

Clomiphene

Clomiphene citrate solid dosage forms (Clomid® by Sanofi Canada, Serophene® by EMD Serono) have been discontinued in Canada. Clomiphene, a selective estrogen receptor modulator (SERM) was indicated for induction of ovulation in patients with persistent ovulatory dysfunction who desire pregnancy. (1)

Place in Therapy

- Clomiphene is useful for women with **WHO class 2** anovulation. (2)
 - **WHO class 1:** hypogonadotropic hypogonadal anovulation (usually amenorrheic, low serum follicle-stimulating hormone (FSH) and low serum estradiol)
 - **WHO class 2:** normogonadotropic normoestrogenic anovulation (most have polycystic ovary syndrome (**PCOS**) and normal FSH and estradiol; luteinizing hormone (LH) may be high.)
 - **WHO class 3:** hypergonadotropic hypoestrogenic anovulation – primary ovarian insufficiency (many amenorrheic, often don't respond to ovulation induction therapies)

Management Options for ovulation induction in women with class 2 anovulation:

Pharmaceutical Alternatives:

- Refer to compounding pharmacy.
- Clomiphene citrate bulk powder (Xenex Laboratories Inc.) is currently available. (3)

Therapeutic Alternatives:

- Weight loss, exercise and lifestyle changes (4)
- Aromatase Inhibitors (letrozole, anastrozole)
 - Letrozole is an effective off-label option that can be used as an ovulation-inducing agent. It is currently considered the first-line option. (2, 5)
 - Aromatase inhibitors block the conversion of androgens (primarily androstenedione and testosterone) to estrogens (estrone and estradiol). The resulting reduced estrogen levels stimulate the pituitary gland to secrete FSH resulting in ovarian follicle recruitment.
 - Letrozole 2.5 mg daily administered for 5 days starting on day 3, 4, or 5 of cycle or following a progestin-induced bleed, induces ovulation. Success rates are similar to clomiphene. The dose may be increased to 5 mg/day for 5 days in subsequent cycles if ovulation does not occur. Maximum dose: 7.5 mg/day (5, 6)
 - Animal data have suggested that aromatase inhibitors could be associated with teratogenicity; however, human studies have not shown risks that are greater than those for clomiphene. Letrozole has a shorter half-life than clomiphene and is cleared before ovulation occurs.
 - Letrozole has a higher live birth rate compared to clomiphene for women with a BMI ≥ 30.3 kg/m².
 - Anastrozole has less evidence for efficacy and has been less well studied than letrozole. It is rarely used for ovulation induction. (7)
- Selective Estrogen Receptor Modulators (tamoxifen, raloxifene)
 - Tamoxifen and raloxifene, like clomiphene, are selective estrogen receptor modulators. (8)

- Tamoxifen 20 to 40mg daily on cycle days 2 to 6 is the current recommended dose for ovulation induction as an alternative on PCOS. (9, 10)
- Results have been mixed when compared to clomiphene when looking at pregnancy rates.
 - One study found tamoxifen to be inferior to clomiphene (11), while another found both had similar results.(12, 13)
 - A Cochrane review on the subject notes there was no clear difference found between clomiphene and tamoxifen but that the dearth of evidence regarding live births (outcomes often ovulation rates, sometimes pregnancy rates) limits the applicability of any of the results.(14) An update of this review drew the same conclusions. (15)
- Gonadotropin
 - Associated with higher costs, greater monitoring requirements, and multiple pregnancy (4)
- Laparoscopic surgery (4)
- In vitro fertilization (4)
- Metformin
 - Note: metformin in combination with clomiphene may result in higher pregnancy rates than either drug on its own; however, metformin on its own has not demonstrated statistically significant greater pregnancy rates compared to placebo.(9)

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