Accuracy of outpatient endometrial biopsy in the diagnosis of endometrial cancer: a systematic quantitative review


Authors' objectives
To determine the accuracy of out-patient endometrial biopsy in diagnosing endometrial cancer in women with abnormal uterine bleeding.

Searching
MEDLINE and EMBASE were searched from 1980 to 1999. MeSH terms with 'diagnosis' were combined with the textwords 'endometrial biopsy' and 'diagnosis'. The reference lists of all known reviews and primary studies were examined, and the manufacturers of out-patient endometrial biopsy devices were contacted. Articles in any language were considered.

Study selection
Study designs of evaluations included in the review
Prospective observational studies or comparative cross-sectional studies were eligible for inclusion. The included studies had to meet specified minimal validity criteria: an independent blind or non-blind comparison with a reference standard, among an appropriate population of consecutive patients or among non-consecutive patients and confined to a narrow population of study patients. Lower quality studies with the following characteristics were excluded: trials in which the reference standard was not applied to all patients; and studies in which the reference standard was not applied independently or expert opinion with no explicit criteria, based on physiology, bench research or first principles.

Specific interventions included in the review
Any out-patient endometrial biopsy device was eligible for inclusion. The specific devices used in the included studies were Accurette, Gynoscann, Novak curette, Pipelle, Vabra aspirator and Z-sampler.

Reference standard test against which the new test was compared
To be included in the review, the studies had to compare out-patient endometrial biopsy with endometrial histology obtained by in-patient sampling. The included studies used hysterectomy, directed biopsy, and dilatation and curettage as the reference standard.

Participants included in the review
Women with abnormal pre- or postmenopausal uterine bleeding were eligible for inclusion. Most of the participants (79%) were postmenopausal women.

Outcomes assessed in the review
Studies that reported the accuracy with which endometrial cancer was diagnosed were eligible for inclusion. The secondary outcomes were device failures and rates of inadequate specimens for histological assessment.

How were decisions on the relevance of primary studies made?
Two reviewers independently scanned the titles and abstracts. The final decisions on inclusion or exclusion were determined using a checklist of eligibility criteria that had been tested and piloted. Any disagreements were initially resolved by consensus and, if required, using arbitration by a third reviewer. Agreement regarding eligibility was 90% (weighted kappa 0.7).

Assessment of study quality
Validity was assessed using the following criteria, based on existing checklists: recruitment (adequate if prospective recruitment); method of sampling (adequate if consecutive recruitment of eligible women); population details (inadequate if menopausal status was not reported); description of use of biopsy device (ideal if sufficient detail to
allow replication); confirmation of diagnosis by reference standard (adequate if hysterectomy, directed biopsy and dilatation and curettage under anaesthesia, in that order); blinding (ideal if clearly reported that the pathologists were unaware of outpatient biopsy results); and decision to perform reference test (inadequate if decision taken in response to out-patient biopsy result). Included studies were rated from level I (highest quality) to level IV. Two reviewers independently and in duplicate assessed validity. Any disagreements were resolved by consensus and the agreement statistics between reviewers ranged from 73 to 100%.

**Data extraction**
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. The tables presented in the review included the following information: the author and year of publication, study design, method of patient selection, menopausal status, adequacy of description of intervention, reference standard, and blinding of results. The data were extracted from each study as 2x2 tables to allow calculation of the sensitivity, specificity and likelihood ratio. Unsuccessful sampling was classified as either failed procedures or as histologically inadequate specimens.

**Methods of synthesis**

- How were the studies combined?
  Summary likelihood ratios were estimated by weighting the log likelihood from each study in inverse proportion to its variance. Publication bias was assessed using a funnel plot, and by testing the correlation between the estimated diagnostic odds ratio and the variance using the adjusted rank correlation method (see Other Publications of Related Interest no.1). The post-test probabilities were calculated for positive and negative out-patient tests.

- How were differences between studies investigated?
  Statistical heterogeneity was assessed using the chi-squared test. Sources of heterogeneity were explored by performing subgroup analyses after stratifying the studies by specific study characteristics (population, intervention, outcome and study quality). Inadequate specimens were used in a sensitivity analysis by including them with the negative results and re-analysing the data.

**Results of the review**
Eleven diagnostic accuracy studies (1,013 women) were included in the review.

Study recruitment was prospective in 9 studies (82%), details of the patient were complete in 8 studies (73%), and patient selection was consecutive in 4 studies (36%). Two studies were rated I for quality, 2 studies were rated III and 7 studies were rated IV. A meta-analysis was only possible for the Pipelle device; no other device was evaluated in more than 2 trials.

The overall failure rate for out-patient biopsy was 7% (95% CI: 5, 8). The failure rate for the Pipelle device (7 studies, 546 women) was 8% (95% CI: 6, 11).

The rate of histologically inadequate specimens (no specimen or insufficient) was 15% (95% CI: 12, 17) overall, and 13% (95% CI: 10, 16) for the Pipelle device. One case of cancer was found in all of the inadequate specimens.

The pooled likelihood ratio for endometrial cancer was 66.48 (95% CI: 30.04, 147.13) for a positive out-patient test and 0.14 (95% CI: 0.08, 0.27) for a negative out-patient test. The post-test probability of endometrial cancer was 81.7% (95% CI: 59.7, 92.9) for a positive test and 0.9% (95% CI: 0.4, 2.4) for a negative test. There was no evidence of statistical heterogeneity (p=0.996). Subgroup analyses stratified by study quality did not affect the pooled likelihood ratio estimates. There was no evidence of statistically-significant publication bias (rank correlation, r=0.4, p=0.17).

**Authors' conclusions**
Out-patient endometrial biopsy has a high overall diagnostic accuracy in diagnosing endometrial cancer when an adequate specimen is obtained. A positive test result is more accurate for ruling in disease than a negative test is for
ruling it out. Therefore, in cases of abnormal uterine bleeding where symptoms persist despite negative biopsy, further evaluation is warranted.

CRD commentary
This well-conducted review was clearly written and presented. The aims of the review were stated and the inclusion criteria were defined in terms of the diagnostic test, reference standard, participants, study design and outcome. Several sources of relevant trials were searched, no language restrictions were applied, the methods used to select the studies were described, and publication bias was assessed. Validity was assessed using defined criteria and only studies meeting the minimal quality standard were included in the review. The methods used to assess validity were described. Relevant data were extracted and tabulated. Statistical heterogeneity was assessed and the meta-analysis was appropriately performed. The evidence presented supports the authors' conclusions.

Implications of the review for practice and research
Practice: The authors state that a positive out-patient biopsy test is highly accurate, but a negative test is of limited value. They further state that malignant pathology can be missed by out-patient biopsy and an additional endometrial assessment should be undertaken where the tests are negative, especially if symptoms persist or intra-uterine structural abnormalities are suspected.

Research: The authors did not report any implications for further research.

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Other publications of related interest

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.