

Ovulation Induction



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KEYWORDS

- Ovulation induction • Clomiphene citrate • Letrozole • Gonadotropins
- Ovulation monitoring

KEY POINTS

- Before initiating ovulation induction, it is important to evaluate the underlying cause of a patient's anovulation and to make lifestyle modifications or treat underlying medical conditions, as appropriate.
- Clomiphene citrate has historically been the first-line treatment for patients with anovulatory infertility and can be used alone or with adjuvants.
- Recent evidence suggests that the aromatase inhibitor, letrozole, is the most effective oral agent for ovulation induction in women with polycystic ovarian syndrome.
- Exogenous gonadotropins may be required for women with hypothalamic hypogonadism and as an alternative to oral agents.
- Monitoring for an ovulatory response is imperative as it allows for appropriately timed intercourse or intrauterine insemination and assists in guiding alternative therapies when ovulation does not occur.

OVERVIEW

Ovulation induction is a phrase commonly used to describe the use of medication to stimulate normal ovulation in women with ovarian dysfunction. The medications used for ovulation induction can also promote follicular development or enhance ovulation in patients with other causes of infertility (male factor, age related, and unexplained), and they can be used to hyperstimulate ovaries for egg harvesting in assisted reproductive technologies or in vitro fertilization.¹

Before initiating ovulation induction agents, it is important to evaluate the underlying cause of a patient's infertility with a complete history and physical examination. Laboratory evaluation and imaging with the following may be indicated:

- Thyroid-stimulating hormone with or without thyroid profile

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- Prolactin for pituitary disease
- Testosterone or androgen panel with clinical signs of androgen excess
- 17-hydroxy progesterone with suspicion for congenital adrenal hyperplasia
- Hemoglobin A1c with obesity or evidence of glucose intolerance
- Semen analysis
- Hysterosalpingogram, saline infusion sonogram or transvaginal ultrasound scan

After an initial evaluation, simple modifications such as weight loss (of 5%–10% of body weight in obese patients) or treatment of underlying endocrinopathies (in patients with thyroid disease, diabetes, hyperprolactinemia, or congenital adrenal hyperplasia) lead to the return of ovulation for some patients, thus, negating the need for ovulation induction agents.² For others, ovulation induction agents will be necessary, and a stepwise approach to treatment, coupled with appropriate monitoring and the strategic use of adjuvant therapies, lead to the practice of the most cost-effective, evidence-based medicine. Here, the agents commonly used for ovulation induction are reviewed with attention to their pharmacology, indications for use, therapy regimens, and efficacy.

CLOMIPHENE CITRATE

Pharmacology and Mechanism of Action

Clomiphene citrate (CC) is the oldest and most widely used ovulation induction agent. It is a nonsteroidal triphenylethylene derivative, which is structurally similar to estrogen, allowing it to bind competitively to the estrogen receptor (ER).³ As a selective ER modulator (SERM), CC has both estrogen agonist and antagonist properties; however, it is the compound's agonist properties, which manifest in the setting of low endogenous estrogen levels, that are relevant in the setting of ovulation induction.²

When endogenous estrogen levels are low, CC competitively binds ERs throughout the reproductive system. CC also binds nuclear ERs for longer periods than endogenous estrogen, thus, depleting ER availability and falsely communicating a low estrogen state to the hypothalamus.² This, in turn, triggers natural compensatory mechanisms in the hypothalamic-pituitary-ovarian feedback axis, stimulating the body to alter pulsatile gonadotropin-releasing hormone (GnRH) secretion, which increases pituitary gonadotropin release and subsequently drives ovarian follicular activity.³

Indications for Use

The US Food and Drug Administration (FDA) approved CC for use in infertile patients with ovulatory dysfunction, and when combined with intrauterine insemination (IUI), CC has been found to be beneficial in patients with unexplained infertility. It is traditionally administered in a step-up regimen, and although it is highly efficacious in the appropriately selected patients, CC has significantly reduced efficacy when severe male factor, uterine, or tubal factors are also present.

Anovulatory infertility

CC has traditionally been the first-line treatment for anovulatory and oligo-ovulatory women.³ Within this group, however, patients with hypogonadotropic hypogonadism, classified as World Health Organization (WHO) group I, and hypergonadotropic hypogonadism (WHO group III) are unlikely to respond. Patients with eugonadotropic hypogonadism (WHO group II) including those with polycystic ovarian syndrome (PCOS) comprise the largest percentage of anovulatory women seeking fertility care and are the most likely to benefit from CC.

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