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Clomiphene Citrate - A Review of Its Current Status

Shanbhag *Smruta*, Bhattacharya *Siladitya*,
Assisted Reproduction Unit, University of Aberdeen

Key words : anovulation, clomiphene citrate, ovulation induction, polycystic ovarian disease, unexplained infertility.

Introduction

Clomiphene citrate (CC) is a synthetic non-steroidal anti-estrogenic compound, traditionally used for ovulation induction in oligo-ovulatory infertility[1]. In order to write this review, a literature search was performed in order to identify systematic reviews and primary randomised trials involving CC. Data from observational studies were obtained in areas where randomised trials could not be found. Databases searched included MEDLINE (1966 to July 2002), Embase (1980 to July 2002) and the Cochrane Library. The Key words used were anovulation, clomiphene, clomiphene citrate, pharmacology, ovulation induction, polycystic ovarian disease and unexplained infertility.

Pharmacology

CC is a triphenylethylene derivative and is characterised by its low estrogen activity and a long duration of action. It can thus act as an estrogen agonist as well as an antagonist. It is absorbed from the gastrointestinal tract, metabolised in the liver and undergoes fecal excretion via the bile duct. The biological half-life is about five days, though traces are found in faeces for up to six weeks[2].

Mechanism of action

CC competes with estradiol for estrogen receptors and interferes with the estrogen feedback loop in the hypothalamo-pituitary-ovarian (HPO) axis. In anovulatory women, this increases gonadotrophin releasing hormone (GnRH) pulse amplitude from the hypothalamus, which in turn increases the production of endogenous follicle stimulating hormone (FSH) from the anterior pituitary. In normal cycling women, CC increases the pulse frequency but not amplitude of FSH and luteinizing hormone (LH) via increase in pulse frequency of GnRh[2]. FSH initiates follicle development and maturation and stimulates granulosa cell estrogen production. Due to its prolonged anti-estrogenic action , CC can adversely affect endometrial maturation, quality of cervical mucus and uterine blood f low characteristics.

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Correspondence :
Dr. S Shanbhag, Clinical Research Fellow, Assisted Reproduction Unit, Aberdeen Maternity Hospital, Foresterhill, Aberdeen, Scotland, AB25 2ZD United Kingdom

Clinical settings in which CC is currently used :

1. Anovulatory infertility (normogonadotrophic, normoprolactinemic, normo-estrogenic) including polycystic ovary syndrome
2. Unexplained infertility
3. In-vitro fertilisation (IVF)

CC in anovulatory infertility

Anovulation is associated with 15-20% of cases of infertility[3]. A Cochrane review by Hughes et al[1] has concluded that clomiphene is an effective method of ovulation induction in women with WHO Type II anovulatory subfertility (normogonadotrophic oligo/ amenorrhoeic infertility) (combined odds ratio 3.41, 95% confidence interval 4.23-9.48). In these women, clomiphene is associated with an ovulation rate of 60-90% and a pregnancy rate of 30-40% with a multiple pregnancy rate of 7-10% (mostly twins)[4].

Dose : CC is available as a 50 mg tablet. Treatment is normally commenced on day two (early follicular phase) of the menstrual cycle. In amenorrhoeic women, it is customary to exclude pregnancy, check the baseline endocrine profile and induce a withdrawal bleed prior to commencing CC. The starting dose is 50 mg (one tablet) orally for five days[1]. If midluteal plasma progesterone levels fail to demonstrate evidence of ovulation, the daily dose can be increased by 50 mg each subsequent cycle up to 150 mg per day. Further increments beyond a dose of 150 mg/day, are unlikely to result in ovulation or pregnancy. Failure to ovulate on the highest dose given for three months suggests clomiphene resistance[5]. Approximately 5-12 days after the last (5th) dose of CC, ovulation is expected. Couples are instructed to have intercourse every other day beginning from day 10 of the cycle. There appears to be a significant correlation between body weight and the dose required for ovulation[6]. Women with body mass index (BMI) > 30 kg/m^2 and presence of PCOS (polycystic ovarian syndrome) show decreased response to CC, and should be encouraged to lose weight prior to treatment. Women with WHO Type I anovulation (hypogonadotrophic hypogonadism) are less likely to respond to CC as they have low endogenous estradiol levels. Approximately, 75% of pregnancies occur during the first three cycles of

treatment[7]. The cumulative pregnancy rate with clomiphene continues to increase with six consecutive cycles of treatment and reaches a plateau by 12 cycles.

Monitoring

CC treatment should be monitored to confirm the appropriate dose for ovulation and rule out excessive multi follicular development in order to avoid ovarian hypersimulation and multiple pregnancy. At least the first cycle of CC should be routinely monitored by means of the following

1. Measurement of serum progesterone levels in the mid-luteal phase (day 21)
2. Pelvic ultrasonography for follicular estimation (number and size) and endometrial thickness.

Thereafter, it may be sufficient to check day 21 progesterone levels for evidence of ovulation in each cycle. The dose can be altered in consecutive cycles depending on anovulatory response (increase daily dose by 50 mg) or multi-follicular development (decrease to 25 mg /day) .

Sometimes in the persistent absence of an endogenous LH surge, it may be useful if CC is combined with the use of human chorionic gonadotrophin (hCG) administration. If hCG is used, it may be administered when the leading follicle measures 18-20 mm in diameter and intercourse is advised that night and the next two nights .

CC in Unexplained infertility

Infertility is described as unexplained in 20-30% of all couples where routine investigations including semen analysis and tests for ovulation and tubal patency are normal[8]. The role of empirical CC in unexplained infertility is debatable. The rationale behind ovulation induction in this cohort of ovulating women is to induce multiple follicle maturation and ovulation, thus increasing the odds of a fertilised embryo reaching the uterine cavity. There have been a number of small randomised trials in the use of CC in unexplained infertility. Hughes et al performed a meta-analysis of six randomized controlled trials and concluded that CC is superior to no treatment or placebo in unexplained infertility (OR 2.37 95% CI 1.22-4.62). In an alternative review conducted by the Royal College of Obstetricians and Gynecologists[9], inclusion of data from a trial excluded by Hughes et al[8] resulted in a lower combined OR with confidence levels crossing unity, suggesting that the effectiveness of clomiphene in this setting is uncertain. The small sample sizes in published trials inevitably mean that the present conclusions are likely to be affected by the outcome of future studies.

Clomiphene is seen as an inexpensive and relatively innocuous drug, and its empirical use is prefered by many to the more invasive assisted reproduction techniques. However, concerns regarding multiple pregnancy and long term risks of ovarian cancer should be discussed. The dose too needs to be minimal (50mg) as these women are already ovulatory. Until further evidence is available, it is difficult to be certain about justifying its use without the context of a randomised trial.

CC in IUI/IVF

Although CC is traditionally used for ovulatory dysfunction. It has been used along with intrauterine insemination (IUI) for the treatment of unexplained infertility. Use of CC has been shown to be an effective alternative to gonadotrophins(Gn) for superovulation prior to IUI[10]. Stimulation protocols for ovarian stimulation prior to IUI or IVF have included CC followed by Gn. However, Houmard et al[11] have failed to demonstrate any benefit of the combined regimen over the use of CC alone when used with IUI.

Williams et al[12] compared CC with standard gonadotrophin protocols for ovarian stimulation in IVF cycles and showed comparable pregnancy rates. Concurrent use of GnRH antagonists helps to avoid premature LH surges that can occur with other protocols[12]. Ingerslev et al[13] advocate use of clomiphene ovulation induction alone for IVF cycles. Data regarding the use of CC in this setting come from small observational studies. Most IVF Units continue to use protocols involving gonadotrophins for controlled ovarian stimulation in the context of IVF. Further controlled data relating to the effectiveness of CC in this context are needeed in order to change current practice.

Diagnostic use of clomiphene

One of the most challenging aspects of IVF treatment is predicting ovarian reserve and selecting an appropriate dose of Gn for controlled ovarian stimulation. The CC challenge test is a commonly used clinical test for ovarian reserve in women undergoing IVF treatment. It consists of measuring FSH levels on day 3 and again on day 10 after administration of 100mg CC on days 5-9 of the menstrual cycle. An abnormal test (CC provoked serum FSH >10IU/L) indicates poor ovarian reserve and may be predictive of a low chance of conception[14].

Clomiphene resistance

A woman is 'clomiphene resistant' when she has failed to ovulate on higher doses of CC (up to 150 mg /day). Weight loss is strongly recommended in these women. Management options for these women include

prolonging the duration of CC up to 10 days, steroids, metformin and laparoscopic ovarian drilling[3].

Adverse effects

Side effects of CC include vasomotor symptoms (hot flushes), abdominal distention, bloating, pain, breast discomfort, nausea and vomitting, headaches and reversible loss/dryness of hair. Disturbances in the central nervous system are dizziness, fatigue, vertigo, insomnia, nervous tension, depression and psychosis. In presence of visual disturbances (blurred vision, visual haloes and streaks around light and scotomas), it is recommended that treatment should be stopped immediately. The effects last from a few days to a week or two and may not necessarily be dose related[3].

Mild ovarian hyperstimulation can occur in 5% of women on CC. Symptoms include bloatedness, nausea, vomiting, diarrhoea, lethargy and loss of appetite. Presence of ascites, shortness of breath and/or reduced urine output indicate greater severity and risk of thromboembolic sequelae and accumulation of fluid in third space cavities (ascites, pericardial and pleural effusion). In these cases hospitalisation and close monitoring is necessary[3].

The incidence of multiple pregnancy (mainly twins) associated with CC is 7-10%. However, triplet pregnancies are more likely to occur with ovulation induction (58%) as compared to those with IVF (42%)[4]. Ovarian scans can identify excessive follicle development and at risk couples should be advised to avoid intercourse in order to prevent the possibility of multiple pregnancy.

Current evidence suggests that the miscarriage rates are not significantly increased in anovulatory women treated with CC (13-25%). There is no evidence to suggest that CC is teratogenic in humans although it should be avoided if there is a possibility of pregnancy[5].

Clomiphene and cancer

Rossing et al[6] studied a cohort of infertile women and found that prolonged use of CC (>1 year) may increase the risk of borderline or invasive ovarian tumours as compared with age standardised general controls. On the other hand, Potashnik et al[7] and Ashraft et al[8] studied cohorts of infertile women and did not find any relation between ovulation inducing agents and gynecological and breast cancer. In view of the putative risk of ovarian cancer associated with CC, the Royal College of Obstetricians and Gynecologists (UK) does not recommend its use beyond 12 cycles[9].

CC in male infertility

Although used in the past, available evidence suggest that there is little clinical benefit associated with the use of CC for the treatment of idiopathic male infertility[10].

Conclusion

Clomiphene is an effective, non-invasive, cheap and moderately safe treatment for anovulatory women. Further research is required to evaluate its efficacy in unexplained infertility, and its long term effects. Available guidelines suggest that its use should be preceded by adequate counselling, accompanied by careful monitoring and restricted to no more than 12 cycles.

References

1. Hughes E, Collins J, Vanderkerckhove P. Clomiphene citrate for ovulation induction in women with oligo amenorrhoea (Cochrane Review). In: *The Cochrane Library (Issue 1), 2003. Oxford: Update Software.*
2. Speroff L, Glass R, Kase N. Induction of ovulation In: Clinical Gynecologic Endocrinology and Infertility. Philadelphia. Lippincott Williams and Wilkins. *1999. pg 1097-125.*
3. Templeton A, Ashok P, Bhattacharya S, et al. Management of Infertility for the MRCOG and Beyond, 2000. London, *RCOG Press.*
4. Levene M, Wild J, Steer P. Higher multiple births and the modern management of infertility in Britain. *Br J Obstet Gynaecol 1992; 99:607-13.*
5. Gysler M, March C, Mishell D, et al. A decade's experience with an individualised clomiphene treatment regime including its effect on the postcoital test. *Fertil Steril 1982; 37: 161-7.*
6. Milsom S, Gibson G, Buckingham K, et al. Factors associated with pregnancy or miscarriage after clomiphene therapy in WHO group II anovulatory women. *Aust N Z J Obstet Gynecol 2002; 42: 150-5.*
7. Royal College of Obstetricians and Gynecologists. The management of infertility in secondary care. Evidence based clinical guideline No. 3, 1998. London, *RCOG Press.*
8. Hughes E, Collins J, Vanderkerckhove P. Clomiphene citrate for unexplained subfertility in women (Cochrane Review). In: *The Cochrane Library, Issue 1, 2003. Oxford: Update software.*
9. RCOG (1998) Guidelines for the management of infertility in secondary care. Evidence based guidelines No.3 *RCOG London.*
10. Ecochard R, Mathieu C, Rovere D, et al. A randomized prospective study comparing pregnancy rates after clomiphene citrate and human

menopausal gonadotropohin before intrauterine insemination. *Fertil and Steril 2000; 73 : 90-3.*

2. Howard B, Peter Juang M, Soules M et al. Factors influencing pregnancy rates with a combined clomiphene citrate / gonadotrophin protocol for non assisted reproductive technology fertility treatment. *Fertil Steril 2003; 77 : 384-6.*

3. Williams S, Gibbons W, Muasher S. et al. Minimal ovarian hyperstimulation for in vitro ferilization using sequential clomiphene citrate and gonadotrophin with or without the addition of a gonadotrophin releasing hormone antagonist. *Fertil Steril 2002; 78 :1068-72.*

3. Ingerslev H, Hojgaard A, Hindkjaer J. et al. A randomized study comparing IVF in the unstimulated cycle with IVF following clomiphene citrate. *Hum Reprod 2001; 16 : 696-702.*

4. Csemiczky G, Harlin J, Fried G. Predictive power of clomiphene citrate challenge test for failure on in vitro fertilization treatment. *Acta Obstet Gynecol Scand 2002; 81: 954-61.*

15. McManus J, McClure N. Complications of Assisted Reproduction. *The Obstetrician and Gynecologist 2002; 4:124-9.*

16. Shanbhag S, Bhattacharya S. Current management of ovarian hyperstimulation syndrome. *Hosp Med 2002; 63: 528-32.*

17. Rossing M, Daling J, Weiss N. et al. Risk of breast cancer in a cohort of infertile women. *Gynecol Oncol 1996; 60: 3-7.*

18. Potashnik G, Lerner-Geva L, Genkin L. et al. Fertility drugs and the risk of breast and ovarian cancers: results of a long term follow up study. *Fertil Steril 1999 ; 71:853-8.*

19. Ashrafi M, Alaghebandan R. Tavajjohi S. Frequency of infertility and induction of ovulation in Iranian ovarian cancer patients (Abstract). *Fertil Steril 1999; 72 (Suppl 1, Abstract 341).*