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Original Research Article

Comparative evaluation of different cost effective ovulation induction drugs and their effect on follicular growth, endometrial thickness and pregnancy outcome

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ABSTRACT

Background: Ovulatory dysfunction is a common cause of female infertility, occurring in up to 20 - 30% of infertile women. The most commonly prescribed ovulation drugs are clomiphene citrate (CC), tamoxifen, aromatase inhibitors (such as letrozole) and gonadotropins. Objective of the study was to evaluate the efficacy of clomiphene citrate, letrozole and tamoxifen for ovulation induction in anovulatory infertility.
Methods: Randomized open label interventional clinical trial. Patients were randomized to 3 drug groups. After baseline investigations, they were subjected to ovulation induction and then USG monitoring of follicular growth and ovulation. The primary outcome measured was occurrence of conception. Secondary outcome was effect on endometrial thickness and ovulation rate.
Results: In the study, letrozole group showed 100% mono-follicular response. Mid cycle endometrial thickness in about 17% of cases in CC group is ≤8 mm. But all the cases in tamoxifen and letrozole group have ET >8 mm. This difference is statistically significant. The ovulation and conception rates are highest in letrozole group but the difference was not statistically significant.
Conclusions: Letrozole produces higher mid cycle endometrial thickness, 100% mono follicular development than clomiphene and tamoxifen. This difference is found to be statistically significant. Ovulation rate and conception rate is highest in letrozole group. But there is no statistically significant difference among the three drugs.

Keywords: Anovulatory infertility, Clomiphene citrate, Follicular growth, Letrozole, Ovulation rate, Ovulation induction, Tamoxifen

INTRODUCTION

Infertility is defined as one year of unprotected intercourse without conception.[1] Causes of infertility and prevalence in different regions are diverse. Ovulatory dysfunction is a common cause of female infertility, occurring in up to 20-30 percent of infertile women.[2] When anovulation is the only factor causing infertility, the prognosis is usually good because modern ovulation induction strategies are highly effective. The most commonly prescribed ovulation drugs are clomiphene citrate (CC), tamoxifen, aromatase inhibitors (such as letrozole) and gonadotropins (FSH, LH, human menopausal gonadotropin (hMG), chorionic gonadotropin (hCG). Other medicines used in ovulation induction include bromocriptine, cabergoline, GnRH, GnRH analogs, and insulin-sensitizing agents, which have very specialized applications. Aim of the study was to evaluate the efficacy of clomiphene citrate, letrozole and tamoxifen for ovulation induction in anovulatory infertility.

METHODS

Study was randomized open label interventional clinical trial. The primary outcome measured was occurrence of conception. Secondary outcome was effect on endometrial thickness and ovulation rate. Following are the criteria that were used to select patients for the study.

Inclusion criteria

- Patients with anovulatory infertility
- Patients with unexplained infertility.

Exclusion criteria

- Male factor infertility
- Infertility due to systemic endocrine disorders like hypothyroidism
- Hypogonadotropic hypogonadism
- Ovarian failure
- Tubal factor causing infertility
- Anatomical causes

All the patients in the study were divided into 3 study groups. (Group 1 - clomiphene citrate, group 2 - tamoxifen, group 3 - letrozole) the following baseline investigations were done - baseline USG with antral follicular count, ET, any residual cyst, complete hemogram, ESR, monteux test, random blood sugar, serum TSH, D2/D3 - serum FSH levels, serum AMH and prolactin levels, HSG, semen analysis in male partner, endometrial biopsy for histopathology and AFB staining, TB PCR (in indicated cases).

All the three drugs were administered to the respective group of patients through a fixed regimen which is elaborated in Table 1.

The drugs were started from day 2/3 of cycle and given for 5 consecutive days. Transvaginal USG from day 8 (done on alternative days till ovulation) was done for the purpose of monitoring the following parameters endometrial thickness, dominant follicular size, occurrence of ovulation.

Table 1: Regimen of ovulation induction drugs used in the study.

Drug	Starting dose	Max. dose	Max. cycles
Clomifene Citrate	50 mg OD	150 mg OD	3
Tamoxifen	40 mg (20 mg BD)	80 mg (40 g BD)	3
Letrozole	2.5 mg OD	5 mg OD	3

RESULTS

- The patients in all 3 groups are equally distributed according to age, socio economic class, BMI, antral follicular count, serum AMH and serum FSH. This is confirmed by chi square test
- In the study, letrozole group showed 100% mono-follicular response
- Mid cycle endometrial thickness in about 17% of cases in CC group is ≤8 mm. But all the cases in tamoxifen and letrozole group have ET >8 mm. This difference is statistically significant
- Mean endometrial thickness on D16 is higher in letrozole group than the other 2 groups
- The ovulation and conception rates are highest in letrozole group but the difference was not statistically significant.

DISCUSSION

Tables 2 and 3 show that three study groups were comparable in terms of age of the patients, socio-economic class, BMI, day 3 serum FSH, antral follicular count and serum AMH values.

Table 2: comparison of socio demographic profile of patients of 3 groups.

Groups	Age			S.E.C			BMI		
	≤25	26-30	>30	Upper	Mid	Lower	Under	Normal	Over wt, obese
CC	8	26	1	-	10	25	1	19	15
TAM	5	14	1	-	6	14	1	11	8
LET	8	25	2	-	11	24	1	20	14
P-value	0.982			0.967			0.991		

Table 3: Comparison of clinical characteristics of patients of 3 groups.

Groups	AFC			Sr.AMH (ng/ml)			D3 FSH (mIU/ml)		
	<10	10-15	>16	<1	1-3.5	>3.5	<10	10-15	>15
CC	5	17	12	2	17	16	26	8	1
TAM	3	11	6	1	11	5	15	5	-
LET	6	19	10	2	18	15	25	9	1
P-value	0.984			0.852			0.947		

Table 4: Effect of 3 drugs on follicular growth and endometrial thickness.

Groups	Follicular growth		D16 ET			Mean ET
	Mono	Multi	<8 mm	8-10 mm	>10 mm	
CC	32 (91.5%)	3 (8.5%)	6 (17%)	27 (77%)	2 (6%)	8.77±0.96 mm
TAM	19 (95%)	1 (5%)	-	4 (20%)	16 (80%)	10.4±0.45 mm
LET	35 (100%)	0 (0%)	-	3 (8.5%)	32 (91.5%)	11.2±0.76 mm
P-value	0.218		-			<0.001

Table 5: Ovulation and conception rates of patients of 3 groups.

Groups	Ovulation rate	Conception rate	Ovulation conception ratio
CC	71.4%	20%	3.57
TAM	70%	15%	4.6
LET	74.2%	31.5%	2.3
P-value	0.935	0.32	-

Table 4 shows the percentage of patients showing mono follicular and multi follicular response in the 3 study drugs. In present study, letrozole group showed mono-follicular development in 100% of cases. But CC and tamoxifen showed multi-follicular development in 8.5% and 5% cases respectively. Similar to the results, study by Richard S et al also showed a lesser multiple pregnancy rate in letrozole group (3.4%) than in CC group (7.4%) But Kar S study showed 100% mono follicular response in both CC and letrozole group.[3,4]

Table 4 also shows the mean endometrial thickness on day 16 in the 3 drug groups. It was higher in letrozole group (11.2 mm) than the other 2 groups (CC-8.77 mm and tamoxifen - 10.4 mm). It also showed that mid cycle endometrial thickness in about 17% of cases in CC group was ≤8 mm. But all the cases in tamoxifen and letrozole group had ET >8 mm. Application of chi-square test shows that this difference was statistically significant.

Similar results were seen in a study by Sujata Kar showed that the mean endometrial thickness was slightly higher in letrozole group, 7.65±2.1 compared to CC 7.61±1.96. Similarly, Mitwally and Casper found letrozole was associated with a greater endometrial thickness than other drugs. Badawg et al, study of 438 patients with 1063 cycles, one of the largest studies comparing CC and letrozole, reported significantly higher endometrial thickness in CC group (9.2±0.7) versus letrozole (8.1±0.2, P = 0.021).[4-6]

They attributed this effect to greater number of mature follicles and higher serum E_2 levels. The Table 5 showed the ovulation rate of 3 drugs in the study. Ovulation rate was found to be higher for letrozole (74.2%) than the other 2 drugs (CC - 71.4% and Tamoxifen - 70%). But this difference was not statistically significant.

The result of the study was comparable to that of many previous studies. A study by M. Zeinalzadeh et al showed an ovulation rate of 72% in clomiphene citrate and 86% in letrozole group. A study done by Sujata Kar, to compare Letrozole and clomiphene citrate as first line ovulation induction drug showed ovulation rate was 60.78% in CC group and 73.08% in Letrozole group.[4,7] One study by Badawg et al showed an ovulation rate of 64% in CC group and 51.6% in tamoxifen group.[5,6]

Table 5 also showed the conception rate of 3 drugs in the study. Conception rate was higher for letrozole (31.5%) than the other 2 drugs (CC- 20% and tamoxifen - 15%). But this difference was not statistically significant.

Similar results were seen in a study by Sujata Kar where pregnancy rate per cycle was astonishingly high with letrozole (21.56%) than CC (7.84%). Whereas, Badawg et al, with 438 women (1063 cycles), reported slightly better pregnancy rate in CC group (15.1% in letrozole and 17.9 % in CC group).[4-6] Bayer et al, with 74 women, Zeinalzaden et al with 107 women, both reported slightly better pregnancy rates with letrozole; however, no statistically significant difference between the two groups.[7,8] Seyedoshohadaei F et al reported that pregnancy rate was significantly higher with clomiphene then tamoxifen and letrozole.[9] A meta-analysis by He and Jiang, compared letrozole and clomiphene for ovulation induction in PCOS women.[10] Six RCTs involving 841 patients were analyzed. This showed no significant differences in pregnancy rate between the two groups.

In the study, ovulation: conception ratio was higher in clomiphene citrate (3.5) and tamoxifen (4.6). It was comparatively lower in the letrozole (2.3) group. Clomiphene citrate was introduced half a century ago and still it was one of the most commonly used agents in ovulation induction. However, one major limiting factor with use of clomiphene citrate was that the pregnancy rates were not as good as ovulation rates.

It was concluded by many previous trials that lack of conception despite evidence of ovulation may be due to anti estrogenic effects of clomiphene citrate on the endometrium, which may manifest as a thin endometrium. But tamoxifen and letrozole were devoid of these anti estrogenic effects. So, theoretically the

discrepancy between ovulation and conception should be lesser in tamoxifen and letrozole than in CC group.

CONCLUSION

The study concludes that letrozole produces higher mid cycle endometrial thickness, 100% mono follicular development than clomiphene and tamoxifen. This difference is found to be statistically significant. Ovulation rate and conception rate is highest in letrozole group. But there is no statistically significant difference among the three drugs. Further large scale studies are suggested to be undertaken to confirm these findings.

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