**The performance of CA-125 measurement in the detection of endometriosis: a meta-analysis**


**Authors' objectives**
To assess the diagnostic performance of serum CA-125 measurement in the detection of endometriosis.

**Searching**
MEDLINE (from January 1966 to November 1997) and EMBASE (from January 1988 to November 1997) were searched using the keywords 'CA125' or 'CA-125', 'laparoscopy' and all phrases containing the word 'endometriosis'. Cross-references in selected articles were checked.

**Study selection**

*Study designs of evaluations included in the review*
Diagnostic cohort and case-control studies were eligible for inclusion.

*Specific interventions included in the review*
Articles reporting serum CA-125 measurement were eligible for inclusion. The CA-125 cut-off levels varied between 17 and 85 IU/mL.

*Reference standard test against which the new test was compared*
Studies using laparoscopy as the reference standard were eligible for inclusion.

*Participants included in the review*
Women with subfertility or pelvic pain as an indication for laparoscopy were included. Studies that reported on patients who had a pelvic mass at sonography were excluded.

*Outcomes assessed in the review*
The outcome measures reported by the review were the sensitivity and specificity of serum CA-125 measurement. Studies were excluded if they reported insufficient data to construct a 2x2 contingency table.

**Assessment of study quality**
Validity was not explicitly assessed. However, data on methodological features such as consecutive sampling of patients, whether a prospective study design was used, blinding of the investigators and verification bias, were extracted. Data relating to these design features were tabulated. Two reviewers independently made judgements on validity.

**Data extraction**
Two reviewers independently constructed 2x2 contingency tables. In the event of any disagreement the judgement of a third reviewer was decisive. Data were also extracted on: the period during which the study was performed; inclusion criteria; study design; method of sampling; data collection; blinding; verification bias; and the way in which the final diagnosis was established.

**Methods of synthesis**
How were the studies combined?
The performance of serum CA-125 measurement was evaluated for its discrimination between women without
endometriosis and those with any type of endometriosis, and for its discrimination between mild endometriosis (grade I/II) and severe endometriosis (grade III/IV). Sensitivity and specificity data were calculated from the published data for each study. Sensitivity and specificity points were plotted in a receiver operating characteristic (ROC) space. A summary point estimate of sensitivity and specificity was calculated in case homogeneity could not be rejected.

How were differences between studies investigated?
The homogeneity of the studies was tested using the chi-squared statistic. When heterogeneity was present, a logistic regression analysis was used to evaluate whether study characteristics were associated with differences in the diagnostic performance of serum CA-125 measurement. Generalised likelihood ratio test statistics were used and a P-value of less than 0.05 was considered to indicate statistical significance. If one study characteristic was found to have a statistically-significant impact on the performance of the test, further analysis was performed in subgroups of patients.

Spearman's correlation coefficient was calculated for the association between sensitivity and specificity, to explore possible heterogeneity resulting from a shift in the cut-off levels of serum CA-125 measurement for test positivity. If it was possible to extract data at more than one cut-off value, data on different cut-off levels were used (maximum of five). To control for the increased weight of these studies, the number of patients was divided by the number of cut-off points. If there was a negative correlation between sensitivity and specificity, as defined by a correlation coefficient of -0.5 or less, a summary ROC curve was estimated. To correct for bias resulting from the use of multiple 2x2 tables from one study, a summary ROC curve was estimated using a random-effects regression model.

Results of the review
Twenty-three studies were included: 16 cohort studies and 7 case-control studies. Twenty-two studies reported on the performance of serum CA-125 measurement in the diagnosis of any grade of endometriosis, while 18 studies reported on its performance in the diagnosis of severe endometriosis (grade III/IV).

Diagnosis of any form of endometriosis (n=22).
The sensitivity ranged from 0% (specificity 100%) to 100% (specificity 93%) and the specificity from 38% (sensitivity 50%) to 100% (specificity 0 to 85%). Significant heterogeneity was present for both sensitivity and specificity (P<0.001). The logistic regression analysis showed that the performance of serum CA-125 measurement differed significantly between cohort and case-control studies (ratio of the diagnostic odds ratios = 9.6, P=0.001), showing that the diagnostic odds ratio was higher in case-control studies than in cohort studies. Further analysis was limited to cohort studies, as these are considered superior to case-control studies. Heterogeneity in the sensitivity and specificity remained; Spearman's correlation coefficient was -0.76. A ROC curve was estimated and produced; this showed a low diagnostic performance. When the sensitivity was increased to 50% the specificity decreased to 72%.

Diagnosis of severe endometriosis (n=18).
The sensitivity ranged from 0% (specificity 80%) to 100% (specificity 76%) and the specificity from 44% (sensitivity 60%) to 95% (sensitivity 53%). Significant heterogeneity was present (P<0.001), therefore the summary sensitivity and specificity were not calculated. The logistic regression analysis showed no difference in the performance of serum CA-125 measurement as reported by studies with different designs; Spearman's correlation coefficient was -0.59. A summary ROC curve was estimated; this showed that the capacity of serum CA-125 measurement in the diagnosis of severe endometriosis was better than for any type of endometriosis. For a specificity of 89% the sensitivity was 47%. When the sensitivity was increased to 60% the specificity decreased to 81%.

Authors' conclusions
Despite its limited diagnostic performance, the authors believed that the routine use of serum CA-125 measurement in patients with infertility might be justified. In contrast to laparoscopy, serum CA-125 measurement is an inexpensive test that is not a burden for the patients. It could identify a subgroup of patients who are more likely to benefit from early laparoscopy. Studies reporting on the mutual dependence between serum CA-125 measurement and data from the history and physical examination are needed.
CRD commentary
This was a good review of the area. A reasonably thorough literature search was conducted, although this may have benefited from searching additional databases. No attempts were made to locate unpublished studies, thus the results may be subject to publication bias. No formal validity assessment was conducted, although the authors discussed methodological features of the included studies. Insufficient details of the review methodology, such as how the studies were assessed for inclusion, were presented. The analysis was appropriate and was reported clearly, and the authors attempted to investigate reasons for the observed heterogeneity. The conclusions follow from the results presented.

Implications of the review for practice and research
Practice: The authors stated that, in contrast to laparoscopy, serum CA-125 measurement is an inexpensive test that is not a burden for the patients. It could identify a subgroup of patients who are more likely to benefit from early laparoscopy.

Research: The authors stated that studies reporting on the mutual dependence between serum CA-125 measurement and data from the history and physical examination are needed.

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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.