Clomiphene for anovulatory infertility

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Clinical question

How effective is clomiphene for inducing pregnancy in women with polycystic ovary syndrome (PCOS) presenting as oligomenorrhea or anovulation?

Bottom line

Three small studies show clomiphene induces pregnancy in woman with PCOS. For every 6 women treated, 1 more will become pregnant. Recent larger studies comparing newer agents to clomiphene suggest complications are rare. Clomiphene might be more beneficial in those with body mass index (BMI) ≥30 kg/m².

Evidence

- Systematic review of RCTs of antiestrogens in PCOS[1]:
  -In 3 RCTs (N = 133) that examined clomiphene (50 to 250 mg/d, 1 to 5 cycles) versus placebo, the pregnancy rate was higher with clomiphene (20% vs 3%); the number needed to treat (NNT) was 6. Live births and miscarriages were not reported.
  -Limitations: small sample, variable dosing and number of cycles, high dropout rate, poor adverse event reporting.
- Systematic review of insulin-sensitizing drugs in PCOS[2]:
  -In a subgroup analysis of clomiphene versus metformin, for those with BMI ≥30 kg/m² (2 RCTs, N = 500), clomiphene was superior to metformin for pregnancy (NNT = 7) and live birth (NNT = 5) rates; for those with BMI <30 kg/m² (3 RCTs, N = 349), metformin was superior to clomiphene for pregnancy (NNT = 8); the effect on live births was unclear.
  -There was substantial heterogeneity in trials' reporting of pregnancy and live births.
  -Adding metformin to clomiphene improved pregnancy rates (NNT = 13; 11 RCTs) with no effect on birth rates.

Context

- Most guidelines recommend clomiphene as first-line therapy in PCOS.[3-5]
- A systematic review of aromatase inhibitors in PCOS (26 RCTs, N = 5560) found letrozole improved live births over clomiphene (29% vs 18%, NNT = 10). Questions about selective reporting and publication bias limit application.[4,6] Letrozole is not approved for infertility in Canada.
- A systematic review of 7 RCTs demonstrated no benefit of clomiphene in unexplained infertility.[7]
- One systematic review reported ovarian hyperstimulation syndrome occurred in 2 of 1095 patients treated with clomiphene with or without adjunct therapy.[2]
- An RCT of 626 women reported 6% multiple pregnancies with clomiphene, 0% with metformin, and 3% with both.[8]
- Metformin alone[2] improves pregnancy rates compared with placebo (NNT = 9).

Implementation

Clomiphene is inexpensive, well-tolerated, safe, and effective. Contraindications include liver disease or dysfunction, endometrial carcinoma, ovarian cysts (not PCOS), undiagnosed uterine bleeding, and pregnancy.[9,10] Treatment should be initiated at 50 mg daily on cycle days 2 to 5 (follicular phase) and continued for 5 consecutive days with increases of 50 mg in subsequent cycles if anovulation persists. The Society of Obstetricians and Gynaecologists of Canada[3] and the Food and Drug Administration[10] advise 100 mg or less, but up to 250 mg is used in some specialty practices.[11] Ovulation can be confirmed with a luteal serum progesterone level >25 nmol/L. In women who ovulate, 52% do so taking 50 mg, 22% taking 100 mg, and fewer with subsequent increases.[11] Anovulatory women should be treated for 6 cycles before considering alternate methods of ovulation induction.[12]

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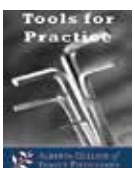
References

1. Brown J, Farquhar C, Beck J, Boothroyd C, Hughes E. Clomiphene and anti-oestrogens for ovulation induction in PCOS. *Cochrane Database Syst Rev* 2009;(4):CD002249.
2. Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. *Cochrane Database Syst Rev* 2012;(5):CD003053.
3. *SOGC clinical practice guideline. Ovulation induction in polycystic ovarian syndrome.* Ottawa, ON: Society of Obstetricians and Gynaecologists of Canada; 2010. Available from: **https://docs.google.com/viewerng/viewer?url=http://sogc.org/wp-content/uploads/2013/01/gui242CPG1005E_000.pdf**. Accessed 2016 Feb 11.
4. National Institute for Health and Care Excellence. *Fertility evidence update March 2015.* London, Engl: National Institute for Health and Care Excellence; 2015. Available from: **www.nice.org.uk/guidance/cg156/evidence/evidence-update-188501869**. Accessed 2016 Feb 9.
5. Legro RS, Arslanian SA, Ehrmann DA, Hoeger KM, Murad MH, Pasquali R, et al. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2013;98(12):4565-92.
6. Franik S, Kremer JAM, Nelen WL, Farquhar C. Aromatase inhibitors for subfertile women with polycystic ovary syndrome. *Cochrane Database Syst Rev* 2014;(2):CD010287.
7. Hughes E, Brown J, Collins JJ, Vanderkerchove P. Clomiphene citrate for unexplained subfertility in women. *Cochrane Database Syst Rev* 2010;(1):CD000057.
8. Legro RS, Barnhart HS, Schlaff WD, Carr BR, Diamond MP, Carson SA, et al. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. *N Engl J Med* 2007;356(6):551-66.
9. *Clomid* [product monograph]. Laval, QC: Sanofi-Aventis Canada Inc; 2013. Available from: **http://products.sanofi.ca/en/clomid.pdf**. Accessed 2016 Feb 16.
10. *Clomid*. Bridgewater, NJ: Sanofi-Aventis; 2012. Available from: **www.accessdata.fda.gov/drugsatfda_docs/label/2012/016131s026lbl.pdf.** Accessed 2016 Mar 29.
11. Von Hofe J, Bates GW. Ovulation induction. *Obstet Gynecol Clin North Am* 2015;42:27-37.
12. Kousta E, White DM, Franks S. Modern use of clomiphene citrate in induction of ovulation. *Hum Reprod Update* 1997;3(4):359-65.



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