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[Intervention Review]

Clomiphene and anti-oestrogens for ovulation induction in PCOS

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ABSTRACT

Background

Subfertility due to anovulation is a common problem in women. First-line oral treatment is with anti-oestrogens, for example clomiphene citrate, but resistance (failure to ovulate) may be apparent with clomiphene. Alternative and adjunctive treatments have been developed such as tamoxifen, dexamethasone, and bromocriptine.

Objectives

To determine the relative effectiveness of anti-oestrogen agents alone or in combination with other medical therapies in women with subfertility associated with anovulation, possibly caused by polycystic ovarian syndrome (PCOS).

Search methods

A search was conducted using the Cochrane Menstrual Disorders and Subfertility Group Trials Register (May 2009), CENTRAL (*The Cochrane Library* 2009, Issue 2), MEDLINE (1966 to May 2009), and EMBASE (1980 to May 2009) for identification of relevant randomised controlled trials (RCTs). The United Kingdom National Institute for Clinical Excellence (NICE) guidelines and the references of relevant reviews and RCTs were searched.

Selection criteria

RCTs comparing oral anti-oestrogen agents for ovulation induction (alone or in conjunction with medical therapies) in anovulatory subfertility were considered. Insulin sensitising agents, aromatase inhibitors, and hyperprolactinaemic infertility were excluded.

Data collection and analysis

Data extraction and quality assessment were done independently by two review authors. The primary outcome was live birth; secondary outcomes were pregnancy, ovulation, miscarriage, multiple pregnancy, overstimulation, ovarian hyperstimulation syndrome, and women reported adverse effects.

Main results

This is a substantive update of a previous review. Fifteen RCTs were included. One trial reported live birth. Miscarriage, multiple pregnancy rates and adverse events were poorly reported.

Clomiphene was effective in increasing pregnancy rate compared to placebo (OR 5.8, 95% CI 1.6 to 21.5) as was clomiphene plus dexamethasone treatment (OR 9.46, 95% CI 5.1 to 17.7) compared to clomiphene alone. No evidence of a difference in effect was found between clomiphene versus tamoxifen or clomiphene in conjunction with human chorionic gonadotrophin (hCG) versus clomiphene alone.

The remaining results had only one study in each comparison. A significant improvement in the pregnancy rate was reported for clomiphene plus combined oral contraceptives versus clomiphene alone. No evidence of a difference in effect on pregnancy rate was found with any of the other comparisons.

Authors' conclusions

This review shows evidence supporting the effectiveness of clomiphene citrate and clomiphene in combination with dexamethasone for pregnancy rate only. There is limited evidence on the effects of these drugs on outcomes such as miscarriage. Evidence in favour of these interventions is flawed due to the lack of evidence on live births.

PLAIN LANGUAGE SUMMARY

Clomiphene and anti-oestrogens for subfertility associated with anovulation

Subfertility due to the absence of ovulation is common for women. Medical treatment may help these women ovulate. Oral anti-oestrogens, for example clomiphene, cause increased stimulation of the ovaries and aid ovulation. The review of studies found evidence for the effectiveness of clomiphene. No evidence of a difference between clomiphene and tamoxifen, a similar anti-oestrogen drug, was found. Dexamethasone (a steroid) and combined oral contraceptives are both used to supplement clomiphene and show promise. Few studies reported beyond the establishment of early pregnancy so that, given the reported risks of miscarriage with clomiphene treatment, no definitive conclusions can be drawn about effective treatment. Evidence was inconsistent and further research is needed.