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Original Article

CLOMIPHENE CITRATE VERSUS LETROZOLE FOR OVULATION INDUCTION IN INTRAUTERINE INSEMINATION CYCLES: AN OBSERVATIONAL COMPARATIVE STUDY.

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ABSTRACT

BACKGROUND & AIM: Ovulation induction is widely practised in conjunction with intrauterine insemination (IUI). The present study is aimed to compare commonly used clomiphene citrate and letrozole for ovulation induction in IUI cycles.

MATERIALS & METHODS: In this observational study 120 infertile couples considered for ovulation induction and IUI were allocated to either clomiphene citrate group or letrozole group. After day2 baseline transvaginal sonography (TVS) tab clomiphene citrate 50mg or tab letrozole 2.5mg administered in respective groups twice daily from day2-6 of period and followed up by TVS adding injection human menopausal gonadotropin (HMG) and tab estradiol valerate accordingly till dominant follicle(s) reached >17mm when trigger for ovulation given and IUI performed 36hours later. Those who conceived were followed till ultrasound confirmation of cardiac activity. Statistical analysis was done using SPS Software 22.

RESULTS: Endometrial thickness on both day9 and the day of ovulation trigger was more favourable in letrozole group (pvalue<0.001). Size of dominant follicle on day9 and day11 were comparable in both the groups, however, on the day of ovulation trigger was statistically more in clomiphene citrate group (pvalue 0.0202). Mean number of dominant follicles was higher in clomiphene citrate group (pvalue<0.0074). Pregnancy up to cardiac activity was similar in both the groups (pvalue 0.836). HMG and estrogen were required more in clomiphene citrate group (pvalue 0.0016).

CONCLUSION: Letrozole can be used as first line treatment for ovulation induction in any infertile women undergoing IUI reducingthe need for gonadotropins and estrogen.

KEY WORDS: Letrozole, Clomiphene Citrate, Ovulation Induction, Intrauterine Insemination.

INTRODUCTION

The term "intrauterine insemination" (IUI) refers to the introduction of sperm into the uterine cavity. The history of IUI dates back to the 18th century. Dr John Hunter, a German physician is

regarded to have performed the procedure for the first time around 1790 which was later published by his executor Sir Everard Home after his death in the year 1799.[1] It has now become a common procedure in infertility practice& involves sorting & washing sperm & transferring it into the uterus around the time of ovulation. Controlled ovarian stimulation is commonly used in conjunction with IUI which usually results in better pregnancy rate than IUI done in natural cycles. Clomiphene citrate is a selective estrogen receptor modulator (SERM)that has been widely used for ovulation induction since its approval for clinical use. In spite of having both estrogen agonistic & antagonistic activity its action is primarily anti-estrogenic except in conditions where endogenous estrogen levels is extremely low.[2]The desirable central anti-estrogenic activity is the basis behind its mechanism of action but the peripheral anti-estrogenic activity as suggested by various studies is related to its associated untoward effects on the endocervix, endometrium, ovary, ovum & the embryo.[2,3,4,5]Estrogen receptor depletion might explain the poor pregnancy rate & increased early pregnancy loss in women receiving clomiphene citrate for ovulation induction.[6] It is also frequently associated with multi-follicular development increasing the overall risk of multiple pregnancy to approximately 7-10%.[2]

Letrozole, a third-generation aromatase inhibitor, has been successfully used for ovulation induction. It decreases estrogen production directly but does not deplete estrogen receptor in target tissues thus having no persistent anti-estrogenic effects. [2,5] Unlike clomiphene citrate it no undesirable effects on the endometrium or the endocervix& the cycles are mono-ovulatory.[2] Therefore, the study was conducted to compare the effects of clomiphene citrate and letrozole on ovulation induction in IUI cycles.

MATERIALS & METHODS

This was an observational study conducted in our infertility clinics from 1st July 2019 to 31st December 2020. Prior institutional ethical committee clearance was taken All infertile couples who attended the infertility clinics underwent basic infertility evaluation. Those who were considered for ovulation induction and IUI were counselled and referred to the assisted reproductive unit of our department. After taking proper consent couples recruited in the study were allocated to either clomiphene citrate group or letrozole group. 120 such couples completed the study (Unperformed) were included for comparison with 60 in each group.

Artificial insemination is considered for treating many couples presenting with unexplained infertility, various types of sexual dysfunction, cervical factor infertility &mild to moderate male subfertility owing to the fact that in IUI gamete density is increased at fertilization site. Couples with severe male infertility (sperm concentration<10million/ml), women> 35 years of age, women with bilateral blocked fallopian tubes, ovarian cyst or reaction to drugs were excluded from the study.

All women underwent baseline day 2 transvaginal sonography (TVS) for antral follicle count (AFC), endometrial thickness (ET) and to rule out any other pathology. Tablet clomiphene citrate 50mg or tablet letrozole 2.5mg administered orally in respective groups twice daily from day2 to day6 of menses. Women of both groups were followed up by TVS on day9, day11 of the cycle and on the day of ovulation trigger. On Day9womenwith more than three follicles of >10mm diameter and on the day of ovulation trigger those with >14 follicles of>11mm diameter or >11 follicles of >10mm diameter were excluded from study. On Day9 if the follicular size was less than 12mm and ET relatively thin (less than 5mm) injection human menopausal gonadotropin (HMG) 75IU intramuscular and tablet estradiol valerate 2mg twice daily orally was supplemented. When mature leading follicle(s) reached >17 mm in diameter, ovulation was triggered with10000 IU of human chorionic gonadotropin (HCG) intramuscularly or injection leuprolide 0.5mg subcutaneously for patients with polycystic ovarian syndrome & IUI was performed 36 hours later. Tablet dydrogesterone 10 mg twice daily orally was started from day16 onwards for 15 days for luteal phase support in all women. Two

weeks after IUI in women with amenorrhoea urine pregnancy test was done and those positive were followed up for 6 weeks till TVS confirmation of cardiac activity. We have performed IUI for maximum three times for each couple. Data collected for each woman was the mean of the outcome of total number of ovulation induction cycles she received.

RESULTS

The results of the present study have been tabulated in Table 1.

Table 1. Comparison of demographic variables causes of infertility

	Clomiphene citrate group		Letrozole group			
	Mean	SD	Mean	SD	CI	p value
Age	28.2273	3.5848	28.4286	3.5426	-1.0872 to 1.4898	0.7576
Body Mass Index	24.33	1.545	24.59	1.089	-0.2232 to 0.7432	0.28
Male factor infertility	14		12			0.825
Anovulatory infertility	19		23			0.5661
Unexplained infertility	27		25			0.854

TABLE 2 PRE-INDUCTION AFC AND RESULTS OF OVULATION INDUCTION

	Clomiphene citrate group	Letrozole group				
	Mean	SD	Mean	SD	CI	p value
ET on Day 9 (in mm)	4.3000	1.0801	5.4714	.2992	0.8849 to 1.4579	<0.0001
ET on day of trigger (in mm)	7.9636	1.8613	11.5643	.3633	-4.0855 to -3.1159	<0.0001
Size of dominant follicle on day 9 or day 11(in cm)	13.7818	1.5380	14.0750	1.3000	0.5148 to 0.5148	1.00
Size of dominant follicle on day of trigger (in cm)	18.47	1.26	18.03	0.712	0.0700 to 0.8100	0.0202
Mean number of dominant follicles	1.3	0.4754	1.1	0.3247	-0.3454 to -0.0546	<0.0074
Post wash sperm count (in million)	30.9091	2.9906	31.5000	2.9627	-0.4853 to 1.6671	0.2791
Post wash sperm progressive motility (in %)	64.1818	3.97	64.14	3.65	64.1429	0.954
Estrogen and HMG requirement (no. of patients)	11		28		-0.3454 to -0.0546	0.0016
Pregnancy upto cardiac activity (no. of patients)	15		17			0.836

DISCUSSION

Both clomiphene citrate and letrozole group participants in our study had comparable baseline characteristics with regards to age, body mass index and cause of infertility (p value non-significant 0.7576, 0.28, 0.825, 0.566, 0.854). Day 2 AFC in both the groups was similar with non-significant p value of 0.1695. Post wash sperm count and progressive motility was also similar in both the groups (p value 0.2791 & 0.954 respectively).

In the present study endometrial thickness on day 9 was statistically higher in letrozole group than in clomiphene citrate group (5.4mm vs. 4.3mm respectively, p value<0.0001). Similarly on the day of ovulation trigger endometrial thickness was higher in letrozole group than in clomiphene citrate group (11.56mm vs. 7.96mm respectively, pvalue<0.0001). Sohrabvand et al. in their study also found that the mean endometrial thickness on the day of HCG administration was significantly higher in letrozole group (0.82±0.13 vs. 0.55±0.28 cm respectively, p value 0.0009) corresponding to the findings of our study.[7] Atay et al. also reported significantly higher endometrial thickness in the letrozole group than in clomiphene citrate group (p value 0.0001).[8]

Mean size of dominant follicle on the day of ovulation trigger in the present study was statistically more in clomiphene citrate group than in letrozole group (18.47±1.26 vs18.03±0.712respectively, pvalue0.02). This may be due to the fact that in clomiphene citrate group sometimes two dominant follicles emerged with a variation from 17mm to22mm. Pregnancy rate, however, was similar in both the groups (pvalue0.836). The peripheral anti-estrogenic action of clomiphene citrate on endometrium and cervical mucus might partly explain the discrepancy in ovulation rate and pregnancy rates. [2,5] Pregnancy rate per cycle was also reported to be similar in both letrozole & clomiphene citrate group in a study by Bayar et. al. (p value 0.9).[9] However a statistically significant higher clinical pregnancy rate was noted in letrozole group in a randomized control trial by Ibrahim et al. (23.07 vs 10.68%, p value

<0.001).[6] Also in the study by Atay et al. pregnancy rate was statistically higher in letrozole group as compared to clomiphene citrate group (p value 0.037).[8] Unlike clomiphene citrate, letrozole is devoid of any anti-estrogenic peripheral action.[5]

Clomiphene citrate acts through the depletion of central estrogen receptors, which in turn reduces the negative feedback mechanism of estrogenon hypothalamus and pituitary.[2] The effect is an increase in gonadotropin secretion leading to multiple follicular development. On the other hand, letrozole causes a decrease in peripheral oestrogen production, which is responsible for the increased gonadotropin secretion in the early part of the cycle; however, due to its short half-life, its effect wears off in the late follicular phase, estrogen production by the growing follicles restores the normal negative feedback mechanism on the gonatotropin secretion ultimately resulting in mono-follicular development in the late follicular phase of the cycle. In our study mean number of dominant follicles was statistically higher in clomiphene citrate group (p value <0.0074). Similarly in a study by Akbary-Asbagh et al.the mean number of dominant follicles was 1.8 in the clomiphene citrate ± HMG group as compared to 1.4 in the letrozole ± HMG group.[10]In another study by Jee et al.the mean number of dominant follicles in the letrozole + HMG group was 3.2 ± 1.7 and in the clomiphene citrate + HMG group was 5.6 ± 2.4, which was statistically significant with a pvalue of <0.0001.[11]In our study the requirement of HMG and estrogen was statistically less in letrozole group (p value 0.0016).

CONCLUSION

Letrozole can be used as first line treatment for ovulation induction in any infertile women irrespective of the indication which would reduce the need for supplemental gonadotropins and estrogen in women undergoing IUI.

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