Aromatase inhibitors for infertility in polycystic ovary syndrome: the beginning or the end of a new era?

Polyzos NP, Tsappi M, Mauri D, Atay V, Cortinovis I, Casazza G

CRD summary
This review concluded that treatment with aromatase inhibitors in comparison with clomiphene citrate was associated with significant improvements in pregnancy and delivery rates in anovulatory women with polycystic ovary syndrome. This conclusion was consistent with the evidence, but may not be reliable due to the paucity of data and potential risk of bias within the studies and review methods.

Authors' objectives
To evaluate pregnancy and delivery rates in women with polycystic ovary syndrome (PCOS) treated for infertility with aromatase inhibitors.

Searching
Cochrane Central Register of Controlled Trials (CENTRAL) and PubMed were searched for studies up to July 2007 without language restriction. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) that compared pregnancy and delivery rates in anovulatory women with PCOS who underwent treatment with aromatase inhibitors in comparison with clomiphene citrate for induction of ovulation were eligible for inclusion in the review. Women were eligible regardless of whether they planned to conceive via sexual intercourse or through use of intrauterine insemination. Studies that used concomitant treatments such as metformin or gonadotropins were eligible if both treatment arms received identical regimens.

Most studies included in the review assessed 2.5mg letrozole (51 to 99 cycles) in comparison with 100mg clomiphene citrate (55 to 95 cycles); one study combined both treatments with metformin and one study compared 1mg anastrozole (12 cycles) with 100mg clomiphene citrate (eight cycles). The mean age of participants ranged from 26.2 to 32.2 years. Mean body mass index (BMI) ranged from less than 25 to 30.2. Mean duration of infertility (where reported) ranged from 2.2 to 3.8 years. Participants in half of the studies had never received previous oral infertility treatments; in the remaining studies patients had shown resistant to previous treatments. In addition to pregnancy and delivery rates the number of ectopic pregnancies and multiple gestations were reported. Half of the included studies were carried out in Turkey; one study was performed in USA and the other in Iran.

The authors did not state how papers were selected for the review.

Assessment of study quality
The authors assessed according to criteria of randomisation, blinding and allocation concealment.

The authors did not state how many reviewers carried out this assessment.

Data extraction
The number of pregnancies/deliveries per patient and per treatment cycle were extracted into 2x2 tables and used to calculate odds ratios (ORs) and 95% confidence intervals (CIs).

The authors did not state how data were extracted for the review.

Methods of synthesis
Studies were grouped by outcome. Pooled odds ratios with 95% CIs were calculated using a fixed effects model.
Statistical heterogeneity was assessed using $\chi^2$.

**Results of the review**

Four RCTs (n=265) were included in the review. Sample sizes ranged from 20 to 106. One trial was double-blind and two were single-blind. All trials except one reported the method of randomisation. One trial reported concealment of allocation.

In comparison with clomiphene citrate, treatment with aromatase inhibitors was associated with significant improvements in pregnancies per patient (OR 2.0, 95% CI 1.1 to 3.8), deliveries per patient (OR 2.4, 95% CI 1.2 to 4.6), deliveries per treatment cycle (OR 2.2, 95% CI 1.2 to 4.1) and pregnancies per treatment cycle (OR 1.8, 95% CI 1.0 to 3.3). No significant heterogeneity was detected for any of the reported outcomes.

Only one miscarriage and one multiple gestation pregnancy were reported; both occurred in clomiphene citrate treatment groups.

**Authors’ conclusions**

Treatment with aromatase inhibitors in comparison with clomiphene citrate was associated with significant improvements in both pregnancy and delivery rates.

**CRD commentary**

This review assessed a well-defined research question. Searches for relevant studies were performed in two electronic databases. Risk of publication was unclear as little attempt was made to identify unpublished studies. Risk of language bias was likely to be low as no restrictions were placed on language. Risk of reviewer error and bias was unclear as the authors did not report the review methods in adequate detail. The reliability of the data was assessed using appropriate criteria. The included studies were relatively small. Studies were comparable in terms of their statistical and clinical characteristics. The methods used to pool data appeared appropriate, although the assessment of statistical heterogeneity was unlikely to be reliable given the small number of included studies.

Overall, the review conclusion was consistent with the evidence, but may not be reliable due to the paucity of data and potential risk of bias within the studies and review methods.

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

**Practice:** The authors stated that clomiphene citrate was the treatment of choice for women with polycystic ovary syndrome who desired pregnancy; aromatase inhibitors may offer an alternative option with improved pregnancy rates and a lower incidence of multiple pregnancies.

**Research:** The authors stated that further large well-designed randomised controlled trials that compared aromatase inhibitors with clomiphene citrate were required. Trials should be adequately powered to detect rates of pregnancy, multiple gestations and miscarriages.

**Funding**

Not reported.

**Bibliographic details**

Polyzos NP, Tsappi M, Mauri D, Atay V, Cortinovis I, Casazza G. Aromatase inhibitors for infertility in polycystic ovary syndrome: the beginning or the end of a new era? Fertility and Sterility 2008; 89(2): 278-280

**PubMedID**

18275882

**DOI**

10.1016/j.fertnstert.2007.10.016
Original Paper URL
http://www.fertstert.org/article/S0015-0282(07)03869-1/abstract

Indexing Status
Subject indexing assigned by NLM

MeSH
Aromatase Inhibitors /therapeutic use; Clinical Trials as Topic; Female; Humans; Infertility, Female /drug therapy /etiology; Ovulation Induction /methods /trends; Polycystic Ovary Syndrome /complications; Pregnancy

AccessionNumber
12008005821

Date bibliographic record published
03/02/2009

Date abstract record published
26/01/2011

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.