Intraperitoneal dissemination of endometrial cancer cells after hysteroscopy: a systematic review and meta-analysis

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CRD summary
This review aimed to estimate whether hysteroscopy increased the risk of intraperitoneal cancer cell dissemination and disease-upstaging in patients with endometrial cancer and concluded that it hints a risk for cancer cell seeding within the peritoneal cavity and disease upstaging. The conclusion appeared to reliably reflect the results presented, but there was uncertainty regarding the study validity and review process.

Authors' objectives
To estimate whether hysteroscopy increases the risk of intraperitoneal cancer cell dissemination in patients with endometrial cancer and the risk of disease upstaging in patients with clinically early-stage disease.

Searching
The authors searched Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science and PubMed for articles published until July 2009. References of eligible studies were manually searched. No language restrictions were applied. Search terms were reported. Additional searches were conducted in PubMed by cross-searching for articles written by the lead authors of included studies.

Study selection
Eligible studies could be retrospective, prospective or use a randomised controlled design and needed to use hysteroscopy (along with or after other diagnostic procedures) before surgery for endometrial carcinoma. Studies included other diagnostic procedures or no procedure before surgery as a comparison. Patients had to have histologically confirmed endometrial carcinoma, regardless of stage and type, and to have undergone peritoneal washings before hysterectomy for endometrial cancer to confirm the presence or absence of endometrial cancer cells within the peritoneal cavity.

Studies were excluded if they did not include a control group or were comparisons between fluid and gas hysteroscopy. Studies had to report as primary outcomes the incidence of malignant cells in peritoneal washings before hysterectomy or incidence of tumour upstaging due solely to the presence of positive peritoneal cytologic features in patients with apparent clinical early-stage disease limited to the uterus. Secondary outcomes of interest included overall survival, disease-free survival and disease recurrence.

Publication dates ranged from 2000 to 2007. Study countries included Israel, USA, Slovenia, Spain, Italy, Austria and Czech Republic. Patient age ranged from 60 to 68 years. Most studies had patients at all clinical stages. Where reported, the distension medium used was isotonic sodium chloride. Inflation pressure ranged from 25 to 150mmHg. Follow-up for survival ranged from five to 60 months. The interval between hysteroscopy and peritoneal washing ranged between 12 and 32.7 days.

The authors did not state how many reviewers screened studies for inclusion.

Assessment of study quality
No validity assessment was reported.

Data extraction
Data required to calculate odds ratios (ORs), with 95% confidence intervals (CIs), were extracted to estimate risk of positive peritoneal cytologic features.

The authors did not state how many reviewers extracted data.
**Methods of synthesis**

There was some discrepancy in reporting of the statistical methods used, but it appeared that odds ratios, with 95% CIs, for the odds of peritoneal cytologic features and of disease upstaging due solely to the presence of malignant cells in the peritoneal cavity were pooled using a DerSimonian and Laird random-effects model. The $X^2$ test (and $I^2$ statistic) was used to test for heterogeneity (p<0.10 was considered significant).

Sensitivity analyses were conducted for the primary outcome for the effects of including only studies that stated isotonic sodium chloride was used as the distension medium and those in which inflation pressure of the distension medium reached or exceeded 100mmHg.

**Results of the review**

Nine trials (n=1,715 patients, range 50 to 392 patients) were included in the analysis: one RCT, one prospective study and seven retrospective controlled studies. Only three studies reported controlling for confounding factors. Most studies had no loss to follow-up; those that did lost between 12 and 219 patients.

**Meta-analyses:** Compared to control groups, the odds of malignant cytology (positive peritoneal cytologic features) were significantly higher in women who had undergone hysteroscopy before operation (OR 1.78, 95% CI 1.13 to 2.79, $I^2$=0%; nine studies). The odds of disease upstaging due solely to the presence of malignant cells in the peritoneal cavity were also higher (OR 2.61, 95% CI 1.47 to 4.63, $I^2$=0%; seven studies).

**Sensitivity analyses:** Using only trials that reported using isotonic sodium chloride as a distension medium, the odds of malignant cytology were higher (OR 2.89, 95% CI 1.48 to 5.64, $I^2$=0%; six studies). Using only trials in which inflation pressure reached or exceeded 100mmHg, the odds of malignant cytology were higher in the hysteroscopy group, but the result was statistically non significant (OR 3.23, 95% CI 0.94 to 11.09, $I^2$=0%; four studies).

A number of secondary outcomes were reported.

**Authors' conclusions**

Hysteroscopy in patients with endometrial cancer hints a risk for cancer cell seeding within the peritoneal cavity and disease upstaging, compared with no hysteroscopy.

**CRD commentary**

This review addressed a clear research question with appropriate study selection criteria. The search appeared comprehensive and well reported. Study selection details were clear. Sufficient primary study details were reported, which increased review transparency. No validity assessment was reported, so the risk of bias and internal validity of the included studies was unclear; most included studies were retrospective observational studies, which may be more prone to selection bias than other designs. The method of synthesis appeared appropriate and results were generally clearly reported, but it was unclear within the results whether fixed-effect or random-effects models had been used. Subgroup analyses appeared appropriate in addressing related clinical questions in a systematic fashion. Confidence intervals were wide for some outcomes (which included inflation pressure) so the robustness of the findings was unclear. Few details were reported about the conduct of the various stages of the review process (such as how many reviewers were involved at each stage) and so risks of reviewer error and bias throughout were unclear.

The results appeared to reflect the evidence, but should be interpreted with caution given potential for bias in the review, use of mostly retrospective studies and variability among studies in terms of washing period.

**Implications of the review for practice and research**

**Practice:** The authors stated that hysteroscopy should be performed with concern to keep the inflation pressures low.

**Research:** The authors stated that prospective and sufficiently powered trials were needed to clarify whether the risk of cancer cells spreading was correlated with worse prognosis.
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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.