Statement from the Regional HTA Centre of Region Västra Götaland, Sweden

Liquid-based cytology for screening of precursors of cervical cancer

Question at issue:
Can liquid-based cytology improve the sensitivity and specificity for detecting severe cytological changes (CIN2 or more severe = CIN2+) in tissue samples, compared to conventional cytology (CC, Pap-smear) in connection with gynecological cytology control, and does liquid-based cytology lead to a decreased proportion of not assessible samples?

PICO (Patient, Intervention, Comparison, Outcome)

P= Women 19-70 years.
I= Liquid-based cytology (LBC).
C= Conventional cytology (CC).
O= Sensitivity/detection level for CIN2+ in histopathology.
Specificity/positive predictive value (PPV) for CIN2+ in histopathology.
Proportion not assessable samples.

Summary of the health technology assessment:

Method and target group:
Screening for cellular changes that may progress to cervical cancer is offered to all women between 23 and 60 years in Region Västra Götaland. Women are invited to cellprovstagning at antenatal clinics / midwifery clinics every 3 to 5 years depending on age. At abnormal test result the woman is called to the examination with colposcopy (microscopy examination of the cervix and vagina), new cytology and possibly a sample excision (tissue sample). With the current conventional method of analysis, about 25% of the incidence of cervical cancer is considered to be due to low sensitivity of the test method. The new method, liquid-based cytology, has been evaluated for patient benefit by estimating its sensitivity, ie, if the method has a higher detection rate of high grade cellular changes, and consequently improves the cancer preventive effect. In addition, the specificity (and hence the proportion of false positive samples that need to further examined) and the proportion of not assessible samples (new samples thus need to be taken on a second occasion) have been evaluated. The connection to supplementary viral diagnostics has not been evaluated in the literature review, but was commented upon.

The literature:
The literature is extensive and is based on two HTA reports, a Canadian from February 2008 and a Danish from 2005, as well as a systematic review, and 18 original articles, published after the HTA reports were written. The Canadian HTA report is considered to have good internal and external validity, while the Danish is considered to have an acceptable internal and a good external validity.

Level of evidence for studied patient benefit:
1. Sensitivity and specificity. In the two HTA reports and in the systematic review no significant differences between the liquid-based cytology and conventional cytology were found. Of the six controlled studies of moderate quality, five showed better sensitivity for liquid-based cytology, while one showed no difference. Of the six controlled studies of low quality, three showed higher sensitivity for liquid-based cytology, and three did not show any difference. The specificity varied across the studies: in two out of three Scandinavian studies, of moderate quality, the specificity was found to be decreased.
There is limited evidence (evidence level 3) for liquid-based cytology having a higher sensitivity than conventional cytology, and that the specificity is lower. This means that more

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severe cytological abnormalities could be detected with liquid-based cytology in the screening program at the expense of a moderate reduction in specificity.

2. Assessibility: The Canadian HTA report concludes that liquid-based cytology, has a lower proportion not assessible samples. The Danish report is difficult to evaluate in this respect, but found no scientific evidence for an increased assessibility with liquid-based cytology. All controlled trials of high (n=2) and medium (n=5) quality, showed that liquid-based cytology, was better, ie. had a lower proportion of not assessible samples. Of the four controlled studies with low quality, three showed better outcomes, and one poorer outcome for liquid-based cytology. There is strong evidence (level of evidence 1) that the proportion of not assessible samples is lower in liquid-based cytology, than in conventional cytology.

Risks:
The reduced specificity means that more women with false positive samples will be unnecessarily worried, and are subjected to an additional examination before it can be confirmed that the first (screening) test was false positive

Ethical aspects:
The price we have to pay inorder to find more patients with severe cytological abnormalities is an increased proportion of false positive samples, causing concern among patients. At the same time reducing the proportion of not assessible samples leads to that fewer worried women.

Economical aspects
Investment cost for instrumentation and image analysis systems in Region Västra Götaland is estimated to an annual cost of 400,000 SEK, with a depreciation period of 5 years. An annual materials cost of 4 million SEK needs to be added (about 35 SEK/sample). However, there will be a cost reduction due to reduced need of staff, fewer re-appointments, probably fewer cancer cases, but a cost increase due to more colposcopy examinations.

Concluding remarks
There is strong scientific evidence that the introduction of liquid-based cytology, reduces the proportion of not assessible samples, and thus re-appointments for patients. There is limited scientific support that liquid-based cytology, increases the sensitivity and decreases the specificity, which would imply that more cases with severe cytological abnormalities are detected at the expense of an increased proportion of false positive samples. This could eventually lead to fewer cancer cases, but a certain increase in the volume of examinations.

On behalf of the Regional HTA Centre of Region Västra Götaland, Sweden.

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