# Clomiphene

Clomiphene is a a drug used in the treatment of ovulatory dysfunction. Indications include polycystic ovarian syndrome (PCOS) and infertility. As a selective estrogen receptor modulator (SERM), clomiphene acts as an estrogen antagonist in the hypothalamus. This causes increased release of gonadotropin releasing hormone (GnRH) and gonadotropins (FSH, LH). Increased gonadotropin levels cause stimulation of ovulation. Side effects of clomiphene include multiple gestation, visual disturbances, and hot flashes.


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## Indications

### Infertility

Infertile-female-plant

Clomiphene is commonly used for oligoovulation, or anovulation, in patients with conditions like Polycystic ovary syndrome (PCOS).

### Polycystic Ovarian Syndrome (PCOS)

Peacock with PCOS

Polycystic Ovary Syndrome (PCOS) is a heterogeneous disorder characterized by hyperandrogenism, oligoovulation/anovulation, and/or the presence of polycystic ovaries. In PCOS, there is a disruption in the Luteinizing Hormone (LH)/Follicle Stimulating Hormone (FSH) balance, resulting in impaired follicle maturation and anovulation/oligoovulation. Clomiphene is indicated in women with PCOS seeking treatment for infertility since it induces ovulation.

## Mechanism of Action

### Selective Estrogen Receptor Modulator (SERM)

Selective-easter egg-receptor-mode-dial telephone

Clomiphene is a selective estrogen receptor modulator (SERM). Clomiphene binds to estrogen receptors (ERs) and exerts its primary effects on the hypothalamus, pituitary, ovary, and uterus. Unlike estrogen, clomiphene citrate binds nuclear ERs for a prolonged period and depletes them. Clomiphene inhibits hypothalamic estrogen receptors and the negative feedback of estrogen to the hypothalamus that normally leads to decreased secretion of gonadotropins. This results in an increase in hypothalamic gonadotropin-releasing hormone (GnRH) pulse frequency, increased serum concentrations of follicle-stimulating hormone (FSH), and luteinizing hormone (LH), leading to a hyperestrogenic environment. The hyperestrogenic environment induced by clomiphene explains its main side effects of hot flashes, breast discomfort, ovarian enlargement, and multiple simultaneous pregnancies.

### Hypothalamus

Hippo-Thor

Normally, circulating endogenous estradiol has negative effects on the hypothalamus, leading to a decreased secretion of gonadotropins. Clomiphene works by inhibiting estrogen receptors in the hypothalamus. It, therefore, inhibits the normal negative feedback of estrogen, resulting in an increase in hypothalamic gonadotropin-releasing hormone (GnRH) pulse frequency and increased release of LH and FSH from the pituitary, which stimulates ovulation.

**Estrogen Antagonist**

Ant-toga with Easter-egg

It appears that the primary site of clomiphene action is the hypothalamus where it binds to and depletes hypothalamic estrogen receptors, thereby blocking the negative feedback effect of circulating endogenous estradiol. This results in an increase in hypothalamic gonadotropin-releasing hormone (GnRH) pulse frequency and increased serum concentrations of follicle-stimulating hormone (FSH) and luteinizing hormone (LH).

**Increased GnRH, LH and FSH Secretion**

Up-arrow Gonad-gopher-harmonica, Luge, and Fish

Impairment of estrogen negative feedback signal results in increased pulsatile GnRH secretion from the hypothalamus and subsequent pituitary gonadotropin (FSH, LH) release. This causes the growth of the ovarian follicle, followed by follicular rupture and subsequent oocyte extrusion. This then allows the egg to become fertilized.

**Induction of Ovulation**

Egg released

The ovarian actions of clomiphene are secondary to the effects of elevated FSH and LH on ovarian follicular development. They promote the growth of the ovarian follicle, luteinization of the follicle, and the rupture of the follicle wall and release of a fertilizable ovum.

## Side Effects

**Multiple Gestations**

Multiple Children

Multiple gestations, or multiple pregnancies, refers to pregnancies with two or more fetuses. Induction of ovulation with Clomiphene increases the probability of multifetal pregnancy.

**Visual Disturbances**

Wavy Eyes

Visual symptoms, such as blurring, double vision, and/or scotomata, develop in 1 to 2% of women and are usually reversible. The mechanism of visual disturbances is not well understood, it has been thought to represent retinal toxicity but some studies show that clomiphene appears to affect the visual cortex rather than the retina. Physicians should actively check for visual changes in a patient receiving clomiphene.

**Hot Flashes**

Burning Flash

Hot flashes are common, occurring in 10 -20% of women. They are mediated by thermoregulatory dysfunction at the level of the hypothalamus and are induced by estrogen withdrawal. Clomiphene occupies hypothalamic estrogen receptors and disturbs the feedback mechanisms of the hypothalamic-pituitary-ovarian axis.