Repeat cervical cytology at the time of colposcopy: is there an added benefit?

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of the Pap smear (PS), repeated at the time of colposcopic evaluation, for the correct diagnosis of cervical neoplasia.

Type of intervention
Diagnosis.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised women referred because of an initial abnormal cervical smear (PS), those on low-grade squamous intraepithelial lesion (LSIL) surveillance, and those followed after surgical therapy for high-grade lesions. Diagnostic or therapeutic loop electrocautery excision procedure, large loop excision of the transformation zone and cold knife cone biopsy specimens were not included.

Setting
The setting was an institution. The economic study was carried out at two institutions in Maryland, USA. These were the Departments of Pathology and of Obstetrics and Gynecology, University of Maryland Medical System, and the Department of Pathology, National Naval Medical Centre (Bethesda).

Dates to which data relate
The effectiveness evidence and resource use data were collected from January to August 1997. The price year was not reported.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was undertaken prospectively on the same patient sample as that used in the effectiveness analysis.

Study sample
Power calculations were not performed to determine the sample size. In the study period, 852 women underwent colposcopy with biopsy and/or endocervical curettage along with concurrent PS. No baseline characteristics of the women were provided.
Study design
The study design was a diagnostic test evaluation, which used a cohort of patients who underwent both PS and cervical biopsy. It was carried out in two institutions. The patients were not stated to have been followed after the diagnostic tests. However, a follow-up PS was reported to have been used to help constitute a true positive. No further details were given. All PSs obtained at the time of colposcopy and the cervical biopsy specimens were reviewed independently by two pathologists, who were blinded to the original diagnosis. All cases without complete consensus were reviewed simultaneously by three study pathologists.

Analysis of effectiveness
All women included in the study were accounted for in the analysis. Sensitivity was the primary outcome measure. The results of cervical biopsies and repeated PSs were compared in terms of three possible diagnostic categories. These were negative, LSIL (mild dysplasia or cervical intraepithelial neoplasia), and HSIL (moderate and severe dysplasia). Sensitivity was calculated by first determining what constitutes a true positive SIL. This was defined as either SIL on repeat PS and/or cervical biopsy, or when repeat PS and biopsy were both negative, but SIL was found on the follow-up PS or biopsy. It was also stated that “a discrepancy between the PS and biopsy was defined as one degree of magnitude difference in the diagnosis.”. Statistical analyses were conducted to determine the differences in sensitivity between the diagnostic techniques.

Effectiveness results
Repeat PS identified 172 LSIL cases. Of these, 103 (60%) were diagnosed as LSIL on biopsy, 14 (8%) as HSIL cases, and 55 (32%) as negative on biopsy.

Of the 114 HSIL cases detected by repeat PS, 91 (80%) were diagnosed on biopsy as HSIL, 10 (8.8%) as LSIL cases, and 13 (11%) as negative on biopsy.

Of the 134 LSIL cases identified on biopsy, 103 (77%) were diagnosed as LSIL cases in the repeat PS, 21 (16%) were negative and 10 (7%) were diagnosed as HSIL cases in the repeat PS.

Of the 119 HSIL cases identified on biopsy, 91 (76%) were diagnosed as HSIL cases in the repeat PS, 14 (12%) were negative and 14 (12%) were diagnosed as HSIL cases in the repeat PS.

The total number of true LSIL, including 15 detected at follow-up, was 194.

The total number of true HSIL, including 2 detected at follow-up, was 144.

In the comparison of repeat PS and cervical biopsy, the sensitivity values were:

for repeat PS, 0.89 for the detection of LSIL, (p<0.0001), 0.74 for HSIL, and 0.83 for both LSIL and HSIL, (p<0.0001); and

for cervical biopsy, 0.69 (biopsy) for the detection of LSIL, (p<0.0001), 0.77 for HSIL, and 0.72 for both LSIL and HSIL, (p<0.0001).

In the comparison of the alternatives, cervical biopsy and repeat PS with cervical biopsy, the sensitivity values were:

for cervical biopsy, 0.69 for the detection of LSIL, (p<0.0001), 0.78 for HSIL, (p<0.0001), and 0.72 for both LSIL and HSIL, (p<0.0001); and

for repeat PS with cervical biopsy, 0.92 for the detection of LSIL, (p<0.0001), 0.98 for HSIL, (p<0.0001), 0.96 for both LSIL and HSIL, (p<0.0001).

Clinical conclusions
Repeat PS and biopsy did not always concur in detecting cases. PS was more sensitive than biopsy when using the
definition of true positive, i.e. positive SIL with any of the second tests (repeat PS or biopsy) or on follow-up biopsy or PS.

Measure of benefits used in the economic analysis
No summary benefit measure was used in the economic analysis. A cost-consequences analysis was therefore carried out.

Direct costs
Discounting was irrelevant due to the short time horizon of the study. The unit costs and the resource quantities were reported separately. Only the direct costs of PS, as performed at the study institutions, were considered. It appears that the costs have been estimated using actual data. The resources used in the analysis were collected from January to August 1997. The price year was not reported.

Statistical analysis of costs
No statistical analysis of the costs was reported.

Indirect Costs
The indirect costs were not included.

Currency
US dollars ($).

Sensitivity analysis
No sensitivity analysis was carried out.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The cost of a single PS was approximately $25. The total costs of the repeated PSs performed during the study was $21,300, assuming all patients (852) in the study underwent a second PS. The cost of biopsy was not given.

Synthesis of costs and benefits
Not applicable.

Authors' conclusions
The PS should be repeated at the time of colposcopy, in combination with a biopsy, to increase the diagnostic yield in the treatment of potential cervical neoplasia in women with abnormal PSs. The combination of a repeat PS and cervical biopsy would result in a sensitivity value of 98%, therefore reducing the false negative rate at a reasonable cost to the hospital.

CRD COMMENTARY - Selection of comparators
The rationale for the selection of the comparator was unclear. Colposcopic biopsy was not considered the "gold standard". You should consider whether it represents a widely used technology in your own setting.
Validity of estimate of measure of effectiveness
The effectiveness measure was derived using a single study without an explicit comparison group, because the same group of patients was used for both the procedures. This would have eliminated selection bias, thus enhancing the internal validity of the study. Double-blinding was also used in the outcome assessment phase.

It would have been useful to have assessed not only the sensitivity, but also the specificity of the tests. However, there were two main flaws with the study. Firstly, without a "gold standard", to measure sensitivity by assuming that every second positive result is a true positive will bias sensitivity in favour of the test. Thus, more positives will be obtained, regardless of their actual status.

Secondly, and more fundamentally, there appears to have been a logical flaw in the study. The standard practice does not have any second testing of PS negatives, only biopsy of PS positives. This implies that there is little concern that the negatives could be false negatives. Therefore, any second testing (biopsy or repeat PS) should be carried out to exclude false positives from the first PS. However, all second test positives were assumed to be true positives, thus implying that there is no faith in second test negatives being true negatives. This means that the concern is that the second test (biopsy or repeat PS) will miss positives. Therefore, there is a contradiction between the implicit assumptions at the first and second tests. If the first is true, then second test negatives should sometimes be counted as true negatives, thus reducing sensitivity. If the second is true, then the first PS negatives should have a second test.

Validity of estimate of measure of benefit
No summary benefit measure was used.

Validity of estimate of costs
Only the direct costs (both unit and total costs) of PS were reported in the study, and the source of such costs was unclear. Statistical analyses on the quantities were not carried out. Also, the price year was not reported, although the resources were gathered in 1997. A total of $21,300 could be saved by not performing a repeat PS. However, the potential cost of an untreated HSIL would surely outweigh the savings derived by eliminating the repeat PS in a high-risk population.

Other issues
The authors made numerous comparisons of their results with those from other studies. However, the generalisability of the study to other settings was not discussed. The generalisability could be quite limited because sensitivity analyses were not conducted and the cost results were incomplete.

Implications of the study
Some implications of the study, as identified by the authors, should be highlighted. First, repeat PS and biopsy should continue to be used as a complementary approach after a first abnormal PS, to diagnose cervical neoplasia. Second, repeating the PS before biopsy did not confuse the clinical picture, for example disrupting the diagnostic area, resulting in a false negative biopsy. Third, although biopsy was considered the 'gold' standard, the study showed that "not only are most cytohistologic discrepancies the result of colposcopic sampling errors, but also the biopsy diagnosis itself might be wrong", due to difficulties in biopsy interpretation. However, in contrast, the methodological flaws outlined show that there is insufficient evidence to support these recommendations.

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