Treatment of unexplained infertility with aromatase inhibitors or clomiphene citrate: a systematic review and meta-analysis

Polyzos NP, Tzioras S, Mauri D, Tsappi M, Corinovis I, Tsali L, Casazza G

CRD summary
This review compared the effectiveness of aromatase inhibitors with clomiphene citrate for the treatment of unexplained infertility in women, concluding that both yielded similar pregnancy rates. In light of shortcomings in the review process, paucity of outcome data, small sample sizes and lack of good quality data, the authors' conclusions should be interpreted with caution.

Authors' objectives
To compare the effectiveness of aromatase inhibitors and clomiphene citrate for the treatment of unexplained infertility in women.

Searching
PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) were searched without language restrictions to December 2007. Search terms were reported. From eligible trials, searches were cross-referenced in MEDLINE using lead authors names and reference lists were searched to identify any additional articles.

Study selection
Randomised controlled trials (RCTs) comparing aromatase inhibitors with clomiphene citrate in women with unexplained infertility were eligible for inclusion. Trials comparing concomitant treatments, such as gonadotrophins or progestins, were eligible if the treatments did not systematically differ between treatment arms. Single arm studies, non-randomised or pseudo randomised trials were excluded. Also excluded were trials where aromatase inhibitors were compared against treatments other than clomiphene, or where the comparisons differed in the use of additional fertility-related treatments. Eligible women were those with unexplained infertility planning to conceive through either sexual intercourse or intrauterine insemination. To qualify as eligible (with unexplained fertility), trials included women who had documented ovulation by measuring progesterone on day 21 or by ultrasound in the mid-luteal phase, had patent tubes on hysterosalpingogram, and had partners with normal semen analysis.

The primary outcome was the number of viable pregnancies (defined as the presence of an intrauterine sac with the embryonic pole demonstrating cardiac activity). Secondary outcomes included multiple pregnancies, number of miscarriages, number of mature follicles (defined by the authors) and endometrial thickness on the day of human chorionic gonadotrophin administration or day of intrauterine insemination.

In the included trials, clomiphene citrate (100mg) was compared with either letrozole (2.5 or 7.5mg) or anastrozole (1mg). The mean or median age of the included women ranged from 28.2 to 33.4 years; where stated, the mean body mass index (BMI) ranged from 21 to 30, the number of cycles ranged from 13 to 123, and the minimum duration of infertility was one year.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Trial quality was assessed using the following criteria: randomisation, allocation concealment, withdrawals and blinding.

The authors did not state how the validity assessment was performed.

Data extraction
Data for each study were extracted as a 2x2 table to calculate odds ratios (OR) and 95% confidence intervals (CIs), to compare the odds of pregnancy in the aromatase inhibitors group with the clomiphene citrate group.

The authors did not state how many reviewers performed the data extraction.

**Methods of synthesis**

Pooled odds ratios and their 95% confidence intervals were calculated using a Mantel-Haenszel fixed-effect model. Heterogeneity was assessed using the $\chi^2$ test, with significant heterogeneity defined as $p < 0.1$.

**Results of the review**

Five RCTs were included in the review (n=273 women, range 15 to 154). Trials were generally of poor quality; all appropriately described the randomisation method, and two reported being at least single blind and undertook allocation concealment.

There was no significant difference in the relative risk of pregnancy between the aromatase inhibitors group compared with the clomiphene citrate group (OR 0.87, 95% CI 0.46 to 1.65). Insufficient evidence was available for an analysis of secondary outcomes.

**Authors' conclusions**

Treatment with aromatase inhibitors and clomiphene citrate yielded similar clinical pregnancy rates.

**CRD commentary**

The review addressed a clear question with well-defined inclusion criteria. The limited literature search was undertaken without language restrictions, reducing the likelihood of language bias. There was no apparent search for unpublished studies, so some studies may have been missed. The methods used for trial selection and data extraction were not reported, so it was unclear whether methods were used to reduce error and bias.

Appropriate criteria were used to assess the quality of the of the included trials, although, as acknowledged by the authors, these were generally of poor quality. In addition, four of the five included trials had very small sample sizes, with 41 women or less. Suitable methods were used for the meta-analysis; heterogeneity was assessed and found to be absent.

In light of the shortcomings highlighted for the review process, paucity of outcome data, small sample sizes and lack of good quality data, the authors' conclusions should be interpreted with caution.

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

**Practice:** The authors did not state any implications for practice.

**Research:** The authors recommended large properly designed trials adequately powered to assess multiple pregnancy rates and miscarriages for carefully selected groups of women with a short duration of unexplained infertility.

**Funding**

Not stated.

**Bibliographic details**


**PubMedID**

18559123
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.