VOLUME - 10, ISSUE - 04, APRIL - 2021 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper | Obstetrics & Gynaecology

COMPARATIVE STUDY OF CLOMIPHENE CITRATE AND ENCLOMIPHENE CITRATE FOR OVULATION INDUCTION IN AN INFERTILE WOMAN

Dr Nishu Goyal	Senior Registrar, Departments of Obstetric and Gynecology Government Medical College Kota, Rajasthan; Ravindra Nath Medical College, Udaipur, Rajasthan.
Dr Sanjana Jourwal	Assistant Professor, Departments of Obstetric and Gynecology Government Medical College Kota, Rajasthan.
Dr Girdhar Gopal Nagar	Senior Registrar, Departments of Obstetric and Gynecology Government Medical College Kota, Rajasthan.
Dr Pradeep Kumar Agrawal*	Assistant Professor, Department of General Surgery, Government Medical College Kota, Rajasthan. *Corresponding Author

ABSTRACT

Introduction:- Anovulation is the major cause for female infertility for which ovulation induction with clomiphene citrate (CC) is the current first line treatment. Zuclomiphene is one of the isomer of CC has antiestrogenic side effects in the forms of decreased endometrial thickness and thickening of cervical mucus. This study determined the efficacy of enclomiphene citrate (EnCC) with CC for controlled ovarian stimulation in women with anovulatory infertility. **Materials and methods:** This was a prospective analytic randomized study in which 120 women with anovulatory infertility included. They randomized into two groups: CC and EnCC group. In CC group, 60 women received tablet CC 100 mg/day, patients in another group tablet EnCC 100 mg/day given orally from day 3-7 of the menstrual cycle. Main outcomes measured were number of follicles, endometrial thickness, ovulation rate and pregnancy rate. **Results:** Both groups were comparable with regard to mean age, duration of infertility. Ovulation occurred in 60% in CC group and 63.3% in EnCC group without significant difference. The total number of follicles with size >18 mm during stimulation were more in EnCC group (2.33±.802 verses 2.26± .743) without significant difference between two group. ET at hCG was higher in EnCC group (10.16±.461 versus 8.13±.472) and the difference was not statistically significant. Pregnancy rate was higher in EnCC group (40%) compared to CC group (26.6%). **Conclusion:** Comparative study of EnCC & CC shows that administration of EnCC in patient with anovulatory infertility results in more endometrial thickness which might result in higher pregnancy rate.

KEYWORDS : Anovulation, Infertility, Clomifene citrate, Enclomifene citrate

INTRODUCTION-

A couple may be considered infertile if, unable to conceive after one years of regular sexual intercourse without contraception. Worldwide between 10-15% of all couple have unresolved problem of infertility. The main cause of infertily include male factor, ovulatory disorders, tubal factor, uterine factor, pelvic factor, systemic condition, cervical and immunological factor and unexplained factor.

Female factor infertility accounts for 40 to 55%; out of which anovulation is the major cause [1]. Induction of ovulation in anovulatory women is a landmark achievement in the history of reproductive endocrinology. The last century has seen major advancement in the field of infertility and the discovery of various medical and surgical methods of ovulation induction has changed the face of treatment worldwide.

Drugs used for ovulation induction include Clomiphene citrate (CC), Follicular Stimulating Harmones (FHS), Human chorionic gonadotropin (hCG), Gonadotropin-releasing hormone (GnRH) analogs and Aromatase inhibitor [2]. Clomiphene citrate has been traditionally used as the first line drug in all cases [3-6]. It contains two stereoisomers: zuclomiphene (38%) and enclomiphene (62%). Enclomiphene is cleared rapidally while zuclomiphene has a long half life. Zuclomiphene is centrally estrogenic and peripherally antiestrogenic which results in poor cervical mucus and endometrial thinning [7].

Enclomiphene is the active isomer of clomiphene citrate responsible for ovulation induction acting centrally by it's antiestrogenic effects. Enclomiphene is estrogenic peripherally. This effect is very much desirable for endometrial thickness as well as production of good quality of cervical mucus. The overall result will be increased implantation. There are lack of study or evidence about efficacy of enclomiphene citrate as commpared to clomiphene citrate is still conflicting for ovulation induction and pregnancy.

OBJECTIVE-

Comparative study of clomiphene citrate and enclomiphene citrate for ovulation induction in an anovulatory infertility, with respect to ovulation rate and pregnancy rate.

MATERIALS AND METHODS-

This prostective analytic study was conducted in 120 patients of primary infertility with anovulation present in Panna Dhai Mahila Chikitsalaya R.N.T. Medical College, Udaipur in OPD over a period of two years from 2012 to 2014.

Inclusion criteria:

1. Patient's age group 20-40 year.
2. Women with anovulatory cycles (ultrasound proved)
3. Patent tubes by HSG / Laparoscopy / SSS
4. Euthyroid patient (normal TSH)
5. Normal husband semen analysis (HAS)

Exclusion criteria:-

1. Other cause of infertility e.g. tubal factor, uterine factor.
2. Chronic illness e.g. liver disease
3. Hyperprolectinaemia - untreated.
4. Uncontrolled diabetes

Procedure of study:-

After getting Institutional Ethical Comittee clearance from the institute and written consent from the patients enrolled in our study, they were subjected for thorough examination for confirmation of anovulation. Patients were selected according to the inclusion criteria. Following a detailed history, patients were completely evaluated clinically.

Patient randomization into two groups either (a) clomiphene citrate (CC) and (b) enclomiphene citrate (EnCC) were done. In CC group, 60 women were given tablet clomiphene citrate 100 mg/ day orally from day 3-7 of the menstrual cycle. Another 60 patients in EnCC group were given tablet enclomiphene citrate 100 mg/ day orally from day 3-7 of the menstrual cycle.

- **Follow up-** Patients were asked to report back on 10^{th} to 14^{th} day of menstrual cycle. Transvaginal ultrasound (TVS) for follicular development and endometrial thickness was done on day 10 to 16 of the cycle. Injection of hCG was given when atleast one follicle measured >18 mm. Patients were adviced to have intercourse 24-36 hours after the hCG injection. If a dominant follicle was not found in both the ovaries and multiple small follicles were found less than 10 mm, we considered that she would not ovulate in that cycle and was asked to review in the next cycle.
- **Next menstrual cycle** –In the absence of menstruation, as in most of our cases diagnosis of pregnancy was confirmed by either urine pregnancy test or TVS. If not found to be pregnant, progesterone was given to induced withdrawal bleeding and same regimen was given. Treatment was given for a maximum of 3 cycles.
- Main outcomes measured were number of follicles, endometrial thickness, ovulation rate and pregnancy rate.
- Statistical Analysis were reported as mean (SD) for continuous variables, frequencies (percentage) for categorical variables. Data were statistically evaluated with IBM SPSS Statistics for Windows, Version 20.0, IBM Corp, Chicago, IL.

RESULTS-

This study comprised 120 patients who were enrolled to Panna Dhai Mahila chikatsalaya and RNT Medical College, Udaipur. Demographic characters of patients of both group are shown in table 1. There was no statistical significant difference between the two groups regarding age, duration of infertility, socioeconomic status and literacy. The majority of patients were in age group of 20-30 years in both CC (72.7%) and EnCC group (83.4%). Mean age of patients in CC group was 27.9±4.36 year and in EnCC group 26.66±4.38 year. Majority of patients were from urban area in both groups. 80% of the patients were literate in CC group while 72.7% in EnCC group. Mean married life duration in CC group was 5.01 year and 5.76 year in EnCC group. Most of the patients had middle socioeconomic status in both CC (56.67%) and EnCC group (63.3%). Primary infertility was present in 83.33% in CC and 90% in EnCC groups. Most common menstrual disorder in both the groups was oligomenorrhoea followed by amenorrhoea.

Outcome in CC and EnCC group were summerised in table 2. Ovulation occurred in 60% in CC group and 63.3% in EnCC group without significant difference. The total number of follicles with size >18 mm during stimulation were more in EnCC group (2.33±0.802 verses 2.26±0.743) without significant difference between two group. Serum E2 was higher in EnCC group without significant statistical difference. The mean estradiol (E2) level in EnCC group was 314.9 (pg/ml) but without a significant difference. There was no significant difference regarding pretreatment endometrial thickness (ET) between two groups. ET at hCG was higher in EnCC group (10.16±.461 versus 8.13±.472) and the difference was not statistically significant. Pregnancy rate was higher in EnCC group (40%) compared to CC group (26.6%). In our study no significant difference was found in length of luteal phase. A slight delay was noted in LH surge in both the groups. No case of ovarian hyperstimulation syndrome was noted. There were two cases of twin pregnancy in CC group & one case of twin pregnancy in EnCC group.

DISCUSSION:-

Clomiphene citrate is widely used to induce ovulation in women with anovulatory infertility and to stimulate multiple follicular developments [6, 8]. Commercially available form of CC is a mixture of two isomer Enclomiphene and Zuclomiphene. Animal studies suggest that the Zu isomer is more oestrogenic of the two isomers and Enisomer has more potent antioestrogenic property (Clark and Markaverich, 1982[9]). In humans, it is clear that clomiphene citrate may act as an oestrogen or antioestrogen depending on clinical situation when administered (Adashi, 1984[10]).

Enclomiphene is the active isomer of CC responsible for ovulation induction. Centrally enclomiphene show antioestrogen effect which is desired for ovulation induction. This study reports the effect of CC & EnCC on follicular development separately [11].

In this study ovulation rate of CC was 60% & pregnancy rate was 26.6%. Ovulation by CC does not produce a much higher pregnancy rate. Most studies of ovulation induction with CC showed success rate of 80%, but pregnancy rate was <50% (Lunenfeld & Insler, 1978) [12].

This discrepancy between ovulation and pregnancy rate may be partly explained by the peripheral anti-estrogenic effects of CC at the level of the endometrium and cervical mucus or by hypersecretion of LH (Eden JA et al.) [13]. While the depression of the cervical mucus may be overcome by performing IUI, suppression of endometrial proliferation, unrelated to dose or duration of treatment but apparently idiosyncratic, indicates a poor prognosis for conception if the endometrial thickness on ultrasound scanning does not reach 8 mm at ovulation CC not only increases the desired FSH but also produces an increase in LH concentrations. This increase in LH, whose basal level is often already high in women with PCOS, may compromise pregnancy rates in those receiving CC.

Thorneycroft et al. [14] reported that CC given to regularly cycling volunteers caused no difference in the length of the luteal phase but delay the LH surge. In this study slight but not significant delay was noted in both CC & EnCC treated cycle, perhaps due to the anti-estrogenic effects of the preparation. The oestrogenic properties of the Zu isomer may account for the advancement of the day of LH noted in this study.

Pregnancy rate was more in EnCC (40%) in this study. It may be due to estrogenic effect of EnCC on endometrium. Enclomiphene is estrogenic peripherally. This effect is very much desirable for endometrial thickness as well as production of good quality of cervical mucus. The overall result will be increased implantation. Endometrial thickness at hCG was more in EnCC group (10.16±o.461 vs. 8.13±.465) which may result in higher pregnancy rate in EnCC group. EnCC was proven to be effective in improving the pregnancy rate. A study done by P Gupta et al [15] stated that Enclomiphene citrate leads to multiple follicle recruitment compared to clomiphene citrate, however there is no benefit of its use in terms of better endometrial development.

CONCLUSION:-

Result obtained from women treated with EnCC were indistinguishable from those achieved by the administration of CC in term of the numbers of preovulatory size follicle, number of follicle, preovulatory concentration of E2. No difference in gonadotropin concentration between those CC and EnCC group.

Comparative study of EnCC & CC shows that administration of EnCC in patient with anovulatory infertility results in more endometrial thickness which might result in higher pregnancy rate.

Disclosure statement:- The authors report no conflicts of interest.

Table 1. Patients demographic characters

	Group 1 (CC)	Group 2 EnCC)
Age groups (years)		
20-30	46(72.7%)	50(83.4%)
31-40	14(23.3%)	10(16.6%)
Mean age	27.9±4.36 year	26.66±4.38 year
Residence		
Urban	46(72.7%)	48(80%)
Rural	14(23.3%)	12(20%)
Literacy		
Literate	48(80%)	46(72.7%)
Illiterate	12(20%)	14(23.3%)
Duration of marital life		
<5 year	34(56.6%)	30(50.0%)
5-10 year	20(33.4%)	26(43.33%)
>10 year	6(10.0%)	4(6.67%)
Mean married life	5.01 year	5.76 year
Socioeconomic status		
Low	0	0
Middle	34(56.6%)	38(63.3%)
High	26(43.33)	22(36.7%)
Characteristic of infertility		
Primary	50(83.33%)	54(90.0%)
Secondary	10(16.67%)	6(10.0%)
Menstrual pattern		
Regular	6(10.0%)	4(6.67%)
Oligomenorrhoea	42(70%)	38(63.3%)
Amenorrhoea	12(20%)	18(30.0%)

Table 2. Outcome in CC and EnCC group

	CC group	EnCC group	T	P value
Ovulation/cycle	55/90(61.1%)	57/90(63.3)	-	0.791
Total no. of follicle > 18mm	2.26±0.743	2.33±0.802	-0.335	0.739
Pretreatment ET	4.75±0.511	4.74±0.427	-1.947	.104
ET at HCG	8.13+.465	10.17±0.461	-16.87	4.82
Day of LH peak	14.90±0.305	15.1±.367	7.153	.185
Serum E2 (pg/ml)	302.6±36.286	314.00±35.479	2.133	.133
Serum progesterone (pg/ml)	10.25±0.736	10.27±0.736	0.000	.934
Pregnancy /cycle	7/90(7.7)	11/90(12.2)	--	0.405

REFERENCES:-

1. Aghajanova L. Obstetrics and gynecology residency and fertility needs: national survey results. Reprod Sci. 2016.
2. American College of Obstetricians and Gynecologists (2002, reaffirmed 2008). Management of infertility caused by ovulatory dysfunction. ACOG Practice Bulletin No. 34. Obstetrics and Gynecology, 99(2): 347-358.
3. Campenhout JV, Borreman ET, Wyman H et al: Induction of ovulation with cisclomiphene. Am J Obstet Gynecol 115: 321, 1972
4. Carlier P, Choulika S, Efthymiou ML: Clomiphene-exposed pregnancies:Analysis of 39 information requests including 25 cases with known outcome. Therapie 51: 532, 1996
5. Clark JH, Markaverich BM: The agonistic-antagonistic properties of clomiphene: A review. Pharmacol Ther 15: 467, 1982
6. Correy JF, Marsden DE, Schokman FC: The outcome of pregnancy resulting from clomiphene induced ovulation. Aust N Z J Obstet Gynecol 22: 18, 1982
7. Dickey RP, Olar TT, Taylor SN, Curole DN, Matulich EM. Relationship of endometrial thickness and pattern of fecundity in ovulation cycles: effect of clomiphene citrate alone and with human menopausal gonadotropin. Fertil Steril 1993; 59:756–60
8. Dodge ST, Strickler RC, Keller DW: Ovulation induction with low doses of clomiphene citrate. Obstet Gynecol 67: 63, 1986
9. Clark JH, Markaverich BM: The agonistic-antagonistic properties of clomiphene: a review. *Pharmacol Ther.* 1982; 15: 467-519
10. Adashi, E.Y. Clomiphene citrate: mechanism(s) and site(s) of action—a hypothesis revisited. Fertil. Steril. 1984; 42, 331–344.
11. Glasier AF, Irvine DS, Wickings EJ, et al. A comparison of the effects on follicular development between clomiphene citrate, its two separate isomers and spontaneous cycles. Hum Reprod 1989; 4:252.
12. Insler, Lunenfield. Anovulation Contr. Gynae. Obstet., vol. 4, pp. 6-77 (Karger, Basel 1978)
13. Eden JA, Place J, Carter GD et al: The effect of clomiphene citrate on follicular phase increase in endometrial thickness and uterine volume. Obstet Gynecol 73: 187, 1989
14. Thorneycroft et al. The effects of superovulatory doses of clomiphene citrate on spontaneous luteinizing hormone peaks in regularly ovulating women. American Journal of Obstetrics and Gynecology Volume 149, Issue 4, 15 June 1984, Pages 375-378
15. P Gupta et al. Enclomiphene citrate veresus clomiphene citrate for ovulation induction in women with unexplained infertility. Fertility and Sterility Volume 100, Issue 3, Supplement, September 2013, Page S143