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[Intervention Review]

Immediate referral to colposcopy versus cytological surveillance for minor cervical cytological abnormalities in the absence of HPV test

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ABSTRACT

Background

A significant number of women are diagnosed with minor cytological abnormalities on cervical screening. Many authorities recommend surveillance as spontaneous regression might occur. However, attendance for cytological follow-up decreases with time and might put some women at risk of developing invasive disease.

Objectives

To assess the optimum management strategy for women with minor cervical cytological abnormalities (atypical squamous cells of undetermined significance - ASCUS or low-grade squamous intra-epithelial lesions - LSIL) at primary screening in the absence of HPV (human papillomavirus) DNA test.

Search methods

We searched the following electronic databases: Cochrane Central Register of Controlled Trials (CENTRAL Issue 4, 2016), MEDLINE (1946 to April week 2 2016) and Embase (1980 to 2016 week 16).

Selection criteria

We included randomised controlled trials (RCTs) comparing immediate colposcopy to cytological surveillance in women with atypical squamous cells of undetermined significance (ASCUS/borderline) or low-grade squamous intra-epithelial lesions (LSIL/mild dyskaryosis).

Data collection and analysis

The primary outcome measure studied was the occurrence of cervical intra-epithelial neoplasia (CIN). The secondary outcome measures studied included default rate, clinically significant anxiety and depression, and other self-reported adverse effects.

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We classified studies according to period of surveillance, at 6, 12, 24 or 36 months, as well as at 18 months, excluding a possible exitexamination. We calculated pooled risk ratios (RR) and 95% confidence intervals (CI) using a random-effects model with inverse variance weighting. Inter-study heterogeneity was assessed with I² statistics.

Main results

We identified five RCTs with 11,466 participants that fulfilled the inclusion criteria. There were 18 cases of invasive cervical cancer, seven in the immediate colposcopy and 11 in the cytological surveillance groups, respectively. Although immediate colposcopy detects CIN2+ and CIN3+ earlier than cytology, the differences were no longer observed at 24 months (CIN2+: 3 studies, 4331 women; 17.9% versus 18.3%, RR 1.14, CI 0.66 to 1.97; CIN3+: 3 studies, 4331 women; 10.3% versus 11.9%, RR 1.02, CI 0.53 to 1.97). The inter-study heterogeneity was considerable (I² greater than 90%). Furthermore, the inclusion of the results of the exit examinations at 24 months, which could inflate the CIN detection rate of cytological surveillance, may have led to study design-derived bias; we therefore considered the evidence to be of low quality.

When we excluded the exit examination, the detection rate of high-grade lesions at the 18-month follow-up was higher after immediate colposcopy (CIN2+: 2 studies, 4028 women; 14.3% versus 10.1%, RR 1.50, CI 1.12 to 2.01; CIN3+: 2 studies, 4028 women, 7.8% versus 6.9%, RR 1.24, CI 0.77 to 1.98) both had substantial inter-study heterogeneity (I² greater than 60%) and we considered the evidence to be of moderate quality).

The meta-analysis revealed that immediate referral to colposcopy significantly increased the detection of clinically insignificant cervical abnormalities, as opposed to repeat cytology after 24 months of surveillance (occurrence of koilocytosis: 2 studies, 656 women; 32% versus 21%, RR 1.49, 95% CI 1.17 to 1.90; moderate-quality evidence) incidence of any CIN: 2 studies, 656 women; 64% versus 32%, RR 2.02, 95% CI 1.33 to 3.08, low-quality evidence; incidence of CIN1: 2 studies, 656 women; 21% versus 8%, RR 2.58, 95% CI 1.69 to 3.94, moderate-quality evidence).

Due to differences in trial designs and settings, there was large variation in default rates between the included studies. The risk for default was higher for the repeat cytology group, with a four-fold increase at 6 months, a six-fold at 12 and a 19-fold at 24 months (6 months: 3 studies, 5117 women; 6.3% versus 13.3%, RR 3.85, 95% CI 1.27 to 11.63, moderate-quality evidence; 12 months: 3 studies, 5115 women; 6.3% versus 14.8%, RR 6.39, 95% CI 1.49 to 29.29, moderate-quality evidence; 24 months: 3 studies, 4331 women; 0.9% versus 16.1%, RR 19.1, 95% CI 9.02 to 40.43, moderate-quality evidence).

Authors' conclusions

Based on low- or moderate-quality evidence using the GRADE approach and generally low risk of bias, the detection rate of CIN2+ or CIN3+ after two years does not appear to differ between immediate colposcopy and cytological surveillance in the absence of HPV testing, although women may default from follow-up. Immediate colposcopy probably leads to earlier detection of high-grade lesions, but also detects more clinically insignificant low-grade lesions. Colposcopy may therefore be the first choice when good compliance is not assured. These results emphasize the need for an accurate reflex HPV triage test to distinguish women who need diagnostic follow-up from those who can return safely to routine recall.

PLAIN LANGUAGE SUMMARY

Management of minor cytological abnormalities identified on cervical screening

The issue

Cervical screening programmes reduce the risk of cervical cancer, through the use of cervical cytology (smear tests), which aim to detect and treat any precancerous changes which might put some women at risk of developing invasive disease (invasive cervical cancer) in the future. Usually only severe precancerous changes require treatment, however, there is some discrepancy in how to manage women with minor cytological changes (atypical squamous cells of undetermined significance (ASCUS/borderline) or low-grade squamous intraepithelial lesions (LSIL/mild dyskaryosis) if HPV (human papillomavirus) testing is not routinely available.

The aim of the review

We aimed to assess whether immediate colposcopy or 'watchful waiting', with repeat cervical cytology, was better for women with minor cervical cytological abnormalities.

What are the main findings?

We included 5 randomised controlled trials including 11,466 participants with minor abnormalities on cervical cytology, treated either with immediate colposcopy or repetitive cytology. The included studies assessed differences in occurrence of cervical precancerous lesions between the two treatments.

The results suggested that women attending immediate colposcopy after a single low-grade abnormal cervical cytology test were more likely to have clinically insignificant findings detected than women who were managed with 'watchful waiting'.

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There were 18 cases of invasive cervical cancer, seven in the immediate colposcopy and 11 in the cytological surveillance groups. The detection rate of clinically insignificant low-grade lesions was higher in the immediate colposcopy group, as was the detection rate of clinically more significant high-grade precancerous lesions (CIN2 or CIN2 or worse) at 18 months, but not by 24 months.

The risk of non-compliance was significantly greater for the repeat cytology arm and increased with the length of the follow-up.

What is the quality of the evidence?

We graded the evidence as low to moderate quality.

What are the conclusions?

HPV DNA testing has been shown to be an effective triage tool for women with minor cervical cytology abnormalities. However, this test is not currently routinely available globally. Therefore, if HPV DNA testing is not available, immediate colposcopy is likely to detect more precancerous lesions earlier than cytological surveillance, but after two years there does not seem to be a difference between the two approaches. Women could be referred for immediate colposcopy after a single low-grade abnormal or borderline cervical cytology test, if compliance with cytological surveillance is expected to be poor. When follow-up compliance is expected to be good, repeat cervical cytology may be offered, as this may reduce the risk of over-diagnosis and over-treatment.

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