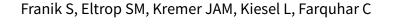


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# Aromatase inhibitors (letrozole) for subfertile women with polycystic ovary syndrome (Review)



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[Intervention Review]

# Aromatase inhibitors (letrozole) for subfertile women with polycystic ovary syndrome

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#### **ABSTRACT**

#### **Background**

Polycystic ovary syndrome (PCOS) is the most common cause of infrequent periods (oligomenorrhoea) and absence of periods (amenorrhoea). It affects about 4% to 8% of women worldwide and often leads to anovulatory subfertility. Aromatase inhibitors (Als) are a class of drugs that were introduced for ovulation induction in 2001. Since about 2001 clinical trials have reached differing conclusions as to whether the AI letrozole is at least as effective as the first-line treatment clomiphene citrate (CC).

# **Objectives**

To evaluate the effectiveness and safety of aromatase inhibitors for subfertile women with anovulatory PCOS for ovulation induction followed by timed intercourse or intrauterine insemination (IUI).

### **Search methods**

We searched the following sources from inception to November 2017 to identify relevant randomised controlled trials (RCTs): the Cochrane Gynaecology and Fertility Group Specialised Register, the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, PsycINFO, Pubmed, LILACS, Web of Knowledge, the World Health Organization (WHO) clinical trials register and Clinicaltrials.gov. We also searched the references of relevant articles. We did not restrict the searches by language or publication status.

#### **Selection criteria**

We included all RCTs of Als used alone or with other medical therapies for ovulation induction in women of reproductive age with anovulatory PCOS.

# **Data collection and analysis**

Two review authors independently selected trials, extracted the data and assessed risks of bias. We pooled studies where appropriate using a fixed-effect model to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for most outcomes, and risk differences (RDs) for ovarian hyperstimulation syndrome (OHSS). The primary outcomes were live birth and OHSS. Secondary outcomes were clinical pregnancy, miscarriage and multiple pregnancy. We assessed the quality of the evidence for each comparison using GRADE methods.

#### **Main results**

This is a substantive update of a previous review. We identified 16 additional studies for the 2018 update. We include 42 RCTs (7935 women). The aromatase inhibitor letrozole was used in all studies.



### Letrozole compared to clomiphene citrate (CC) with or without adjuncts followed by timed intercourse

Live birth rates were higher with letrozole (with or without adjuncts) compared to clomiphene citrate (with our without adjuncts) followed by timed intercourse (OR 1.68, 95% CI 1.42 to 1.99; 2954 participants; 13 studies;  $I^2 = 0\%$ ; number needed to treat for an additional beneficial outcome (NNTB) = 10; moderate-quality evidence). There is high-quality evidence that OHSS rates are similar with letrozole or clomiphene citrate (0.5% in both arms: risk difference (RD) -0.00, 95% CI -0.01 to 0.00; 2536 participants; 12 studies;  $I^2 = 0\%$ ; high-quality evidence). There is evidence for a higher pregnancy rate in favour of letrozole (OR 1.56, 95% CI 1.37 to 1.78; 4629 participants; 25 studies;  $I^2 = 1\%$ ; NNTB = 10; moderate-quality evidence). There is little or no difference between treatment groups in the rate of miscarriage by pregnancy (20% with CC versus 19% with letrozole; OR 0.94, 95% CI 0.70 to 1.26; 1210 participants; 18 studies;  $I^2 = 0\%$ ; high-quality evidence) and multiple pregnancy rate (1.7% with CC versus 1.3% with letrozole; OR 0.69, 95% CI 0.41 to 1.16; 3579 participants; 17 studies;  $I^2 = 0\%$ ; high-quality evidence). However, a funnel plot showed mild asymmetry, indicating that some studies in favour of clomiphene might be missing.

# Letrozole compared to laparoscopic ovarian drilling

There is low-quality evidence that live birth rates are similar with letrozole or laparoscopic ovarian drilling (OR 1.38, 95% CI 0.95 to 2.02; 548 participants; 3 studies;  $I^2 = 23\%$ ; low-quality evidence). There is insufficient evidence for a difference in OHSS rates (RD 0.00, 95% CI -0.01 to 0.01; 260 participants; 1 study; low-quality evidence). There is low-quality evidence that pregnancy rates are similar (OR 1.28, 95% CI 0.94 to 1.74; 774 participants; 5 studies;  $I^2 = 0\%$ ; moderate-quality evidence). There is insufficient evidence for a difference in miscarriage rate by pregnancy (OR 0.66, 95% CI 0.30 to 1.43; 240 participants; 5 studies;  $I^2 = 0\%$ ; moderate-quality evidence), or multiple pregnancies (OR 3.00, 95% CI 0.12 to 74.90; 548 participants; 3 studies;  $I^2 = 0\%$ ; low-quality evidence).

Additional comparisons were made for Letrozole versus placebo, Selective oestrogen receptor modulators (SERMS) followed by intrauterine insemination (IUI), follicle stimulating hormone (FSH), Anastrozole, as well as dosage and administration protocols.

There is insufficient evidence for a difference in either group of treatment due to a limited number of studies. Hence more research is necessary.

#### **Authors' conclusions**

Letrozole appears to improve live birth and pregnancy rates in subfertile women with anovulatory polycystic ovary syndrome, compared to clomiphene citrate. There is high-quality evidence that OHSS rates are similar with letrozole or clomiphene citrate. There is high-quality evidence of no difference in miscarriage rates or multiple pregnancy rates. There is low-quality evidence of no difference in live birth and pregnancy rates between letrozole and laparoscopic ovarian drilling, although there were few relevant studies. For the 2018 update, we added good-quality trials, upgrading the quality of the evidence.

## PLAIN LANGUAGE SUMMARY

### Aromatase inhibitors for subfertility treatment in women with polycystic ovary syndrome

**Review question:** Cochrane authors examined the evidence about aromatase inhibitors (Als) for subfertile women with polycystic ovary syndrome (PCOS).

**Background:** PCOS is the most common cause of infrequent or absent menstrual periods, and affects about 4% to 8% of women worldwide. It often causes anovulatory subfertility (subfertility related to failure to ovulate). Als are used to make ovulation happen. Since about 2001 clinical trials have reached differing conclusions as to whether the AI letrozole is at least as effective for treating subfertility as the most commonly used treatment, clomiphene citrate (CC).

**Study characteristics:** The review includes clinical studies where participants were randomly assigned to the intervention or to the comparison group (randomised controlled trials, RCTs). Our review includes 42 RCTs with 7935 women. In all trials the aromatase inhibitor used was letrozole. Comparators included CC, which was used in 25 of the RCTs, and laparoscopic ovarian drilling (a surgical technique to puncture the membrane surrounding the ovary), which was used in five RCTs. Several studies included other treatments in one or both arms.

**Key results:** Letrozole appears to improve live birth and pregnancy rates compared to CC when used to cause ovulation and timed intercourse. The quality of this evidence was moderate and seems to be reliable. There appeared to be no difference for miscarriage rate or multiple pregnancy rate. There appeared to be no difference between letrozole and laparoscopic ovarian drilling for any observed outcomes, although there were few relevant studies. Ovarian hyperstimulation syndrome (OHSS), a serious adverse event of hormonal stimulation, was a very rare event and in most studies it did not occur. The evidence is current to January 2018.

**Quality of the evidence:** The overall quality of the evidence ranged from moderate to high. Some studies in favour of clomiphene citrate may never have been published. It appears that studies that reported live births report higher clinical pregnancy rates in the letrozole group than studies that failed to report live births. This suggests that results might be somewhat less favourable to letrozole if all studies reported live births.