Comparison of tamoxifen and clomiphene citrate for ovulation induction: a meta-analysis

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CRD summary
This review compared the effectiveness of tamoxifen and clomiphene in terms of ovulation induction and pregnancy rates. The authors concluded that there are no substantial differences in ovulation rates between tamoxifen and clomiphene, while limited data show no significant differences in pregnancy rates or outcomes. This was generally a well-conducted review and the authors' conclusions are likely to be reliable.

Authors' objectives
To compare the effectiveness of tamoxifen and clomiphene in terms of ovulation induction and pregnancy rates.

Searching
MEDLINE (1966 to January 2005), PREMEDLINE, CINAHL, International Pharmaceutical Abstracts, the Cochrane Database of Systematic Reviews, ACP Journal Club, DARE, the Cochrane Controlled Trials Register and BIOSIS Previews (all to January 2005) were searched without language restrictions using the reported search terms. Experts in the field provided papers from personal files. The reference lists in identified studies and reviews were also screened.

Study selection
Study designs of evaluations included in the review
Prospective clinical trials (including crossover studies) were eligible for inclusion. Abstracts were included only where additional information could be obtained from the authors. All of the included studies were randomised controlled trials (RCTs).

Specific interventions included in the review
Studies that compared tamoxifen with clomiphene for the induction of ovulation were eligible for inclusion. In the included studies, tamoxifen was administered in doses ranging from 20 to 80 mg per treatment day of cycle and clomiphene in doses ranging from 25 to 200 mg per treatment day of cycle (full details of treatment cycles were reported).

Participants included in the review
Studies of infertile couples with isolated anovulatory infertility were eligible for inclusion if they enrolled oligo-ovulatory or anovulatory women with no known tubal disease and partners with normal semen analysis.

Outcomes assessed in the review
The primary review outcomes were ovulation and pregnancy per cycle. The review also assessed the live-birth rate.

How were decisions on the relevance of primary studies made?
Three reviewers performed the initial screening of titles and abstracts, and two reviewers independently selected studies. Any disagreements were resolved by consensus.

Assessment of study quality
The authors did not report a formal validity assessment process, although data on the methods of treatment allocation, allocation concealment, blinding and reporting of a power calculation were briefly summarised. Two reviewers independently assessed study design and resolved any disagreements by consensus.

Data extraction
Two reviewers independently extracted the data and resolved any disagreements by consensus. For each study, the
number of events of interest per cycle was extracted for all cycles.

**Methods of synthesis**

*How were the studies combined?*

Pooled odds ratios (ORs) with 95% confidence interval (CIs) were calculated using the random-effects model of DerSimonian and Laird. The potential for publication bias was tested using Begg's test (P<0.1 indicated statistical significance).

*How were differences between studies investigated?*

Statistical heterogeneity was assessed using the Cochran Q statistic (P<0.1 indicated statistical significance).

**Results of the review**

Five RCTs were included in the review, but only 4 RCTs were included in the meta-analyses (273 women with a total of 921 cycles). The number of patients or cycles in the fifth RCT was not reported.

In terms of study quality, 3 studies described the method of treatment allocation, one described adequate methods of allocation concealment, and one performed a power calculation.

Ovulation induction (4 studies): there was no statistically significant difference in ovulation between tamoxifen and clomiphene (OR 0.7555, 95% CI: 0.513, 1.111). No statistically significant heterogeneity was detected (P=0.141).

Pregnancy rate (3 studies with 743 cycles including 504 anovulatory cycles): there was no statistically significant difference between tamoxifen and clomiphene, either in pregnancies per cycle (OR 1.056, 95% CI: 0.583, 1.912) or pregnancies per anovulatory cycle (OR 1.162, 95% CI: 0.632, 2.134). No statistically significant heterogeneity was detected (P=0.815).

Live-birth rate (1 study, n=40 women): there was no statistically significant difference between tamoxifen and clomiphene in live births per cycle (OR 0.261, 95% CI: 0.005, 2.711).

**Authors' conclusions**

There were no substantial differences in ovulation rates between tamoxifen and clomiphene. Limited data on pregnancy rates and outcomes showed no significant differences between the treatments.

**CRD commentary**

The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. Several relevant sources were searched and attempts were made to minimise publication and language bias; appropriate methods were used to assess the presence of publication bias, and no evidence of it was found. Methods were used to minimise reviewer errors and bias in the review process. Statistical heterogeneity was assessed and the studies were appropriately pooled in a meta-analysis. The authors calculated the power of the meta-analysis to detect a treatment difference, which adds support to the finding of no difference between treatments. This was a generally well-conducted review and the authors’ conclusions are likely to be reliable.

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

**Practice:** The authors stated that clinicians may choose whichever regimen they are familiar with.

**Research:** The authors stated that there is a need for further studies to compare tamoxifen with clomiphene in clinical settings. They also stated that further studies are required to assess and compare the effects of tamoxifen and clomiphene in women with polycystic ovarian syndrome or obesity.

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