JOURNAL CLUB

Multiple high-risk HPV infections are common in cervical neoplasia and young women in a cervical screening population. Cuschieri KS, Cubie HA, Whitley MW, et al. *J Clin Pathol* 2004; **57:** 68–72

There are more than 80 types of human papillomavirus (HPV) and approximately 30 strains are associated with genital infection. Several of the strains can be associated with cervical neoplasia. Evidence is accumulating to show that detection of persistent HPV infection could help detect those at most risk of cervical neoplasia disease progression.

This study looked at the diversity of HPV infection and its association with cervical neoplasia. It used 3444 randomly selected samples, which were residual from liquid-based cytology samples. Its aim was to investigate the overall prevalence of HPV, the type specific prevalence and the number with multiple infections. This was then compared with the cytological assessment for neoplasia.

Approximately 10% of the samples showed some degree of neoplastic abnormality. HPV was detected in 20% of samples, and 77% of these showed a high-risk type of HPV. Surprisingly, 42% of the positive samples from under-25-year-olds were HPV-positive.

The results also showed that with increasing severity of dyskaryosis on cervical sample there was an increasing prevalence of HPV virus. Infection with multiple HPV types were found in 3.4% of negative sample and in 33.3%, 41.8% and 40.4% of samples with borderline, mild or high-grade dyskaryosis, respectively. HPV infection with a single type showed a very similar picture.

A second phase of this longitudinal study is in progress and this may influence the addition of HPV testing to the cervical screening programme. The result of current pilot studies looking for HPV in under-25-year-olds may also help with this decision.

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Economic analysis of contraceptives for women. Chiou C-F, Trussell J, Reyes E, et al. *Contraception* 2003; **68:** 3–10

This paper analyses the cost-effectiveness of a contraceptive method when used in the USA in relation to the prevention of pregnancy and cost saving of a method. It does not include all methods, for example, implants, and excludes vasectomy costs.

The probability of a woman discontinuing a method or complications requiring medical treatment was estimated from USA national data and surveys. The model used made some assumptions about how a woman uses contraception. The study only included parous women, and it assumed that if a patient discontinued a method she would start another. It was also assumed that after giving birth a woman would start a method within 2 months and that, when calculating the cost for barrier methods, it was assumed that a woman had 83 acts of sexual intercourse a year.

The conclusions drawn from the calculations were that intrauterine devices or the intrauterine system are the most cost-effective methods to use. The way in which the calculations were carried out was well illustrated and could easily be adapted for the UK. It would be interesting to see if by including implant and vasectomy for the UK figures a subsequent study would come out with a different conclusion.

It has to remembered that this is purely a hypothetical calculation as we all know women who fall outside the standard criteria as described above. Until the variables set by all contraceptive users are fully addressed it is likely that any calculations can only give a rough estimate of the cost-effectiveness of a particular method.

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Mortality in relation to oral contraceptive use and cigarette smoking. Vessey M, Painter R, Yeates D. *Lancet* 2003; **362:** 185–191

This is another report derived from the data acquired from the Oxford Family Planning Association (fpa) Study. Readers will remember that the study recruited around 17 000 married women between the ages of 25 and 39 years, from 17 family planning clinics between 1968 and 1974, who used oral contraceptives (OCs), a diaphragm or an intrauterine device. By the end of December 2000, 889 women had died.

The study found no overall increased risk of death from all causes among women who used OCs (regardless of duration of pill use) compared with women in the study who had never used OCs. Although the data suggested that the overall risk of death might be lower among OC users than among non-users, this did not quite reach statistical significance.

In comparison with non-smokers, light smokers showed an increase in death from all causes of around 25%, and heavy smokers (women who smoked more than 15 cigarettes a day) showed more than a doubling of death risk from all causes. Even in women aged 35–44 years, the harmful effects of smoking were already apparent.

The study provided no surprises in reporting that in users of OCs compared with non-users, there was a decrease in mortality from uterine and ovarian cancers and an increase in cervical cancer mortality. The numbers are all small with wide confidence intervals. Although women who took OCs and did not smoke, or only smoked lightly, showed no increased mortality from ischaemic heart disease, women who took OCs and smoked heavily showed a slightly increased death rate. The study did not show any relationship between length of use of OCs and breast cancer mortality, nor between smoking and breast cancer mortality. These figures need to considered together with the knowledge that this study did not recruit young women starting OCs before their first full-term pregnancy and that only 16% of the total number of women who died had recent or current exposure to OCs. A large number of other causes of death were examined for their relationship to smoking or OC use. This is useful information if you need to discuss specific risks with an individual woman.

The Oxford fpa Study is one of only three large-scale studies of long-term OC safety. It provides valuable data on the long-term effects of contraceptive use as well as morbidity and mortality among women of childbearing age. It does have some limitations. Long-term studies are subject to loss to follow-up and numbers dwindle. The numbers of deaths from any cause in this age group is (thankfully) small. Most of the OCs used in the 1970s and early 1980s contained 50 µg oestrogen. It is unclear whether the findings can be extrapolated to the pills in use currently. Also, some effects of OCs (e.g. on cardiovascular disease or breast cancer) have been shown to apply mainly to current or very recent users. OCs are usually stopped when serious illness occurs, but death may not occur for many years. The analysis of the effects of smoking only considered the amount recorded at recruitment to the study (when 18% were light smokers and 14% were heavy smokers).

The headlines in the news should have been: 'Oral contraceptive use not harmful'. But, as usual, good news is no news. What we did not see either was the bad news: 'Young women are killed by smoking'. This is an important study reporting the harmful effects of smoking on the health of young and middle-aged women. All who work in contraceptive care are in contact with healthy individuals who might otherwise not see a health professional. Our primary task is to help them with their contraceptive needs, but we also have a responsibility to tell them about activities damaging to their future health.

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Emergency contraception. Westhoff C. *N Engl J Med* 2003; **349:** 1830–1835

This is the fourth paper in recent years that has suggested that hormonal emergency contraception (EC) can be used on the fourth or fifth day after unprotected sexual intercourse (UPSI). This paper cites an imaginary woman who reported 4 days after UPSI. The author recommends that progesterone-only emergency contraception (POEC) be prescribed. This is justified by reference to clinical studies[1,2] in which hormonal EC on the fourth and fifth days appeared to be effective. It will be relevant therefore to look at the other three papers. The first paper[1] described POEC given to 131 women before 72 hours after UPSI, compared to POEC given to 169 women between 72 and 120 hours after UPSI. The pregnancy rates were respectively 0.8% and 1.8%. The authors concluded that POEC could be given up to 120 hours after UPSI. The second paper[3] was the World Health Organization (WHO) study previously reviewed in the Journal Club section of this Journal.[4] This was a study of 4136 women requesting EC who were randomly given either mifepristone or levonorgestrel up to 120 hours after UPSI. For the levonorgestrel groups the pregnancy rates on Days 4 and 5 after UPSI were 1.1% and 4.8%, respectively. The mifepristone rates on Days 4 and 5, respectively, were 1.0% and 5.3%. The authors warn that "the small numbers of women given delayed treatments in this trial makes our estimation very imprecise". The third paper[2] compared 675 women who had Yuzpe regime EC within 72 hours with 111 who had Yuzpe regime EC between 72 and 120 hours after UPSI. The users were put into two groups: perfect users and typical users. The pregnancy rates for perfect and typical users in the over 72 hour groups were, respectively, 1.9% and 3.6%. The authors concluded that Yuzpe regime EC could be given up to 120 hours after UPSI especially if an IUD was contraindicated. So perhaps evidence is building in favour of extending the 72-hour limit. Although numbers are limited it is interesting that the highest pregnancy rates in the WHO study did not occur till the fifth day with low rates on the fourth day, suggesting that the best limit may turn out to be 96 hours. Meanwhile, the official Faculty of Family Planning and Reproductive Health Care advice is that the limit should be 72 hours.[5]

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