The role of PAP and HPV test in new era of cervical cancer screening

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Exfoliative cervical cytology has formed the basis of cervical screening since the 1950s and where systematic population based screening programmes have been established the incidence and mortality from cancer of the cervix have fallen as a direct consequence (1–3). The sensitivity of a single conventional cytology test to detect underlying CIN is around 50–70% (4), so repeated cytology is required at regular intervals and this is considered to prevent around 70% of cervical cancer (5).

During the 1990s a new technology was developed, known as liquid based cytology (LBC).The National Institute of Clinical Excellence (NICE) considered LBC in 2003 and recommended national implementation which was completed by 2008. Two technologies, SurePath™ (SP) and ThinPrep® (TP), currently dominate the market and both are exclusively used in the NHS Cervical Screening Programme (NHSCSP).

Around the time liquid based cytology was ready for clinical use, it was becoming clear that testing for high risk oncogenic types of human papillomavirus (HPV) would play a major role in cervical screening because of increased sensitivity and the opportunity for extended screening intervals. In addition it could exploit the high negative predictive value of a negative HPV test in order to streamline protocols such as triage of low grade abnormalities (borderline/ASCUS and low grade dyskaryosis/LSIL) and test of cure following treatment of CIN. LBC is an ideal platform for HPV testing, although a pooled analysis of seven trials published in 2008 concluded that LBC was neither more sensitive nor more specific for detection of high grade CIN than conventional cytology (6).

Pilot evaluation of HPV testing for triage of low grade cytological abnormality embedded in the initial evaluation of LBC in the UK demonstrated that it was feasible; acceptable to women; might lead to increased detection of CIN2+; accelerated the diagnosis of high-grade CIN; avoided the need for repeated cytology; and was cost effective in terms of quality and of life years saved (7, 8). Meta-analysis of HPV test of cure concluded that it was more sensitive and slightly less specific than follow up by cytology (9).

In 2008 the NHSCSP established the Sentinel Site Study to evaluate HPV triage and test of cure in six laboratories. In the triage study the HPV positive rates at the six sites ranged from 34.8% to 73.3% for women with borderline (ASCUS) cytology, and from 73.4% to 91.6% for women with mild dyskaryosis (LSIL). These differences remained after the rates were standardised for age. Overall the HPV positive rate was higher in sites using ThinPrep® than in those using SurePath™; 68.7% and 61.7% respectively ($p<0.0001$). The difference remained after adjustment for age group and initial cytology result. LBC technology was, however, confounded by site, and it was therefore not possible to determine whether this difference was due to variation in the reporting of cytology between sites. In the only site which used both technologies there was no significant difference in positive rates between the two.

It was concluded that HPV triage of women of low grade cytological abnormalities would result in earlier detection and treatment of high-grade CIN, early return of women with low-grade cytology who were HPV negative to routine screening, and avoid the need for repeat cytology (10).

In the test of cure study 78% of women were HPV and cytology negative at 6 months following treatment for CIN and could revert to normal recall.

HPV triage and test of cure has now been implemented throughout the NHSCSP.

Meta-analysis has demonstrated that primary screening by HPV testing is more sensitive but slightly less specific than cytology (11). Following successful implementation of HPV vaccination

programmes there will be a progressive reduction in prevalence of cytological abnormality which will compromise the sensitivity of cytology and there is a strong argument for replacement of cytology by primary HPV testing in vaccinated populations (12). The six Sentinel Site laboratories in England have converted a proportion of the population they serve to primary HPV screening from spring 2013. The protocol will be described. Preliminary results indicate that approximately 15% of women in an unselected screened population are HPV positive and of these approximately one third have cytological abnormality and require referral for colposcopy.

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