CRD summary
The authors concluded that co-treatment with GnRH agonists during chemotherapy was associated with increased odds of preserving a woman's ovarian function and increased chance of pregnancy following treatment. This review is likely to be vulnerable to several sources of bias and the results should not be considered as reliable.

Authors' objectives
To systematically review the effectiveness of GnRH agonists to improve ovarian preservation and maintain fertility during chemotherapy.

Searching
MEDLINE was searched for English-language papers published between 1966 and April 2007. American College of Rheumatology, American Society of Clinical Oncology and American Society of Reproductive Medicine conference proceedings were searched between 2000 and 2006. References lists were checked. Search terms were reported.

Study selection
Eligible studies were controlled studies that compared females under 50 years who underwent potentially ovarian-toxic therapy for treatment of malignancy or rheumatology disease. Comparison was between those who received GnRHa and a similar control group that did not receive GnRHa. Relevant ovarian function outcomes were menstrual history, follicle-stimulating hormone levels (FSH) or antral follicle counts. Pregnancy rates were eligible as a measure of fertility.

Included in this review was a mixture of randomised and non-randomised controlled studies conducted in Israel, Spain, Italy, Argentina, UK and USA. Six studies included women who underwent chemotherapy for lymphoma or leukemia. Three studies included women who were treated with cyclophosphamide (CYC) for severe lupus. Doses of GnRHa were similar across most of the studies (around 3.75mg every four weeks) and given either two weeks prior to chemotherapy or with a short-acting GnRHa. Three types of GnRHa were used: two were given intramuscularly (leuprolide, triptorelin); and one was given nasally (buserelin). Most studies reported regular menses after chemotherapy to indicate ovarian function among other measures. Patient follow-up ranged from two to 17 years.

Studies were selected by two reviewers.

Assessment of study quality
It appeared that randomisation method and length of follow-up period were considered.

The authors did not report how many reviewers performed the validity assessment.

Data extraction
Data were extracted from each study into contingency tables to allow the calculation of relative risks (RR) for ovarian preservation and relative risks of pregnancy following chemotherapy (based on number of initial pregnancies during follow-up).

The authors did not report how many reviewers carried out data extraction.

Methods of synthesis
Meta-analysis was used to calculate summary relative risks and 95% confidence intervals (CI) for the outcomes of interest. Heterogeneity was tested using $\chi^2$ tests. Where significant heterogeneity was present, a random-effects model was used in preference to a fixed-effect model. The fixed-effect model used a variance-weighted method and the random-effects model used an empirical Bayes or restricted likelihood estimation method. Where studies reported no
events they were initially excluded from the analysis, and then reintroduced using 0.5 as the denominator.

**Results of the review**

Nine studies were included in this review (n=366): two RCTs (n=46) and seven controlled studies (n=320). Only one RCT described the process of randomisation. In the second study there were important differences in the length of patient follow-up. Sample sizes ranged from 13 to 157 patients. Eight of the studies were included in the meta-analysis.

**Ovarian preservation (two RCTs, six controlled studies):** GnRHa therapy conveyed significant ovarian preservation according to a random-effects model (RR 1.68, 95% CI 1.34 to 2.1). Adding in one controlled study with no events produced a similar result (RR 1.70, 95% CI 1.36 to 2.13), but with significant statistical heterogeneity (as did use of a fixed effects analysis).

**Pregnancy (two RCTs, three controlled studies):** Women who received GnRHa had significantly more pregnancies than those who did not (RR 1.65, 95% CI 1.03 to 2.6). It appeared that this was based on a fixed-effects model. Inclusion of studies with no events did not significantly alter these results (RR 1.64, 95% CI 1.01 to 2.65). Results were similar using a random effects model (RR 1.63, 95% CI 1.004 to 2.6).

**Authors' conclusions**

Co-treatment with a GnRHa during chemotherapy was associated with increased odds of preserving a woman's ovarian function and increased chance of pregnancy following treatment.

**CRD commentary**

This review addressed a clear question with suitable inclusion criteria. The search was limited to only one database and may have missed potentially relevant articles. Although the authors searched American conference abstracts to reduce the possibility of publication bias, when combined with the lack of attention to non-English language resources it seems likely that this review was vulnerable to both publication and language bias. As the review processes were not clearly reported for data extraction and validity assessment, reviewer error and bias could not be ruled out. There was a lack of comprehensive or systematic quality assessment, which made it difficult to assess reliability of the primary studies and the appropriateness of the decision to use meta-analysis and pool retrospective and prospective data. The authors mentioned issues around variation in the populations and interventions that could lead to clinical heterogeneity, but this was not explored. This review is likely to be vulnerable to several sources of bias and the results should not be considered as reliable.

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

**Practice:** The authors stated that women who required ovarian-toxic chemotherapy should be offered GnRHa co-therapy to preserve ovarian function and fertility.

**Research:** The authors made no specific recommendations for research, but mentioned a number of ongoing larger RCTs that intended to further define the role of GnRHa in ovarian preservation.

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