Mini Review

Effects of Clomiphene citrate on Reproductive System of Birds and Mammals

Muhammad Zubair, Sajid Mahmood Sajid

Faculty of veterinary and Animal Sciences, University of Poonch, Rawalakot, Azad Kashmir.

Abstract | Clomiphene is a non-steroidal fertility medicine. It causes the pituitary gland to release hormones needed to stimulate ovulation. Clomifene is useful in those who are infertile due to anovulation or oligoovulation. Clomifene inhibits estrogen receptors in the hypothalamus, inhibiting negative feedback of estrogen on gonadotropin release and leading to up-regulation of ovulation. It has useful effects on the reproduction of female in terms of reduction in puberty and ovulation induction. The beneficial effects are manifested in male in terms of improvement of semen.

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***Correspondence** | Muhammad Zubair, University of Poonch, Rawalakot, Azad Kashmir; **Email:** drzubairabbasi@gmail.com
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Introduction

Clomiphene citrate is a tissue-selective estrogen receptor modulator (Heldring et al., 2007) and it is a non-steroidal synthetic hormone with estrogenic effect, has been the initial therapy for ovulation induction in women having anovulatory infertility and in couples with unexplained infertility (Bao et al., 2009; Fouda et al., 2011). Clomiphene citrate is part of the triphenylethylene family of compounds. It comprises of two isomeric forms, *cis* and *trans*, which in the current nomenclature corresponds to zuclomiphene and enclomiphene, respectively (Sovino et al., 2002). The accumulation action of zuclomiphene due to its long half-life was the main force in the ovulation inducing action by clomiphene citrate, and thus that the clomiphene citrate's action was mainly caused by zuclomiphene (Young et al., 1999). Contrarily, stated that the major isomer for ovulation induction was enclomiphene, and that zuclomiphene was unable to do ovulation induction. Moreover it was determined that enclomiphene's anti-oestrogenic action inhibits ovulation, and there was the need of administering hCG for ovulation induction (Pakraski et al., 2001; 2006).

Because of structural resemblances of clomiphene citrate to estrogen, it binds competitively with nuclear receptors of estrogen. Through decreasing the negative feedback of estrogen, it stimulates mechanism that alters the releasing trend of GnRH, which enhances pituitary gonadotropin hormones. This mechanism finally stimulates ovarian follicles to develop (Fritz et al., 2011). The objective of this review was to summarize the all information regarding to use in the ovulation.

Reproductive Effects of Clomiphene citrate

Clomiphene citrate has important role in induction of ovulation in amenorrhea and oligomenorrhea conditions (Greenblatt et al., 1961, 1962; Charles et al 1963; Roy et al 1963; Riley and Evans 1964). It is also used the several reproductive complications like hyperplasia of endometerium and persistent lactations (Charles, 1962; Whitelaw, 1963; Kasier, 1963). Treatment of this drug to adult rats results in the tem-

porary inhibition of estrous cycle (Barnes and Meyer, 1962). Higher doses of CC inhibit the activities follicle stimulating hormone (FSH) and luteinizing hormone (LH) while, lower doses play an important role in regulating the level of LH and FSH (Schally et al., 1970). Many other studies have proved that low doses of CC not only increase gonadotropins secretion but also cause ovulation in the intact rat (Coppola and Perrine, 1965; Koch et al., 1971). Hsueh et al., (1978) contradicted each other on the effect of CC on ovulation in rats. The effect of CC is very clear and it can induce ovulation and increase blood level of gonadotropins which is also correlated with follicular growth and elevation of estrogen secretion (Rebar et al., 1976; Ross et al., 1970). Most of the studies on ovulation stimulating effect of CC were done in rats or human. But, unfortunately the effects are just opposite to each other (Greenblatt et al., 1961). The mechanism of action of CC on ovulation are not yet understood and seems to be more complex than the normal mechanisms by which endogenous hormones function. An antiestrogenic property of this compound may be focused to the ability of CC to bind to estrogen receptors to stimulate the gonadotropin secretion. In mice, it was shown to be mainly estrogenic (Emmens, 1965; Pollard and Martin, 1968).

Delayed puberty is one of most common problem of dairy industry due to shortage of fodder and severe climatic conditions. This older age of puberty is responsible for the poor reproductive performance of cattle. The feeding of 300 mg/heifer for 9 days to pre-pubertal Sahiwal-Friesian crossbred heifers, resulted the ovulation induction with a rate of 66% (Rehman et al., 2014). Increase in small and medium sized follicles were observed in clomiphene citrate treated animals than control animals (EL Sherry et al., 2011). Indian researchers consistently reported the efficacy of clomiphene in induction of estrous in cattle and buffaloes when clomiphene citrate was administered at the dose of 300 mg/animal orally (Kankal et al., 2008).

In heifers which experienced ovulation, manifested short luteal phase and this is confirmed with other studies which revealed that luteal phase after first ovulation in most of heifers is shorter (Evans et al., 1994). The higher progesterone concentration was seen after clomiphene citrate treatment in infertile women which is due to developed CL or combined production of more than 1 CL (Downs et al., 1983; Guzick et al., 1990). Number of other studies in boys supports findings in which age of puberty was reduced due to use of clomiphene citerate (Dickerman et al., 1980) Tamoxifen (anti-estrogen), treatment accelerated puberty in both cockerels, (Rozenboim et al., 1993) and hens. Early spermetogenesis was also evident at 9 weeks of sold chicks due to use of Tamoxifen (Rozenboim et al., 1988). Similarly, in male turkeys and Muscovy drakes, treatment with tamoxifen advanced onset of semen production by 4 and 5 weeks, respectively (Rozenboim et al., 1990; Snapir et al., 1990). The role of CC in male reproductive system is controversial (Shanis et al., 1991). A significant increase in volume of semen, sperm density and motility of sperm was noticed in men treated with CC (Micic and Dotlic, 1985). Similarly a significant increase in count of sperm was reported (Soler Rosella et al., 1980). Contrary these results, Shanis et al. (1991) have reported that the treatment of CC to human results in the deterioration of sperm quality parameters. Weissenberg et al. (1992) have stated that in intact male rats LH and testosterone secretion were suppressed by clomiphene treatment. Hideki et al. (1990) have demonstrated that infertile males with low FSH and LH plasma levels tended to respond to CC treatment, while those with elevated levels of FSH and LH did not have any improvement in semen quality.

Conflict of Interest

Authors have no conflict for the publication of this paper.

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