The "Jade Goody effect": what now for cervical cancer prevention?

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Introduction

The illness and early death of the reality television star, Jade Goody, 12 months ago propelled the issue of cervical cancer into the headlines. One significant result of this media attention was an expansion in the demand for and uptake of cervical cytology screening.

The large increase in the number of cytology tests requested had a significant impact on colposcopy and pathology workloads. The effect will continue to be felt for many months, since each newly screened cohort results in more women attending for colposcopy and an increase in appointments for conservative evaluation of low-grade disease, treatment and follow-up. The media attention and the resulting impact on cytology and colposcopy services also provoked interest in examining how the UK screening programme can optimise cost-effective health gain. This article considers the national screening programme and the possible impact of human papillomavirus (HPV) vaccination and HPV testing on screening and the potential long-term effects of the current changes to cervical cancer prevention.

Cervical screening

The UK has seen a reduction of over 50% in deaths from cervical cancer since the introduction of the national call-and-recall screening programme in 1988.[1] This success depends on coverage: cervical screening has a highly significant impact when more than 80% of the 'at risk' population is covered within the recommended screening interval.[2] However, before the publicity surrounding Jade Goody, there was a decline in the number of 25–30-year-old women in the UK responding to their invitations to attend for cytology tests.[3] In some areas of the country, the coverage has been less than 68%.[4]

In discussing the "Jade Goody effect" in the context of cervical screening, the impact on cervical coverage reported in the recent statistical bulletin only partially describes the "effect" as it only includes the period up to 31 March 2009.[5] In a preliminary analysis of the complete "Jade Goody effect", it has been found that there was a slight rise in participation amongst younger women seen after her diagnosis in August 2008. A major effect was noted from February 2009, doubling in March 2009 when she married and died but then declining over the next 3 months, and by July 2009 the status quo was re-established [preliminary analysis by the National Health Service Cervical Screening Programme (NHSCSP), Julietta Patnick, personal communication, February 2010].

To describe this in more detail: in the first 6 months of 2008 in England, 1 517 031 women were screened. Of these, 485 947 were women aged 24.5–49 years who had not been seen in the previous 3.5 years, and 40 868 women aged 50–64.5 years who had not been seen for the previous 5 years. In the same period of 2009, 2 095 468 women were screened, an extra 578 437 women. Of these, 657 234 were women aged 24.5–49 years who had not been seen in the previous 3.5 years (35.2% more than in the previous year) and 51 312 were women aged 50–64.5 years who had not been seen for the previous 5 years (an increase of 25.6%) (Julietta Patnick, personal communication, February 2010). In the long-term the increase in screening coverage triggered by the "Jade Goody effect" should result in a reduction in cervical cancer cases particularly amongst younger women, although in the short term there may be an increased identification of "prevalent" cases.

Age at first screen

In 2003, the English NHSCSP increased the age for first call to 25 years, whereas it remains 20 years in other parts of the UK. There is heated debate between those who advocate a return to earlier screening in England and those who support the later starting age. The issues underlying the decision are complex and involve a risk–benefit analysis as well as an assessment of cost effectiveness.

When the English call-and-recall programme was introduced in 1988, women were invited from age 20 years. Compliance and coverage among those under the age of 25 years was only about 50%, and it became clear that the incidence of cervical cancer in this age group was low, at 3.3 per 100 000.[6] Conversely, the incidence of HPV infection of the lower genital tract in young women is high: a study of college students found a cumulative incidence of 43% over 3 years.[7] For the vast majority of young women, a high-risk HPV infection in the genital tract is a common, self-limiting event:[8] most individuals demonstrate an effective immune response and have no clinical sequelae.[8,9] Some women are slow to demonstrate that response and may be affected by a short-term viral epithelial change that will regress without the need for treatment.[10] Cervical intraepithelial neoplasia (CIN) grade 1 will progress to a higher grade requiring treatment in only 12% of cases.[11] The progression of CIN 3 to invasive cancer has been investigated in untreated women managed only by punch or wedge biopsy. The percentage of women with cancer of the cervix after 5 years was 11.3%, increasing to 17% at 10 years.[12]

Unfortunately, the cytological and colposcopic changes associated with an acute viral effect against the background of very active physiological metaplasia in young women[13] can lead to an over-diagnosis of high-grade CIN. There is, therefore, a danger that screening of young women with a self-limiting viral infection will result in unnecessary investigations and treatment, notably if a "see and treat" policy is adopted for high-grade referral cytology. Although the incidence of side effects following loop excision treatment for CIN is low (about 3%),[14] the resulting shortening of the cervix may put future pregnancies at risk in a small proportion of women; removal of a specimen greater than 1.5 cm in height is associated with an increased risk of preterm labour.[14–16] Arbyn *et al*. suggested that following excisional treatment there may be a significantly increased risk of preterm labour less than 37 weeks (relative risk >2),[14] cold knife

J Fam Plann Reprod Health Care 2010; **36**(2): 51–54

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cone excision was also associated with a significantly higher risk of both severe and extreme prematurity, under 32 and 28 weeks, respectively.[17] Furthermore, a small proportion of women treated for CIN in their early 20s will require a second treatment in their later 20s for persistent or recurrent disease. In a recent article Ørtoft *et al*. reported a further increased risk of preterm delivery after two treatments for CIN 3 (adjusted hazard ratio 9.9), thus significantly contributing to the risk of future pregnancy-related morbidity.[18] Delaying investigation and treatment until after age 25 years reduces the risk of these complications, especially as the average age at first pregnancy in the UK has risen to approximately 30 years.[19]

The counter-argument is that a small number of women under the age of 25 years do develop cervical cancer,[6] and some of these cases could be prevented if screening commenced at age 20 years. In a perfect world we would of course all wish that these could be avoided. However, the risk–benefit argument centres on how many unnecessary colposcopy and loop excision procedures – with the concomitant risk of future pregnancy morbidity – society is prepared to accept to reduce the likelihood of an occasional case of cancer among young women. It can also be argued that with more widespread use of modern fertility-sparing surgery for early invasive cancer, the small number of women who develop cervical cancer in their early 20s might still be treated successfully by their first cone biopsy, an extended second cone biopsy or trachelectomy without completely losing their reproductive potential.[20]

The debate is confounded because the data that formed the basis for the change in policy up to age 25 years are historical.[21] Also, at the time the decision was reached, the savings made by avoiding 'unnecessary' cytology tests in younger women allowed the National Health Service (NHS) to make some definite health gains as follows:

- Introduction of liquid-based cytology (LBC)
- Establishment of 3-yearly screening in England up to the age of 50 years
- Maintenance of 5-yearly screening after the age of 50 years in all areas of the UK.

The key, perhaps, is the length of time from first contact with HPV until there is a realistic possibility that a CIN 3 lesion may become an early invasive lesion. Data from The Netherlands suggest that this interval is about 8 years,[22] which implies that the key determining date for first cytology test is 8 years after first intercourse. Reports continue to show that the age at first intercourse is falling in the UK, with a substantial number of girls under 16 years of age being sexually active.[23] Therefore, now that screening begins at 25 years of age in England, a proportion of women will have come into contact with HPV 10 years or so before their first cytology test.[23,24]

Screening interval: impact of primary and secondary screening tools

The negative predictive value of a negative HPV test is very high.[22] Therefore, normal cervical cytology accompanied by a negative HPV test should enable an increased screening interval – perhaps 5–8 years, given the natural history of HPV-associated CIN.[21] For women aged under 35 years, the prevalence of HPV may be too high to use HPV testing as a primary screening tool (even more so among the under-30s),[25] but the technique would probably be more efficient and effective than cytology screening alone for women over the age of 35 years.[26]

A secondary test used in response to a positive primary test is referred to as a reflex test. Thus a cervical screening programme might consider cytology plus reflex HPV testing at age 25–35 years, and HPV testing plus reflex cytology for women over 35 years of age.

A sudden increase in the number of cytology tests, as was experienced with the "Jade Goody effect", results in detection of a large number of minor abnormalities (borderline nuclear change or atypical cells of undetermined significance) and mild dyskaryosis. Experience from the LBC pilots suggests reflex testing for HPV (QIAGEN© Hybrid Capture 2, QIAGEN Ltd, Crawley, UK) can allow a return to standard recall for up to 50% of those with borderline changes and up to 15% of those with mild dyskaryosis, and earlier onward referral to colposcopy for HPV-positive women.[27]

In the UK, women remain on increased surveillance for up to 10 years following treatment for high-grade dyskaryosis.[28] The introduction of HPV testing alongside cytology screening 6 months after treatment might allow over 75% of treated patients to return to standard recall.[29] The NHSCSP is actively considering the use of HPV testing as triage for minor abnormalities and as a test of cure as part of the sentinel site programme.[30]

In the future it may make sense to introduce HPV testing as the primary screen for vaccinated women, with either type-specific or cytology-based secondary screening. It may also be possible to increase the screening interval for HPV-negative vaccinated 25-year-old women.[31]

HPV vaccination programme

In England, a routine immunisation programme targeting 12–13-year-old females (school year 8) and a catch-up programme for females aged 17–18 years was commenced during the academic year 2008/2009. A phased catch-up programme for females in school years 9 to 12 during the 2008/2009 academic year will be completed during the 2009/2010 academic year. In January 2010, the Department of Health published a report outlining the annual HPV vaccine uptake in England for 2008/2009.[32] Results showed that for the routine programme in England targeting 12–13-year-old females, 80.1% completed all three doses of the vaccine. For the catch-up programme in England aimed at 17–18-year-old females, 62.2% received their first dose of the vaccine, however only 31.8% completed all three doses.[32] This number is expected to become higher in subsequent years.

Girls who receive the vaccine before they start sexual intercourse can expect an up to 70% reduction in their future risk of needing colposcopy and treatment related to CIN.[33–36] The degree of protection for those who are already sexually active at the time of vaccination is not certain, but will be less than among the sexually inactive.[37]

Looking forward

Anxiety: positive or counterproductive?

Anecdotal reports from colposcopy clinics suggest that one of the significant effects of the media attention surrounding Jade Goody's illness was a large increase in anxiety among young women with symptoms such as postcoital bleeding and those who were diagnosed with an abnormal cytology test. In a way, this anxiety had a positive effect, by increasing coverage rates and reducing non-compliance with follow-up. However, it is undesirable to have high levels of anxiety among people who are well or have only minor disease. Studies of the anxiety associated with cytology screening and, in particular, referrals for colposcopy show that the provision of adequate information can reduce high anxiety levels.[38,39]

Although it might appear tempting to increase coverage and uptake for screening by highlighting rare, unhappy

outcomes such as Jade Goody's early death, such an approach is generally counterproductive. The introduction of HPV vaccination should mean that the next generation of women is better informed about HPV and CIN and about the real risks of cancer and the true significance of an abnormal cytology result.

A return to stigma?

An interesting question for the longer term is the effect that vaccination will have on attitudes to CIN. For a time in the 1970s and 1980s, a diagnosis of CIN had a stigmatising effect because it was associated with factors such as multiple sexual partners and young age at first intercourse. To some extent this effect has been ameliorated by the demonstration that HPV infection has a very high cumulative incidence.[6] As such infections become rarer, they may be a danger that some of the old stigma attached to an abnormal cytology test might return. This would not be desirable.

Conclusions

The publicity surrounding the illness and death of Jade Goody has increased the uptake of cytology-based screening and led to calls for a review of the current guidelines on screening intervals and the age at first screen. Those charged with making these difficult decisions are examining the efficacy that may be obtained by using the negative predictive value of a negative HPV test within the current screening programme. In the future it may be possible to modify the programme further by altering the test used for primary screening, most notably among the vaccinated population.

The great success of the current NHSCSP has been based on high coverage and a simple and pragmatic approach to screening guidelines: currently cytology with increased use of HPV testing as triage. Once the 12–13-year-old vaccinated cohort reaches 25 years of age, the prevalence of high-risk HPV types will be significantly lower for this group. A high coverage and simple approach is likely to be maintained, with primary HPV screening becoming the sensible strategy. Care will need to be taken in the crossover period when a partly vaccinated, partially protected, cohort of 14–18-year-olds currently completing vaccination first enter the screening age.

Statements on funding and competing interests

Funding None identified.
Competing interests None identified.

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