to 0.69% of all cervical cytological abnormalities. There was a significant reduction in 'abnormal' cytological samples subsequently found to be associated with no invasive or preinvasive disease but no decrease in the number showing preinvasive or invasive disease. A significant decrease in number of patients having a final diagnosis of normal/inflammatory or wart changes was seen in those patients referred during the LBC period ($p < 0.01$). *Conclusion:* The introduction of LBC in an urban setting decreased cytological glandular neoplasia referrals but not at the expense of missing preinvasive and invasive cancers. It has also increased the PPV of cervical sampling to detect preinvasive and invasive cancer from 59.6% to 76.0%.

Key words: Liquid based cytology; LBC; CIN; CGIN; Glandular neoplasia.

Introduction

The use of LBC has recently been recommended by the National Institute for Health and Clinical Excellence (NICE) as the method of choice for collecting and preparing cervical cytology specimens in England and Wales [1]. All English cytology screening laboratories have now changed to using LBC technology. The recommendation by NICE was based, at least in part, on the results of a pilot project involving three cytology laboratories in England [2]. The pilot study found a clear reduction in the rate of glandular neoplasia (grade 6) detected on routine cytology, with the rate of glandular neoplasia falling from 0.08% to 0.04%. This change in detection rate was similar in all three pilot sites.

This change in rate of detection of glandular neoplasia may be a cause for concern. One study suggested that the finding of glandular neoplasia on cytology is associated with an invasive cancer in 36% of cases while a further 63% of cases have cervical intraepithelial neoplasia (CIN) or cervical glandular intraepithelial neoplasia (CGIN) found at biopsy. In the remaining 44% of cases no evidence of invasive or preinvasive disease was found [3]. In a second study 59% of women had CGIN, 5.3% had endocervical adenocarcinoma and 31.6% had endometrial adenocarcinoma when 'glandular neoplasia' was the cytological diagnosis [4].

There are several possible explanations for this decreased rate of diagnosis of glandular abnormalities on cervical cytology. Firstly that these cervical samples are now being reported as normal and therefore some cases with preinvasive or invasive disease are being missed. Secondly it is possible that these cases are being reported as another form of cervical abnormality, such as squamous dyskaryosis or borderline glandular abnormality, and are still therefore being referred for colposcopy. Thirdly it is possible that LBC has a greater specificity than conventional cytology and is able to differentiate those cases in which there is no proven abnormality from those cases with preinvasive or invasive disease.

In this study we attempted to investigate whether the decreased rate of reporting of glandular neoplasia associated with LBC reflects a global decrease in the subsequent colposcopic and histological diagnoses or whether it represents a specific decrease in one histological diagnostic group.

Methods

This study was performed in the colposcopy department of one of the three units taking part in the English Human Papilloma Virus/LBC pilot project. LBC was introduced into the cytology laboratory on 1 July 2001 following which all samples were reported using this technology. On completion of the pilot study the laboratory has continued using LBC employing the Surepath system. Data were extracted from the colposcopy database – a fully computerised system which records details of all patients referred for colposcopic opinion including details of referral cervical cytology and subsequent histological diagnosis. Patient information was collated over 81 months including a 51-month period when cytology was collected in the traditional manner and 30 months using LBC technology.

All patients referred with cytological abnormalities including glandular neoplasia (grade 6) were identified and their outcome

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Table 1. — *Comparison of outcomes for women referred with glandular abnormalities diagnosed on conventional cytology (preLBC) and using LBC technology (LBC).*

	PreLBC (n = 4,787)		LBC (n = 3,318)		
	Glandular referrals (%)	Number per year[a]	Grandular referrals (%)	Number per year[a]	
Histological outcome					
No invasive or preinvasive disease	22 (42)	5.2	4 (17)	1.5	$p < 0.01$
Presence of CIN/CGIN	29 (55)	6.8	18 (78)	7.2	n.s.
Cancer of cervix	2 (3)	0.47	1 (5)	0.38	n.s.

[a] referrals corrected for time to give average number of patients per year; n.s.: not significant.

was recorded including colposcopic opinion and histological diagnoses from either punch or loop biopsies. All patients referred with glandular neoplasia (grade 6) underwent colposcopic assessment by a British Society for Colposcopy and Cervical Pathology (BSCCP) accredited colposcopist with loop excision of the transformation zone or punch biopsy taken of any abnormality seen. Endometrial sampling using a Pipelle sampler was performed in those who were postmenopausal where no cervical abnormality was seen. All patients, irrespective of whether they underwent treatment, were followed up in the colposcopy clinic until both colposcopy and cervical cytology were reported as negative.

Results

During the preLBC period there were 4,787 referrals of women with abnormal cytology to the colposcopy unit, of which 53 (1.1%) were reported as showing a glandular neoplasia (grade 6), compared with 3,318 referrals during the LBC period, of which 23 (0.69%) were reported as showing glandular neoplasia. This fall does not achieve statistical significance (chi-square test).

All patients with the cytological diagnosis of glandular neoplasia were seen in the colposcopy clinic. Of the 76 patients referred 73 underwent biopsy (with 51 having a large excision of the transformation zone and 22 punch biopsies of the cervix) and histological examination. The remaining three had no colposcopic abnormality and were followed-up with repeat cytology and colposcopy at six months and one year. In these cases both cytology and colposcopy were normal at these subsequent visits. The final diagnoses for 76 patients are shown in Table 1.

A significant decrease in number of patients having a final diagnosis of normal/inflammatory or wart changes was seen in those patients referred during the LBC period (4/3,318 for the LBC period compared with 22/4,787 for the preLBC period ($p < 0.01$; chi-square test). No significant change was seen in the rates of patients subsequently found to have preinvasive (18/3,318 for the LBC period compared with 29/4,787 for the preLBC period) or invasive disease (1/3,318 for the LBC period compared with 2/4,787 for the preLBC period (chi-square test).

When the figures are corrected for time, to give an average number of cases seen per year, this finding corresponds to a decrease in cases of no preinvasive or invasive disease from 5.2 cases per year in the preLBC group to 1.5 cases per year in the LBC group. There was no change in the number of cases per year of preinvasive or invasive disease between the two groups. There were three cases of invasive cancer diagnosed during the study period, two cases of adenocarcinoma in the preLBC period and one case of squamous cell carcinoma in the LBC period. Calculating positive predictive values (PPV) for the ability of cervical cytology to predict preinvasive or invasive disease gives a PPV of 59.6% for the preLBC period and a PPV of 76.0% for the LBC period.

Discussion

Although the numbers of women referred to colposcopy units with 'glandular neoplasia' are small they remain an important group because of the high incidence of invasive and high-grade preinvasive disease [3-5]. It is important therefore that any change to current cervical cytology screening programmes does not deleteriously affect the ability to detect this group of patients.

Study of glandular neoplasia is difficult because of the relative rarity of cytological specimens showing this abnormality along with the challenges of converting from conventional to LBC [6]. This study has used data from a six-year period in an attempt to increase the validity of its findings. Our findings show that following the introduction of LBC the numbers of women referred with cytology suggesting glandular neoplasia (grade 6) fell from 1.1% to 0.69% but not at the expense of missing pre-invasive and invasive cancers. While it is possible that there has been a real change in the incidence of invasive and preinvasive disease in this time it seems unlikely and therefore it is reasonable to conclude that the introduction of LBC has been associated with a true increase in the PPV with no deterioration in the sensitivity of the test.

This study does however suffer from the limitation that it compares a study group with a historical control and it is possible that other factors were responsible for the change in rates of diagnosing glandular abnormalities. In particular, guidance from the National Health Service Cervical Screening Programme (NHSCSP) and the BSCCP may have had an effect on the diagnostic criteria used to determine glandular neoplasia and influenced patterns of cytological reporting.

This retrospective analysis also suggests that LBC has increased the positive predictive value of cervical sampling to detect preinvasive and invasive cancer from 59.6% to 76.0%. PPVs quoted here are for the ability of cervical cytology to detect both CIN and CGIN, and not cervical cytological glandular abnormalities, to predict glandular neoplasia. However from the pragmatic view of the colposcopist and the patient the importance of abnormal cytology is its ability to detect all premalignant lesions which require treatment.

Conclusion

LBC has been introduced into the United Kingdom because of its important advantages over conventional cytology, principally in the reduction in the number of smears reported as unsatisfactory [7]. The finding from the pilot studies suggesting that LBC is associated with a decrease in the rate of glandular abnormalities noted was initially a concern. This study helps to allay those fears by demonstrating that the reduction in number of smears reported as showing glandular abnormalities is principally in the group of patients who were subsequently found to have neither invasive nor preinvasive disease and therefore the introduction of LBC appears to be associated with a decrease in the false-positive rate for cytology. Importantly the introduction of LBC does not appear to affect the rate of diagnosis of invasive or preinvasive disease. This leads to a substantial increase in the PPV of cytology to predict invasive and preinvasive disease of the cervix.

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