

Clomiphene citrate: the changing landscape

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ABSTRACT

Ovulatory dysfunction is one of the leading causes of female infertility. Clomiphene citrate has emerged as a boon in the induction of ovulation in the human female. Clomiphene results in many adverse effects some of which are documented, and some reported spontaneously. Clomiphene citrate is a non-racemic mixture of two isomers, zuclomiphene and enclomiphene, having individual and opposite biological actions. It is accepted that cis isomer (zuclomiphene) is estrogenic and trans isomer (enclomiphene) is anti-estrogenic. Zuclomiphene does not have any ovulation-induction property but gets accumulated for a longer time in the human body and it has more agonistic activity than enclomiphene. Thus, Zuclomiphene may be responsible for the adverse effects by clomiphene citrate. Enclomiphene is being explored for its potential use in male as well as female infertility. Trails are underway to explore its effectiveness and safety in various disorders. This article highlights the pharmacology of Clomiphene with respect to its isomers and the potential uses of enclomiphene based on evidences available.

Keywords: Clomiphene, Enclomiphene, Infertility, Zuclomiphene

INTRODUCTION

Ovulatory dysfunction is one of the leading causes of female infertility. Among all the drugs currently available, clomiphene citrate (CC) remains the most commonly prescribed ovulation-inducing medication and is probably the most appropriate initial choice in the majority of anovulatory infertile women.¹

Clomiphene citrate has emerged as a boon in the induction of ovulation in the human female. This wonder drug, however, was discovered as an antifertility and antiovulatory drug in laboratory animals. The adverse effects observed in the clinical use of this compound have not yet been studied well. One of the worst side effects of

this compound is abortion associated with its use in clinical practice. Considerable knowledge gaps still exist regarding the mode of action of this compound and the effects of this compound in the female reproduction.

This aspect is further complicated by the fact that clomiphene citrate is a non-racemic mixture of two isomers, zuclomiphene and enclomiphene, having individual and opposite biological actions.²

This article highlights the brief historical perspective, describes the pharmacology with respect to its isomers, their mode of action, and indications for use and a discussion on the risks and side effects of CC treatment.

HISTORICAL PERSPECTIVE

The drug was synthesized by Palopoli et al.³ Initial studies of the therapeutic potential of CC, focused on its adverse effects on fertility in animal models and it was first explored for its antifertility and antiovarulatory action.⁴ In 1960, Kistner and Smith performed the first clinical trials for ovulation induction in women.⁵ Later on, Greenblatt and colleagues reported successful induction of ovulation in 80% of amenorrhic anovulatory women, half of whom conceived during the treatment.⁶ Since that time, results of CC treatment have not changed appreciably.

Chemical structure and pharmacology

CC is a synthetic nonsteroidal triphenylethylene derivative. Like other selective estrogen receptor modulators e.g., tamoxifen, CC exhibits both estrogen agonist and antagonist properties, depending on the prevailing levels of endogenous estrogen.⁷ CC acts as estrogen agonist when endogenous estrogen levels are extremely low otherwise, it acts as an antiestrogen.⁸

CC is a non-racemic mixture of two distinct stereoisomers, enclomiphene (trans-isomer) and zuclomiphene (cis-isomer) present in 3:2 ratio (mostly 62% of enclomiphene and 38% of zuclomiphene) and both of them have different properties.⁸ Prior to 1976, the cis isomer was thought to be more anti-estrogenic and the trans isomer, more estrogenic. Following 1976 X-ray crystallographic analysis of the isomer, the cis and trans designations were reversed. Based on the evidence it is accepted that cis isomer (zuclomiphene) is estrogenic and trans isomer (enclomiphene) is anti-estrogenic.^{7,9,10} Zuclomiphene does not have any ovulation-induction property but can get accumulated for a longer time in the human body and it has more agonistic activity than enclomiphene.¹¹ It is believed that the zuclomiphene isomer is the one responsible for estrogenic side effects.¹²

Mode of action

Clomiphene has mixed agonist and antagonist activity. Clomiphene citrate is similar in structure to estrogen, hence it binds to estrogen receptors (ER) throughout the reproductive system; however, in contrast to estrogen, CC binds to nuclear ER for an extended period of time, weeks rather than hours, and ultimately depletes ER concentrations by interfering with the normal process of ER replenishment.⁷

Its effectiveness in ovulation induction can be attributed to actions at the hypothalamic level. As the hypothalamic ER are depleted the estrogen concentration are falsely perceived as low. The decreased levels of estrogen negative feedback, triggers normal compensatory mechanisms that alter the pattern of pulsatile GnRH secretion. There will be increased secretion of GnRH which in turn increases gonadotropin release from pituitary gland and this will in turn increase the ovarian follicular

activity. Normally treatment with CC will increase GnRH pulse frequency.¹³ In anovulatory women, CC will increase pulse amplitude as the frequency is already high in these patients.¹⁴ The evidence suggests that CC induces ovulation primarily through the effects on the hypothalamic GnRH pulse generator, but direct action at the pituitary level may also be involved. During CC treatment, levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) rise and then fall again after the 5-day course of therapy is completed.¹⁵ In successful treatment cycles, one or more dominant follicles emerge and mature (folliculogenesis), generating a rising tide of estrogen that ultimately triggers the midcycle LH surge and ovulation.¹⁶

Clinical pharmacokinetics

The drug is readily absorbed orally in humans. It is excreted principally in the faeces; approximately 85% of administered dose is eliminated after 6 days, although traces may remain in the circulation for much longer.¹⁷

The enclomiphene level rises rapidly after administration of CC and then it falls rapidly to undetectable concentration. Zuclomiphene stays in body for more than a month after treatment and has cumulative effect over consecutive treatment.¹⁷ This is suggestive of stereospecific enterohepatic recycling or sequestering of the zuclomiphene. Thus, it is possible that some active drug may remain in the body during early pregnancy in women on clomiphene citrate therapy. Thus, the long plasma t_{1/2} (5-7 days) is due largely to plasma-protein binding, enterohepatic circulation and accumulation in fatty tissues.¹⁸

In humans, 5 days after oral administration of C¹⁴-clomiphene, 51% of radioactivity was detected in faeces. However, after I.V. administration, only 37% of administered clomiphene was excreted during the same period. Small amounts could still be recovered 6 wks after dosing.¹⁹

More recently in a phase 3 study, a single 50 mg oral dose of clomiphene citrate (containing about 38% of zuclomiphene) was administered to healthy volunteers. The plasma profiles of the two isomers showed different characteristics with enclomiphene having more rapid distribution and elimination. The elimination rate of enclomiphene was 3-5 folds greater relative to that of zuclomiphene. Plasma levels of enclomiphene exceeded that of zuclomiphene after I.V. administration, while the reverse situation was observed after oral administration.²⁰

In summary, clomiphene is not only a mixture of two drugs, with different pharmacodynamics, but the relative plasma concentrations of the two isomers also change with time and the route of administration. Enclomiphene has much lower bioavailability than zuclomiphene as it is eliminated more rapidly. Zuclomiphene also accumulates in the plasma after repeated doses, possibly because of

stereo selective enterohepatic circulation. This accumulation is clinically important since the usual dosage is 50mg/day for 5 days and therapy could continue for as long as several months.

INDICATIONS FOR CLOMIPHENE TREATMENT

Anovulation

Whenever possible, treatment should be directed at correcting the underlying cause which may be quite varied as correct diagnosis may suggest a specific treatment and many of these conditions may have longer-term health consequences. The causes like thyroid disease, pituitary tumours, eating disorders, extremes of weight loss and exercise, hyperprolactinemia, polycystic ovary syndrome, and obesity may be identified but often the immediate cause of anovulation cannot be easily defined. CC is the treatment of choice for anovulatory, euthyroid, eu-prolactinemic with normal levels of estrogen in infertile women.¹

Luteal phase deficiency

In luteal phase deficiency ovulation occurs but progesterone production from corpus luteum is inadequate in amount and duration to support implantation.¹⁹ The corpus luteum is derived from the follicle that ovulates, it's functional capacity is dependent on the quality of preovulatory follicle development. Treatment with CC increases progesterone levels by improving preovulatory follicle development.^{21,22}

Unexplained infertility

In young couples with relatively brief duration of infertility and those unwilling or unable to pursue more aggressive therapies the empirical treatment with CC may be justified as it corrects ovulatory dysfunction and superovulation of more than a single ovum.^{1,23} Treatment is most effective when it is appropriately timed with intrauterine insemination (IUI).²⁴

Indications for Enclomiphene

Hypogonadism

Enclomiphene is presently in phase 3 trials in patients with functional secondary hypogonadism and its efficacy is compared to direct testosterone replacement. It may have potential advantages over testosterone replacement like induction of testosterone secretion endogenously by testes with a more physiological effect and preservation and enhancement of testes volume and fertility.²⁵

Male infertility

Enclomiphene is currently in phase 2 clinical trials for male infertility. It enhances secretion of gonadotropin and is expected to have a beneficial effect on fertility. The

period of treatment should be at least of 6 to 12 months for a meaningful effect of enclomiphene on spermatogenesis.²⁵

Syndrome X

There is evidence of a bidirectional relationship between low serum testosterone and metabolic syndrome in men.^{26,27} Short-term safety data for enclomiphene has been satisfactory as compared to testosterone gels and placebo. The drug is presently in phase 2 clinical trials for this medication.²⁵

FDA Status

Clomiphene is FDA approved drug for ovulatory dysfunction in women desiring pregnancy. Enclomiphene has completed phase III clinical trial in its safety study in men with secondary hypogonadism.²⁸ It is under development for treatment of males with reproductive age with low testosterone levels for improvement of fertility and sperm function.²⁹

Clomiphene- safety and tolerability

At recommended dosages, CC is generally well tolerated. Adverse reactions are mild and transient and disappear promptly on discontinuation of treatment. 10% of treated women have vasomotor flushes which are dose dependent.¹ Visual disturbances like blurred vision, scotomata, and light sensitivity can happen but are not very common. They are usually reversible on stopping the treatment.³⁰ An increase in appetite, constipation/diarrhoea, dermatitis or rash, dizziness, fatigue, light-headedness, insomnia, depression, vaginal dryness, vertigo and weight gain or loss have also been occasionally reported.³¹ Other less specific side effects with clomiphene include breast tenderness, pelvic discomfort, and nausea etc. Patients on prolonged therapy with CC may show elevated serum levels of desmosterol.³² Apart from these, there are list of adverse events reported spontaneously with CC however, the causal relationship of these is not clearly known.³¹ These include skin disorders like acne, pruritus, urticaria, allergic reaction, erythema multiforme, erythema nodosum, hypertrichosis; CNS disorders like migraine headache, paresthesia, seizure, stroke, syncope; Psychiatric problems like anxiety, irritability, mood changes, psychosis; Cardiovascular disorders like shortness of breath, tachycardia, palpitation, chest pain, edema, hypertension, thrombophlebitis, pulmonary embolism, arrhythmia; musculoskeletal symptoms like arthralgia, back pain, myalgia; liver derangements like increase serum transaminases and hepatitis; neoplasms involving various organs like liver, breast, endometrium, ovary, trophoblastic tumours and others like neoplasms of offspring like neuroectodermal tumour, hepatoblastoma, lymphocytic leukemia; genitourinary system disorders like endometriosis, ovarian cyst, ovarian hemorrhage, tubal pregnancy, uterine hemorrhage; eye problems like loss of accommodation,

cataract, macular edema, optic neuritis, photopsia, retinal hemorrhage, retinal thrombosis, retinal vascular spasm; fetal abnormalities like delayed development; abnormal bone development including skeletal malformations, deafness, mental retardation, and neural tube defects and others like leukocytosis, thyroid disorder, fever, tinnitus, weakness.³¹

Associated risks with clomiphene treatment

Multiple gestations

Multifollicle development on CC use is relatively common (about 8%) and there is increased risk of multiple gestations.^{33,36} Multiple pregnancies are usually twin gestations/ triplets but even higher order pregnancies may rarely occur. Prolonged treatment with CC is generally futile and may result in unnecessary increased risk of ovarian cancer.

Others

Foetal abnormalities have also been reported at the rate of <1%. Spontaneous abortions with CC have been reported, though not common.^{34,35} CC may produce some antiestrogenic adverse effects in the periphery (endocervix, endometrium, ovary, ovum and embryo). Studies in women have demonstrated adverse effects on quality and quantity of cervical mucus, endometrial growth, corpus luteum, steroidogenesis, ovum fertilisation and embryo development etc. These effects are apparent at higher doses or after long treatment.^{36,37}

Contraindications of clomiphene treatment

Hypersensitivity, pregnancy, liver disease, abnormal uterine bleeding, ovarian cyst, uncontrolled thyroid and adrenal dysfunction and intracranial lesions such as pituitary tumour are some known contraindications for the use of CC.³⁴

Recommended dosage and administration of clomiphene

The starting dose of clomiphene citrate is 50mg tablet to be taken once a day for 5 days starting from the 5th day of menstrual cycle. If patients do not ovulate in response to this dose, second course is started with 100mg daily for 5 days starting from the 5th day of next menstrual cycle. Increasing the dose beyond this is not recommended. In majority of patients ovulation will occur after the first course of therapy. However, if ovulation does not occur even with 3 courses of therapy then patients need to be re-evaluated. Long term treatment beyond 6 cycles is not recommended.^{8,38}

After a course of clomiphene citrate it takes 5-10 days to ovulate. On day 12 of menstrual cycle ultrasound monitoring of ovarian follicles is recommended to appropriately time coitus with the expected time of ovulation.³⁹

Effects of enclomiphene

Treatment with enclomiphene with 12.5mg and 25mg produced normal testosterone levels in the highest proportion of hypogonadal men. Mean improvements in total serum testosterone were greatest in the enclomiphene-treated groups compared with placebo and topical testosterone gel. Levels of LH, FSH and estradiol increased dose dependently to the normal range in the enclomiphene treated men but was unchanged with placebo and was significantly reduced with topical testosterone gel. DHT levels were also increased by enclomiphene, but did not exceed the normal range.⁴⁰⁻⁴³

It is also known to cause reduction in fasting plasma glucose (FPG) in men in the high-glucose group more in enclomiphene treated groups than the testosterone and placebo treated groups.⁴⁴ It also has proven to have effect on metabolic variables as cholesterol and triglycerides tended to decrease with enclomiphene, but not with placebo.⁴⁵ Mean testicular volume also increased by 2 to 2.5ml with enclomiphene treatment but was reduced by 0.5ml with topical testosterone.⁴⁰⁻⁴³

Studies on enclomiphene

A study conducted by Gupta et al, at AIIMS, New Delhi, India where in enclomiphene citrate (100mg) versus clomiphene citrate (100mg) was studied for ovulation induction in women with unexplained infertility. The drugs were administered from cycle day 3 to 7. The study concluded that enclomiphene citrate leads to multiple follicle recruitment compared to clomiphene citrate but does not benefit in terms of better endometrial development.⁴⁴

In another study conducted by Alexander et al., it was found that enclomiphene causes more significant and sustained increase in testosterone and estradiol and more significant and sustained decrease in total cholesterol and LDL cholesterol than testosterone gel therapy. Effect on triglycerides was inconsistent for both enclomiphene and testosterone gels. Whereas testosterone therapy is associated with elevated haemoglobin and hematocrit, erythrocytosis and elevated PSA, enclomiphene has insignificant effect on all these. The study concluded that enclomiphene can be effective and safe treatment for androgen deficient men with fewer adverse effects.⁴⁵

Another study by Sevam Halo et al, to find serum levels of enclomiphene and zuclomiphene in hypogonadal men on long term clomiphene citrate treatment. After prolonged treatment with Clomiphene in these men, Zuclomiphene is the predominant isomer present in serum. Because of the different biochemical properties of the two isomers, the study emphasizes on the development of pure enclomiphene isomer for treatment of hypogonadal men.⁴⁶

Edward D. Kim, Andrew McCullough and Jed Kaminetsky conducted a study to compare oral

enclomiphene with topical testosterone gel and concluded that enclomiphene citrate consistently increased serum testosterone, luteinizing hormone and follicle stimulating hormone, restoring normal levels of serum testosterone and also maintained sperm concentrations in the normal range. Testosterone gel also restored total testosterone but sperm counts were not maintained.⁴⁷

Ronald D Wiehle et al, conducted phase I pilot clinical study to study the effect of oral enclomiphene on physiological total testosterone (TT) levels in men with low to normal testosterone levels. The study found increase in TT 14 days after daily administration of two 12.5mg per oral capsules. Increase was more in men with normal TT at baseline (but within normal range). After 14 days of treatment subjects were assessed for 24hr TT levels every 2hrs. The peak rise in TT occurred at 4 hrs after administration of dose, trough occurred after 12 hrs of administration (mid-day trough) followed again by night time rise (16-24 hrs).

TT returned to baseline within 28 days following last dose of enclomiphene citrate.⁴⁸

Side effects of enclomiphene

Serious adverse effects reported in the safety study with enclomiphene citrate in the treatment of men with secondary hypogonadism were bradycardia, chest pain, biliary colic, transient ischemic attacks, seminoma, dyspnoea, deep vein thrombosis and hypotension in patients on 12.5mg administered once daily orally. Atrial flutter, cholelithiasis, diverticulitis, food poisoning, kidney infection, pulmonary embolism, cellulitis and deep vein thrombosis were reported in patients on 25mg oral dose of enclomiphene.⁴⁹ Other adverse events reported were hot flushes, infections like upper respiratory infections, influenza, sinusitis, muscle spasms, headache, dizziness and pollakiuria seen with both doses of enclomiphene.⁴⁹

CONCLUSION

Evidence base approach to enclomiphene makes it clear that this pure antiestrogenic enantiomer of clomiphene citrate is more effective and safer than the conventional therapy for various disorders like secondary hypogonadism, male as well as female infertility and is also being explored for some indications like syndrome X. Further studies will be helpful in establishing the efficacy and safety of enclomiphene.

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