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Original Research Article

Road to fertility: comparison of letrozole and clomiphene citrate-estradiol valerate for ovulation induction in female with unexplained infertility to see ovulation and conception rate

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ABSTRACT

Background: Clomiphene citrate was considered as first line of treatment for ovulation and induction in patients with unexplained infertility, but there are differences in results which can be explained by anti-estrogenic effect of CC resulting in estrogen receptor depletion. Letrozole is potent non-steroidal aromatase inhibitor which increases gonadotrophin secretion with ovarian follicle stimulation. Research question was that which drug is more efficacious for ovulation and induction in patients with unexplained infertility.
Methods: This comparative study was conducted at OBGYN OPD of RMCH and RC, Kanpur. Patients were 50 females with unexplained infertility randomly divided into 2 groups. Group A received letrozole 2.5 mg from D3-D7 of menstruation. Group B received CC 50 mg from D3-D7 plus 2 mg estradiol valerate BD on D8-D14 of menstruation. Female aged 18-35 years with complete fertility workup i.e. D3 FSH, LH, prolactin, serum TSH, HSG, USG-pelvis, mid luteal phase progesterone, semen analysis within normal limits are included in study. Patients with male infertility, hyperprolactinemia, thyroid disorders and BMI>30 kg/m^2 were excluded.
Results: There was statistically significant difference in endometrial thickness (ET) between two groups, (p value <0.03) as mean ET was 9.3±1.7 in group A (L) and 8.3±1.5 in group B (CC+E). The number of follicles after stimulation were better with CC+E 2.9±1.1 and L 2.1±1.2 showing statistically significant difference with p value <0.01 but clinical pregnancy rate was higher with letrozole as compared to CC-E without statistically significant difference.
Conclusions: Letrozole has better effect on endometrial thickness with statistically significant difference. CC+E had advantage towards multifollicular development with statistically significant difference, but there was no significant difference in case of clinical pregnancy rate, abortion, ectopic, multiple gestation.

Keywords: Infertility, Letrozole, Ovulation

INTRODUCTION

Infertility is defined as a couple's inability to conceive after one year of unprotected sexual intercourse. Unexplained infertility is most common type of infertility in 10-30% of infertile couples. Superovulation is one of the most effective modalities in patients with unexplained infertility, it is the first step of infertility treatment in couples in which other causes are excluded. Clomiphene citrate is first choice and commonly used drug for the induction of ovulation in women with anovulatory infertility and for superovulation in couples with unexplained infertility. However, some women are resistant to it, in addition different studies have revealed a discrepancy between ovulation and its conception rates during treatment. Abu Hashim said that "clomiphene citrate is not equally effective in all situations for induction of ovulation".[1] This can be explained by anti-estrogenic effect of CC resulting in estrogen receptor depletion which have deleterious effect on endometrial proliferation leading to its thinning. ET is most important factor for implantation. The pregnancy rate can be very low,

especially if endometrial thickness is less than 6-8 mm. CC is known for reducing ET so we should adjust ET and its proliferation during ovulation induction to avoid this. Thus, combination of CC with estradiol valerate is used for maintaining endometrial thickness. As CC is cheap with good ovulation rate some researchers try using drugs to improve endometrial thickness, e.g. ethinyl estradiol in follicular phase.[2] Gonadotrophins can do this but it significantly increases the cost of treatment and risk of ovarian hyperstimulation. Letrozole is potent non-steroidal aromatase inhibitor as it inhibits aromatase enzyme by competitively binding to it, resulting in decreased synthesis of estrogen, this hypoestrogenemia results in release of gonadotrophin secretion via negative feedback to hypothalamo pituitary axis, which stimulate ovarian follicle development. This comparative study was done to compare letrozole (L) and clomiphene citrate-estradiol valerate (CC+E) for ovulation induction in female with unexplained infertility to see ovulation and conception rate.

METHODS

This comparative study was conducted at OPD of OBGY department at Rama Medical College Hospital and Research Centre, Kanpur.

Patients

50 females with unexplained infertility randomly divided into two groups group A received leterozole 2.5 mg from D3 to D7 of menstruation. Group B received clomiphene citrate 50 mg from D3 to D7 and estradiol valerate 2 mg BD from D8 to D14 of menstruation.

Inclusion criterion

Female aged between 18-35 years. Prior complete fertility workup within normal limits (Table 2) i.e., D3 FSH, LH, and prolactin; serum TSH; hysterosalpingography; USG-pelvis; mid luteal phase progesterone levels; normal semen analysis of husband.

Exclusion criterion

Male factor infertility, hyperprolactinemia, thyroid disorders, BMI>30 kg/m^2.

Medications

The group A patients received letrozole i.e. tablet letroz (2.5mg): Sun Pharama Andheri east Mumbai from day 3 to day 7 of menstruation.

The group B patients received clomiphene citrate i.e. tablet clomid (50 mg): Parthweb Solution Private Limited, Pune from day 3 to day 7 of menstruation with estradiol valerate i.e. tablet valest 2 mg two times a day: Walter Bushnwll Pvt. Ltd., Gurgaon from day 8 to day 14 of mensturation. Day 2 TVS scan was done in every patient to rule out any ovarian cyst or any exclusion criterion. Treatment was started according to group of patient and follow up scan was done on day 8 to monitor growth of follicle and endometrial thickness. Human chorionic gonadotrophin 10,000 IU was administered to trigger ovulation when there was at least one follicle >18 mm in mean diameter, this was followed by timed sexual intercourse. UPT test was done after 2 weeks to detect pregnancy. USG scan done after 5 weeks to confirm the fetal cardiac activity.

Statistical analysis

Data collected by asking questions and mainly history taking, all data outcome measures coded, entered and analysed using Microsoft excel software, data were then imported into statistical package for social sciences (SPSS version 26.0) software for analysis according to type of data both groups represent by mean and standard deviation. Difference between frequencies and percentages in groups were calculated by chi square test and p value was identified which showed significant results if was less than <0.05.

RESULTS

A total of 50 patients were involved in this study in which 25 patients were assigned to each group, each patient completed the cycle with 2 lost to follow up cases in group A and 3 was there in group B. There was no significant difference between age groups, body mass index, duration and type of infertility of patients of both groups (Table 1).

Table 1: Demographic criteria of studied patients.

	Letrozole	CC+E	P value
Age/years	25.2±3.1	23.8±3.4	0.13
BMI	21.5±2.9	21.7±2.5	0.79
Duration of infertility	3.2±1.1	3.5±1.2	0.36
Type of infertility			
Primary	17 (68%)	16 (64%)	0.76
secondary	8 (32%)	9 (36%)	

Table 2: Parameters of infertility workup.

	Letrozole	CC+E	P value
TSH	1.7±0.45	1.6±0.5	0.46
PRL	1.5±2.1	15.3±1.6	0.57
FSH	5.8±0.67	5.9±0.48	0.54
LH	5.2±0.2	5.2±0.47	1.0
Day 2 TVS			
AFC	7.1±0.8	7.6±1.1	0.07
ET	5.8±0.9	5.5±0.7	0.19

After intervention the endometrial thickness in group A (letrozole) was 9.3±1.7 and in group B (CC+E) was 8.3±1.5, so there was significant difference with p value 0.03. The number of follicles with size more than 18 mm in group A (letrozole) 2.1±1.2 and in group B (CC+E)

2.9±1.1 (Table 3) which shown significant difference with p value 0.01. The total number of clinical pregnancies in group A (letrozole) 39.1% and group B (CC+E) 31.8% with no significant difference i.e. p value of 0.6. there was 1 abortion in each group, and 1 multiple pregnancy was seen in group B (CC+E). There was higher number of ongoing pregnancies with letrozole group.

Table 3: Stimulation characters.

	Letrozole	CC+E	P value
No. of follicles (>18 mm)	2.1±1.2	2.9±1.1	0.01
Endometrial thickness	8.3±1.5	9.3±1.7	0.03
Stimulation day	12.7±1.1	12.4±0.6	0.20

Table 4: Outcome of pregnancy.

	Letrozole	CC+E	P value
Clinical pregnancy	9 (39.1%)	7 (31.8%)	0.6
Ongoing pregnancy	8 (34%)	6 (27.2%)	0.6
Abortion	1 (0.04%)	1 (0.04)	1
Multiple pregnancy	0	1 (0.04)	0.9
Ectopic pregnancy	0	0	0

DISCUSSION

Endometrial thickness is one of the most important factors for implantation that effects pregnancy. It was found that pregnancy rate will be very low if ET is <6-8 mm.[3] Zhao studied ET and its patterns on USG and said that the endometrial thickness predicts pregnancy outcome with high sensitivity and

specificity, the cutoff value was 9 mm Induction of ovulation is one of the first steps of infertility treatment among infertile couples who have polycystic ovarian syndrome, or other causes of infertility such as unexplained infertility. Clomiphene citrate (CC) is a known and proven first-line treatment for ovulation induction.[4] Data confirms that ovulation rate with this method is about 80%, but pregnancy rates are about 40%.[5] This is mainly because of anti-estrogenic effect of clomiphene it results in estrogen receptor depletion which effects endometrial thickness, thus adding estradiol valerate with clomiphene increases ET and can affect the pregnancy rates this is supported by study done by Harrira et al, the mean of endometrial thickness in group A and B before the intervention was 5.44 mm and 5.75 mm respectively.[6] There was no significant statistical difference between two groups (p=0.55). After intervention the mean±SD of endometrial thickness was 8.28±1.7 in group A (CC + E2) and 9.2±1.8 mm in group B (letrozole) respectively, so there was significant difference with (p value 0.00). Thus, adding estradiol from day 8 to day 14 of menstruation with clomiphene decreases the detrimental effects of clomiphene on estrgen receptors. This study shows that endometrial thickness increases from 5.44 mm to 8.28 mm ±1.7 after addition of estradiol valerte to clomiphene. Letrozole is a third generation aromatase inhibitor that acts by preventing negative feedback inhibition of the hypothalamopituitary axis by estrogen, thus increasing FSH level and also increasing the follicular sensitivity to FSH.[7] Also Mitwally and Casper found that letrozole was associated with greater endometrial thickness when they give aromatase inhibitor (letrozole) orally in a dose of 2.5 mg on days 3-7 of menses, to twelve patients with anovulatory polycystic ovary syndrome (PCOS) and ten patients with ovulatory infertility, all of them had previously received CC with an inadequate outcome (no ovulation and/or endometrial thickness of ≤0.5 cm).[8] The result of this study shows statistically significant difference in endometrial thickness (ET) between two groups, (p value <0.03) as mean ET was 9.3±1.7 in group A (L) and 8.3±1.5 in group B (CC+E). The number of follicles after stimulation were better with CC+E 2.9±1.1 and L 2.1±1.2 showing statistically significant difference with p value <0.01 but clinical pregnancy rate is higher with letrozole as compared to CC-E without statistical significant difference, study by Al-Fozan et al also shows higher clinical pregnancy rate with letrozole number of abortion was equal in both groups and multiple pregnancy was shown with group B drugs (Table 4).[9] Regarding abortion rate and multiple pregnancies, this study showed, there was no difference between both medications which was convenient with results of meta-analysis done by Jiang et al, who concluded, there were no significant differences in pregnancy, abortion and multiple pregnancy rates between the letrozole and CC in PCOS infertile patients.[10]

CONCLUSION

letrozole has better effect on endometrial thickness with statistically significant difference. CC+E had advantage towards multifollicular development with statistically significant difference, but there was no significant difference in case of clinical pregnancy rate, abortion, ectopic, multiple gestation.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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