CRD summary
This review found that women treated with fertility medications may have no greater risk of ovarian cancer than untreated infertile women. While the review took steps to minimise bias, the conclusions are limited because they are based on observational data and do not account for confounding factors such as treatment regimen, parity and specific infertility diagnosis.

Authors' objectives
To examine the relationship between assisted reproductive technology and ovarian cancer.

Searching
The Cochrane Controlled Trials Register, Cancerlit, MEDLINE, PubMed - in process, CINAHL and Current Contents were searched (all 1966 or inception to January 2003); the search terms were reported. The authors also searched bibliographies and 10 years of conference proceedings from the American Society of Reproductive Medicine and the Canadian Fertility and Andrology Society. Experts in the field were contacted, five journal titles were handsearched, and reference lists, editorials and letters to the editor were searched for additional studies. Published and unpublished studies were eligible for inclusion. There were no language restrictions, although one Hungarian study was not assessed.

Study selection
Study designs of evaluations included in the review
The authors originally aimed to include studies with infertile control groups. However, a preliminary literature search found that controls were often analysed as subgroup analyses, if at all. Therefore, the criteria were modified to accept case-control studies with ovarian cancer patients as cases, or cohort studies.

Specific interventions included in the review
Studies were eligible if they included one of the following fertility treatments: clomiphene citrate, gonadotropins, human chorionic gonadotropin, gonadotropin-releasing hormone agonists.

Participants included in the review
Studies of previously untreated infertile women with an explicit and reproducible diagnosis of infertility were eligible for inclusion. Information about age, parity and specific fertility diagnoses was not provided.

Outcomes assessed in the review
The main outcome was primary ovarian cancer of any type.

How were decisions on the relevance of primary studies made?
Titles and abstracts were screened and articles were retrieved if they passed a 'relevance filter'. Two authors independently reviewed all potential articles using preset inclusion criteria. Any discrepancies were resolved by discussion and consensus. The authors were not blinded to publication details.

Assessment of study quality
Two authors used the Newcastle-Ottawa Quality Assessment Scales to assess study quality independently. Factors assessed included selection of cases/cohorts and controls, comparability and outcome/exposure.

Data extraction
Two authors independently extracted data on study methods and characteristics, participants, interventions, sources of
bias, and outcomes using a data extraction sheet. The outcomes were collected as dichotomous data (cancer present: yes/no; exposure to fertility drugs: yes/no).

**Methods of synthesis**

How were the studies combined?
The authors used meta-analysis to combine case-control and cohort study data separately. Infertile controls provided a reference group. For cohort data, the authors calculated a pooled relative risk for disease occurrence. For case-control data, they calculated a pooled odds ratio (OR) for exposure. Both fixed-effect and random-effects models were used, to allow for heterogeneity in observational data. Funnel plots were used to assess potential publication bias.

How were differences between studies investigated?
The Q test was used to measure heterogeneity. Ovarian stimulation agents were analysed together because there was insufficient information to analyse them separately. There was not enough information available to perform subgroup analyses according to drug regimen, specific infertility diagnosis, or confounders.

**Results of the review**

Three cohort studies (33,393 participants) and 7 case-control studies (13,480 participants) were included in the quantitative analyses.

In quality assessments, the case-control studies scored between 5 and 7 out of a possible 9 whilst the cohort studies scored either 6 or 7.

Combined data from case-control studies, based on a fixed-effect model, suggested that women with ovarian cancer may be more likely to have been treated with fertility medications than general population controls (OR 1.52, 95% CI: 1.18, 1.97). When cases were compared to controls without ovarian cancer, the risk of exposure to fertility drugs was not elevated. Data from cohort studies suggested that infertile women who received medication did not have an increased risk of ovarian cancer compared with untreated infertile women (OR 0.67, 95% CI: 0.32, 1.41).

There was no evidence of publication bias.

The Q statistic suggested no statistically significant heterogeneity.

**Authors’ conclusions**

Compared with untreated infertile patients, there is no evidence that fertility treatment increases the risk of ovarian cancer.

**CRD commentary**

This review included a defined research question and inclusion criteria. However, the authors changed their inclusion criteria for eligible study designs after a preliminary literature search. The authors reported the methods used to select and assess the studies in detail. The search was thorough and included attempts to obtain unpublished material, and the review methods appeared robust. Although no publication bias was reported, the authors acknowledged that a number of unpublished studies were not included in the review. The methods used to assess and combine the studies appeared appropriate. The authors suggested a trend towards increased incidence of cancer in untreated women with fertility problems in comparison with treated women. However, the results were not statistically significant so it was questionable whether such findings should be reported as trends. The authors acknowledged that subgroup analyses may have been beneficial, but there were insufficient data to analyse findings according to drug type, treatment regimen, infertility diagnosis, or other confounders. This may limit the usefulness of the conclusions.

The review was based on observational data which cannot prove causality and, as such, the conclusions must be treated with caution or as hypothesis generating.
Implications of the review for practice and research
Practice: The authors did not state any implications for practice. However, they noted that if further, large prospective cohort studies suggest that fertility treatment may lower cancer risk, treatment options may need to be reassessed.

Research: The authors stated that future, large prospective cohort studies with longer duration of follow-up, which compare treated infertile patients with untreated infertile controls, are needed. More information on confounders such as parity, oral contraceptive use, family history, fertility diagnoses, treatment regimens, and the histology and stage of ovarian tumours is required.

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