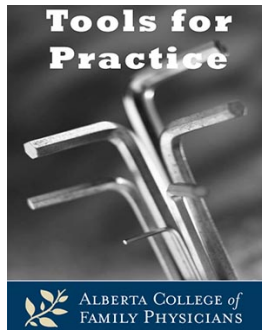


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Can we count on Clomiphene for Anovulatory Infertility?

Clinical Question: How effective is clomiphene for inducing pregnancy in females with polycystic ovarian syndrome (PCOS) presenting as oligomenorrhea or anovulation?

Bottom Line: Three small studies show clomiphene induces pregnancy in females with PCOS. For every six women treated, one more will become pregnant. Recent larger studies comparing newer agents to clomiphene suggest complications are rare. Clomiphene may be more beneficial in those with a BMI ≥ 30 .

Evidence:

- Results presented statistically significant:
 - Systematic review of Randomized Controlled Trials (RCTs) of anti-oestrogens in PCOS:¹
 - Three RCTs examined clomiphene (50-250 mg/day, 1-5 cycles) versus placebo, 133 patients.
 - Clomiphene:
 - Increased pregnancy rate: Clomiphene (20%) versus placebo (3%), Number Needed to Treat (NNT)=6.
 - Live births and miscarriages: Not reported.
 - Limitations: Small sample size, variable dosing/cycles, high dropout, poor adverse event reporting.
 - Systematic review of insulin sensitizing drugs in PCOS (44 RCTs, 3,992 women).²
 - Clomiphene versus metformin:
 - Subgroup analysis:
 - BMI ≥ 30 : Clomiphene superior to metformin for pregnancy NNT=7 and live birth rate NNT=5, (two RCTs, 500 women).
 - BMI ≤ 30 : Metformin superior to clomiphene for pregnancy NNT=8, (three RCTs, 349 women) live birth unclear.
 - Significant heterogeneity in trials reporting pregnancy and live births.
 - Adding metformin to clomiphene:
 - Improves pregnancy, NNT=13 (11 RCTs).
 - No effect birth rates.

Context:

- Most guidelines recommend clomiphene as first-line therapy in PCOS^{3,8,9} starting 50mg per day for five days, first dose on day 2-5 of menses. If ovulation is not achieved, dose may be increased to 100mg. Use maximum of six cycles.^{3,4}
- Recent systematic review of aromatase inhibitors in PCOS (26 RCTs, 5,560 women) found letrozole improved live birth over clomiphene (29% vs 18%, NNT = 10). Questions about selective reporting and publication bias limit application.^{7,8} Letrozole is not approved for infertility in Canada.
- Systematic review of seven RCTs demonstrated no benefit of clomiphene in unexplained infertility.⁵
- One systematic review reported ovarian hyperstimulation syndrome occurred in 2/1,095 patients treated with clomiphene +/- adjunct therapy.²
- RCT of 626 women reported 6% multiple pregnancy with clomiphene, 0% with metformin, and 3% with the combination of the two.⁶
- Metformin alone² improves pregnancy rate versus placebo, NNT=9.

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Disclosure:

Authors do not have any conflicts to disclose.

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