Systematic review of the treatment of ovulatory infertility with clomiphene citrate and intrauterine insemination

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CRD summary
This review determined the effectiveness of clomiphene citrate (CC) combined with intra-uterine insemination (IUI) for ovulatory infertility. The authors concluded that CC with IUI is more effective than timed intercourse in the natural cycle, but less effective than gonadotrophins with IUI. Poor reporting of the review methods and differences between the few identified studies weaken the robustness of the conclusions.

Authors’ objectives
To determine the effectiveness of clomiphene citrate (CC) and intra-uterine insemination (IUI) for the treatment of ovulatory infertility.

Searching
MEDLINE and EMBASE were searched from inception to April 2003; the search terms were reported. In addition, the references of relevant articles were checked. Studies published as full papers and as abstracts were included in the review.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion in the review. The included studies were a mixture of crossover (n=4) and parallel-group designs (n=3).

Specific interventions included in the review
Studies comparing CC plus IUI using freshly prepared partner’s sperm with timed intercourse (TI) in the natural cycle (NC), IUI in the NC, CC with TI, gonadotrophin (Gn)-stimulated cycles with IUI, or Gn with in vitro fertilisation were eligible for inclusion. The studies used different doses of CC and cycle days of administration of CC; some studies also used periovulatory human chorionic gonadotropin as a trigger in IUI cycles. The number of treatment cycles per couple ranged from 1 to 8.

Participants included in the review
Couples with ovulatory infertility were eligible. Ovulatory infertility was defined as infertility arising from unexplained fertility, male factor, minimal to mild endometriosis, cervical or unilateral tubal factor; it did not include anovulatory or oligo-ovulatory infertility. Causes of infertility included in the review were classed as unexplained, surgically corrected endometriosis, male, cervical and minimal-mild endometriosis. Most trials included participants with mixed causes of infertility, whereas 2 studies were in participants with single causes of infertility. Where reported, the mean age of the women ranged from 31.7 to 33 years and duration of infertility ranged from 3.5 to 6.5 years.

Outcomes assessed in the review
The primary outcomes in the review were the cycle pregnancy rate (CPR) and live births. None of the included trials evaluated live birth as an end point.

How were decisions on the relevance of primary studies made?
The author did not report how the articles were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The review reported results for an assessment of method of treatment allocation, blinding and power calculations. The
The author did not state how many reviewers performed the validity assessment.

**Data extraction**
The author did not report how the data were extracted from the primary studies, or how many reviewers performed the data extraction. For each study, the CPR was extracted for each treatment and the odds ratio (OR) and associated 95% confidence interval (CI) were extracted or calculated (the review did not report which applied).

**Methods of synthesis**
- **How were the studies combined?**
  Individual and combined results were presented, grouped according to the interventions compared for CPR. Pooled ORs and their associated 95% CIs were calculated.

- **How were differences between studies investigated?**
The Breslow-Day test was used to assess statistical heterogeneity between studies; a P-value of less than or equal to 0.05 was taken to indicate significant heterogeneity. Differences between the studies were also discussed in the text.

**Results of the review**
Seven RCTs (713 couples) were included.

All 7 trials were considered to be of a reasonable methodological standard. Two studies clearly described the method used for random allocation. None of the included trials were blinded and none performed a power calculation.

- CC and IUI versus NC and TI: 3 RCTs (141 couples undergoing 862 cycles) were identified. A statistically significant improvement in CPR was found with CC plus IUI compared with NC combined with TI (OR 4.6, 95% CI: 1.9, 11.3); no statistical heterogeneity was found.

- CC and IUI versus NC and IUI: 2 RCTs (96 couples undergoing 162 cycles) were identified. No statistically significant difference in CPR was demonstrated between the treatment groups (OR 2.4, 95% CI: 0.8, 7.3); no statistical heterogeneity was found.

- CC and IUI versus CC and TI: 2 RCTs (197 couples undergoing 138 cycles) were identified. A non-statistically significantly higher CPR was found for treatment with CC and IUI compared with CC and TI (OR 0.9, 95% CI: 0.3, 3.0); statistically significant heterogeneity was found (P=0.02).

- CC and IUI versus Gn and IUI: 3 RCTs (279 couples undergoing 348 cycles) were identified. A statistically significantly higher CPR was demonstrated with Gn combined with IUI in comparison with CC and IUI (OR 2.9, 95% CI: 1.3, 6.2); no statistical heterogeneity was found.

- CC and IUI versus Gn and in vitro fertilisation: no RCTs were identified.

**Authors' conclusions**
CC combined with IUI is more effective than TI in the NC in achieving pregnancy in couples with ovulatory infertility. However, treatment with Gn and IUI is more effective than CC combined with IUI.

**CRD commentary**
The review question was clear and was addressed with clear inclusion criteria. Limiting the search to two electronic databases might have excluded other relevant studies and also raised the possibility of publication bias, which was not assessed. It was unclear whether any language limitations had been applied, so the potential for language bias could not be assessed. The reporting of an assessment of the methodological quality of the included studies, as well as the review process itself, was limited. It was therefore difficult to assess the potential for the introduction of bias or errors during the review process, or as a result of methodological flaws in the included studies.
The author acknowledged several potential sources of clinical heterogeneity amongst the studies. Given this clinical heterogeneity, pooled estimates might not have been appropriate. Statistical heterogeneity was assessed, and possible causes were discussed in the text. The poor reporting of the review process, the small data sets for each treatment comparison, and the apparent clinical heterogeneity between studies suggest that caution should be taken when interpreting these results.

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

Practice: The author did not state any implications for practice.

Research: The author suggested that further well-conducted, adequately powered prospective RCTs comparing CC and IUI with NC and IUI or CC and TI are needed before firm conclusions on effectiveness can be drawn.

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Record Status
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.