Ushering in a new era: human papillomavirus (HPV) testing comes to the NHS Cervical Screening Programme

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Background

The National Health Service Cervical Screening Programme (NHSCSP) has announced that from April 2011, human papillomavirus (HPV) testing will be incorporated into the national screening programme in England. Initially, HPV testing will be used for the triage of borderline and mildly dyskaryotic smears, but there are also plans, at a later date, for its use as a 'test of cure' following treatment for cervical abnormalities (Figure 1).¹ It would have been interesting to see the data underpinning the proposals, but no references were given.

The announcement follows 8 years of pilot projects. The first pilots were completed in 2006² and were followed by the Sentinel Site Implementation Project, which was launched in January 2008, to examine the practical implementation of a national roll-out of HPV testing. A report from the latter does not appear to be publicly available, so it is not possible to tell whether the problems identified in the pilots have been overcome and, if so, how. It is thus impossible to judge the results of the changes.

HPV triage

The majority of low-grade cytological abnormalities (at least 70%) will regress without treatment.³ If it was possible to identify those women whose abnormalities were very likely to regress, they could be spared the anxiety of repeat testing and colposcopy referral. Testing for high-risk HPV types is currently the most effective way of doing this: a negative HPV test means there is very little chance of any abnormality being present.³ The introduction of liquid-based cytology into the NHSCSP paved the way for 'reflex' testing of cytology samples, in which those showing borderline or mild dyskaryosis

could automatically have an HPV test performed on their sample, without the need for the woman to be re-examined. If high-risk HPV is found they will be referred for colposcopy; if HPV is not found they will be returned to routine screening.

Why has the NHSCSP chosen to use triage in the management of women with mild, as well as borderline, dyskaryosis? The American College of Obstetrics and Gynecology published guidelines on the use of HPV triage in 2009, but only recommended its use in women with atypical squamous cells of unknown significance (ASCUS) (roughly equivalent to borderline) smears, since a very high proportion of women with low-grade squamous intraepithelial lesions (LSIL) (equivalent to mild dyskaryosis) would test positive and be referred for colposcopy anyway.⁴ This is borne out by the results of the pilots, in which HPV positivity rates were 46% for women with borderline smears and 83% for those with mild dyskaryosis.² Similar figures were shown in the UK ARTISTIC study, in which HPV positivity rates were 31% for women with borderline smears and 86% for those with mild dyskaryosis.⁵ HPV positivity is higher in young women, reflecting the high incidence of transient infections, and indeed, in the pilots, two centres decided not to continue to refer HPV-positive women under the age of 35 years directly for colposcopy, because the number of referrals had more than doubled. In the ARTISTIC trial, HPV positivity rates in women aged 25–29 years were 48% in women with borderline dyskaryotic smears.⁵

It would therefore appear that the majority of women with a single borderline or mildly abnormal smear will in fact be referred straight to colposcopy. How will the clinics cope if they suddenly have a large increase in the number of referrals?

HPV Triage and Test of Cure Protocol

For women aged 25 to 64 years

¹ If sample is unreliable/inadequate for the HPV test, refer mild and recall borderline for 6 month repeat cytology. At repeat cytology HPV test if Neg/Bord/Mild. If HPV negative return to routine recall, refer if HPV positive. Refer moderate or worse cytology.

² Untreated CIN1 should be managed as per untreated CIN1 following borderline/mild.

³ Follow up of 12 month cytology only should follow normal NHSCSP protocols.

⁴ Women in annual follow up after treatment for CIN are eligible for the HPV test of cure at their next screening test.

⁵ Women ≥50 who have normal cytology at 3 years will then return to 5 yearly routine recall.

⁶ Women referred due to borderline/mild cytology or normal cytology/HPV positive, who then have a satisfactory and negative colposcopy can be recalled in three years.

N.B Women who reach 65 still require to complete the protocol and otherwise comply with national guidance.

HPV Triage and Test of Cure Protocol April 2010

Figure 1 National Health Service Cervical Screening Programme (NHSCSP) flow diagram of 'HPV Triage and Test of Cure Protocol for Women Aged 25 to 64 Years'.¹ Figure available at: <http://www.cancerscreening.nhs.uk/cervical/hpv-triage-test-flowchart-v2.pdf>.¹ This flow diagram is reproduced with the kind permission of the NHSCSP.

Admittedly, colposcopy clinics have become less busy since the decision to raise the screening age to 25 years, but many will also have fewer staff as a result. It is likely that there will be an increase in the detection of high-grade cervical intraepithelial neoplasia (CIN), both due to the higher sensitivity of HPV testing compared to cytology and to the fact that fewer women are lost to follow-up. This is to be welcomed. However, it should not be forgotten that, in the pilots, women who were HPV-positive were significantly more anxious, distressed and concerned about their test results, mainly because they did not understand what their results meant.² It could be argued that, since then, the introduction of HPV vaccination should have improved public knowledge around HPV; unfortunately, while awareness is certainly higher, knowledge does not appear to be much greater.⁶ More education of both the public and health professionals is still needed.⁷

The triage programme is to start in April 2011, but in reality only the current Sentinel Sites (Sheffield, Manchester, Liverpool, Bristol, Norwich and Northwick Park Hospital in London) are actually ready. There are many issues to be resolved elsewhere; laboratories will need to be reorganised and equipment purchased, staff will need training and administrative practices will need to be altered. In practice, then, in the rest of the country, the national programme is unlikely to even start being rolled out before October 2011.

Test of cure

In addition to HPV testing in triage, an HPV 'test of cure' is being introduced (though it is not clear exactly when) for women who have undergone treatment for CIN. The proposal is that women will have cytology performed 6 months after their treatment; if the result is negative, an HPV test will be carried out, using the same cytology sample. If the HPV test is negative, women will be discharged back to routine recall in 3 or 5 years; if they are aged over 60 years, this would mean they do not attend again (since recall ceases at aged 64 years). If, however, the HPV test is positive or cytology screening does show an abnormality then the women will be referred back to colposcopy (Figure 1).¹

Many clinicians have been eagerly awaiting the introduction of HPV 'test of cure' as there is evidence that HPV negativity is a good predictor of disease clearance. However, studies suggest that it often takes longer than 6 months to clear HPV infection after treatment, which means women will be worried unnecessarily by positive tests.⁸⁻⁹ A recent Australian study found that while over 90% of HPV 16 and 18 infections cleared within approximately 24 months post-treatment, only around 50% had cleared within 6 months of treatment.¹⁰ A UK study that followed women for 2 years suggested that a strategy of HPV testing at 6 months might be safe, but this was carried out in three centres of excellence, with an extremely low residual disease/recurrence rate.¹¹ Several studies

of residual disease rates after large loop excision of the transformation zone (LLETZ) treatment have demonstrated that negative excision margins are associated with lower risk and positive excision margins with higher risk of residual disease but this does not appear to be taken into account in the new management algorithm (Figure 1).¹ Meanwhile, most of the HPV 'test of cure' studies have only followed up women for around 2 years. Can we be sure it is safe to return these women to routine screening when it is known that they continue to be at higher risk of developing cancer for at least 10 years?¹²⁻¹³

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