Aromatase inhibitors for subfertile women with polycystic ovary syndrome

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RHL summary

Findings of the review: Polycystic ovary syndrome occurs in 4%–8% of women worldwide and usually leads to anovulatory subfertility. Aromatase inhibitors (AIs) were introduced in 2001 for induction of ovulation. This review aimed to evaluate the effectiveness and safety of aromatase inhibitors in women with polycystic ovary syndrome with subfertility. This review included 26 randomized controlled trials with 5560 women. All trials compared letrozole with either clomiphene citrate or laparoscopic ovarian drill. In terms of live birth, letrozole yielded better results than clomiphene citrate when used with timed intercourse. For clinical pregnancy, letrozole was better than clomiphene citrate when used with timed intercourse as well as with intrauterine insemination. There was no evidence of any difference between letrozole and laparoscopic ovarian drill in terms of either live births or clinical pregnancy. Ovarian hyperstimulation syndrome was absent or very rare.

Implementation: Letrozole appears to be superior to clomiphene, but not different from laparoscopic ovarian drill in women with polycystic ovary syndrome with subfertility. Further studies are needed to investigate appropriate regimen and dosage of letrozole.

Cochrane review

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Abstract

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 (AIs) are a novel class of drugs that were introduced for ovulation induction in 2001. Over the last ten years 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).

To evaluate the effectiveness and safety of aromatase inhibitors for subfertile women with anovulatory PCOS.
We searched the following sources from inception to 24/10/2013 to identify relevant randomised controlled trials (RCTs): the Menstrual Disorders and Subfertility Group Specialised Register, the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, PsycINFO, Pubmed, LILACS, Web of Knowledge, the World Health Organisation (WHO) clinical trials register and Clinicaltrials.gov. Furthermore, we manually searched the references of relevant articles. The search was not restricted by language or publication status.

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

Two review authors independently selected trials, extracted the data and assessed trial quality. Studies were pooled where appropriate using a fixed effect model to calculate pooled 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 pregnancy, miscarriage and multiple pregnancy. The quality of the evidence for each comparison was assessed using GRADE methods.

We included 26 RCTs (5560 women). In all studies the aromatase inhibitor was letrozole.

**Live birth (12 RCTs)**

One RCT compared letrozole with placebo in women who were clomiphene resistant and the results were inconclusive (OR 3.17, 95% CI 0.12 to 83.17, n=36).

Nine RCTs compared letrozole with clomiphene citrate (with or without adjuncts) followed by timed intercourse. The birth rate was higher in the letrozole group (OR 1.63, 95% CI 1.31 to 2.03, n=1783, I²=3%).

Two RCTs compared letrozole with laparoscopic ovarian drilling. There was no evidence of a difference between the groups in live birth rate (OR 1.19, 95% CI 0.76 to 1.86, n=407, I²=0%).

**OHSS (16 RCTs)**

There was no evidence of a difference in OHSS rates when letrozole was compared with placebo (one RCT, n=36), clomiphene citrate (with or without adjuncts) followed by timed intercourse (nine RCTs, n=2179), clomiphene citrate (with or without adjuncts) followed by intrauterine insemination (IUI) (two RCTs, n=1494), laparoscopic ovarian drilling (one RCT, n=260) or anastrozole (one RCT, n=220). Events were absent or very rare, and no study had more than 2 cases of OHSS.

**Clinical pregnancy (25 RCTs)**

One RCT compared letrozole versus placebo in women who were clomiphene resistant and the results were inconclusive (OR 3.17, 95% CI 0.12 to 83.17, n=36).

Fourteen RCTs compared letrozole versus clomiphene citrate (with or without adjuncts) followed by timed intercourse. The pregnancy rate was higher in the letrozole group (OR 1.32, 95% CI 1.09 to 1.60, n=2066, I²=25%).

Three RCTs compared letrozole versus clomiphene citrate (with or without adjuncts) followed by IUI. The pregnancy rate was higher in the letrozole group (OR 1.71, 95% CI 1.30 to 2.25, n=1597).

Three RCTs compared letrozole versus laparoscopic ovarian drilling. There was no evidence of a difference in the clinical pregnancy rate (OR 1.14, 95% CI 0.80 to 1.65, n=553, I²=0%).

Two RCTs compared letrozole versus anastrozole, one RCT compared a five day versus a 10 day administration protocol for letrozole and another RCT compared 5 mg of letrozole versus 7.5 mg of
Letrozole. There was no evidence of a difference in the clinical pregnancy rate in these comparisons.

The quality of the evidence was rated as low for live birth and pregnancy outcomes. The reasons for downgrading the evidence were poor reporting of study methods, possible publication bias and the tendency for studies that reported live birth to report higher clinical pregnancy rates in the letrozole group than studies that failed to report live birth (suggesting that results might be somewhat less favourable to letrozole if all studies reported live birth).

Letrozole appears to improve live birth and pregnancy rates in subfertile women with anovulatory PCOS, compared to clomiphene citrate. The quality of this evidence is low and findings should be regarded with some caution. There appears to be no difference in effectiveness between letrozole and laparoscopic ovarian drilling, though there were few relevant studies. OHSS was a very rare event, with no occurrences in most studies.

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