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Original Research Article

COMPARISON OF EXTENDED LETROZOLE REGIMEN AND CONVENTIONAL LETROZOLE REGIMEN FOR OVULATION INDUCTION IN INFERTILE WOMEN

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Abstract

Background: Infertility is defined as the failure to achieve a successful pregnancy after 12 months or more of regular, unprotected sexual intercourse, or due to an impairment of a person's capacity to reproduce either as an individual or with a partner. This study aimed to compare the extended and conventional letrozole regimens in patients undergoing ovarian stimulation. **Material and Methods:** A prospective observational study was conducted on 67 patients at the Sri Ramachandra Institute of Higher Education and Research Centre, Chennai, from June 2022 to February 2023. In all infertile women fulfilling the selection criteria, the detailed history pertaining to infertility was recorded and general and gynaecological examinations performed. Patients who received conventional letrozole regimen in the previous cycle were given extended letrozole regimen and the results were compared. **Results:** The study population consisted of 71.6% patients with primary infertility and 82% aged 20-30 years. The mean duration of infertility was 4 ± 2.6 years, and 73% belonged to the < 5 years group. Most patients had female factor infertility (62.7%), and polycystic ovary syndrome (PCOS) was detected in 67% of the population. The most common phenotype was D (57.7%), followed by A (35.5%). The duration of stimulation and the number of follicles were similar between the two groups, with no statistically significant differences. Ovulation rates were 91% in Group A and 92.5% in Group B, with no significant differences between the groups. **Conclusion:** The extended letrozole regimen for ovulation induction showed better follicular development and endometrial thickness than the conventional regimen.

INTRODUCTION

Infertility is defined as the failure to achieve a successful pregnancy after 12 months or more of regular, unprotected sexual intercourse or due to an impairment of a person's capacity to reproduce either as an individual or with her/his partner (ASRM 2013). Approximately 15% of reproductive-aged couples face infertility problems globally (ISAR).[1] Infertility has a complex aetiology, with anovulation accounting for 30%.[2] Ovulation can be induced by oral ovulogens such as clomiphene citrate (CC), tamoxifen, and letrozole or injectable gonadotropins, or in combination. Although monofollicular development is the aim of ovulation induction in anovulatory patients, multifollicular development is desired in patients undergoing IUI. Several studies have revealed that the number of mature follicles is an important factor in predicting IUI success.[3]

Clomiphene citrate causes multifollicular development, but its anti-oestrogenic action on the cervical mucus and endometrium leads to a decreased pregnancy rate. The conventional letrozole regimen causes monofollicular development, whereas the extended letrozole regimen causes multifollicular development with a good endometrium and cervical mucus. It is cheaper than gonadotropins and there is no risk of multiple pregnancies or OHSS.[4]

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Aim

This study aimed to compare the extended and conventional letrozole regimens in patients undergoing ovarian stimulation.

MATERIALS AND METHODS

This prospective observational study included 67 patients at the Sri Ramachandra Institute of Higher Education and Research Centre, Chennai, from June 2022 to February 2023. The study was approved by the institutional ethics committee before initiation, and informed consent was obtained from all patients.

Inclusion Criteria

Patients aged 21–35 years, with BMI ranging from 18 to 30 kg/m2, unexplained infertility, PCOS, non-PCOS, and endometriosis stages 1 and 2 were included.

Exclusion Criteria

Patients with a known case of pelvic tuberculosis, a known case of thin endometrium, ovarian cysts on day 2 (>10 mm), severe male factor, and stage 3 and stage 4 endometriosis were excluded.

Methodology

In all infertile women fulfilling the selection criteria, the duration of infertility, menstrual history, marital history, sexual history, obstetric history, medical history, surgical history, and treatment history were recorded.

Height, weight, BMI, evidence of clinical hyperandrogenism (hirsutism, acne, male pattern alopecia), breast atrophy, lump and galactorrhea and thyroid enlargement were noted. systemic examination and local examination (for abnormalities such as clitoromegaly), per speculum examination, and per vaginal examination were done.

Baseline investigations such as haemoglobin, blood group, FBS, PPBS, HbA1c, HIV, VDRL, HbsAg, and HCV levels were recorded, and hormonal evaluations such as free T4, TSH, prolactin, and total testosterone (if needed) were included. Transvaginal ultrasonography was performed on day 2 or day 3 of the cycle to determine uterine pathology, endometrial thickness, ovarian volume, and AFC.

Tubal evaluation was performed by Hystero Salpingo Graphy (HSG) or Saline Infusion Sonography (SIS). Semen analysis was done for male partners. Patients who received letrozole 5 mg for 5 days in the previous cycle were included in group B, and the above details were recorded. On Day 2/3 of the cycle, baseline TVS was performed to rule out ovarian cyst. Endometrial thickness, and AFC were noted.

All patients administered an extended letrozole regimen were grouped as group A. Letrozole 2.5 mg was administered once daily for 10 days from day 2/3 of the cycle. Serial follicular monitoring was started daily from day 12 (the day after the last tablet) or on alternate days according to follicular growth. The ovulatory trigger was administered via injection. HCG 5000IU or 10000IU IM when the dominant follicle was more than or equal to 20 mm. Patients were advised to have a natural relationship or IUI 24 to 48 h after the trigger as per the departmental protocol.

Age, BMI, type and duration of infertility, duration of stimulation, number of follicles > 14 mm, lead follicle size, and endometrial thickness were studied on the day of the trigger. Groups A and B were compared in terms of the above parameters.

Statistical Analysis

Collected data were analysed using IBM SPSS statistics for Windows Version 23.0 (Armonk, NY: IBM Corp). To describe the data, descriptive statistics, frequency analysis, and percentage analysis were used for categorical variables, and the mean and SD were used for continuous variables. To find a significant difference between the bivariate samples in the paired groups, a paired sample t-test was used. The chi-square test was used to determine the significance of qualitative categorical data. Statistical significance was set at p-value < 0.05.

RESULTS

Most of the study population (71.6%) had primary infertility. 82% were aged 20–30 years. The mean duration of infertility in the study population was 4 ± 2.6 years, and 73% belonged to the < 5 years group. The majority of the patients were female (62.7%). The most common female factor was PCOS (88%). PCOS was detected in 67% of the study population. [Table 1]

The most common phenotype was D (57.7%), followed by A (35.5%). Tubes were evaluated in 80% (n = 54) of the patients. In 20% of cases (n = 13), the tubes were not evaluated because of anovulatory cycles. [Table 2]

The duration of stimulation in Group A ≤12 days in 10 patients (18%), 13 to 15 days in 21 patients (36%), and ≥16 days in 26 patients (46%). In Group B, 12 patients (20%) had a stimulation duration of ≤12 days, 30 patients (48%) had 13 to 15 days, and 20 patients (32%) had ≥16 days. Regarding the number of follicles, Group A had 6 patients (9%) with 0 follicles, 52 patients (78%) with 1 follicle, and 9 patients (13%) with 2 follicles. Group B had 5 patients (8%) who had 0 follicles, 53 (79%) had 1 follicle, and nine (13%) had 2 follicles. [Table 3]

The mean duration of stimulation was 13.1±6.1 days for Group A and 13.7±4.7 days for Group B, with no statistically significant difference (p = 0.517). The number of follicles observed was identical between the groups, with 67 follicles in each group (100%), indicating an insignificant difference (p = 0.951). Likewise, the lead follicle size was measured as 18.4±7.9 mm for Group A and

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19.2±5.8 mm for Group B, showing no significant difference (p = 0.464). [Table 4]

In comparing Groups, A and B, the ovulation rate was 91% in Group A and 92.5% in Group B, resulting in an insignificant difference (p = 0.753). Furthermore, the rate of cycle cancellation was 9% in Group A and 7.5% in Group B, with an insignificant difference (p = 0.753). [Table 5]

Table 1: Demographic details

		Frequency	Percentage (%)
Age	≤20	1	2
	21-25	26	39
	26-30	29	43
	>30	11	16
Type of infertility	Primary	48	72
	Secondary	19	28
Duration in years	<3	27	40
	3-5	22	33
	>5	18	27
Menstrual history	Regular	23	34
	Irregular	44	66
Cause of infertility	Female	42	63
	Male	5	7
	Combined	3	5
	Unexplained	17	25
Cause-female factor	PCOS	37	88
	DOR	1	2.5
	TUBAL	1	2.5
	PCOS and TUBAL	3	7
Distribution of study population	PCOS	45	67
	Non-PCOS	22	33

Table 2: Clinical parameters

		Frequency	Percentage (%)
PCOS Phenotypes	A	16	35.5
	B	0	0
	C	3	6.6
	D	26	57.7
Tubal evaluation	One tube patent	7	13
	Both tubes patent	47	87

Table 3: Various outcomes of the study

		Group A	Group B
Duration of stimulation (days)	≤12	10 (18%)	12 (20%)
	13-15	21 (36%)	30 (48%)
	≥16	26 (46%)	20 (32%)
Number of follicles	0	6 (9%)	5 (8%)
	1	52 (78%)	53 (79%)
	2	9 (13%)	9 (13%)
Lead follicle size (mm)	16.1-18	0	2 (3%)
	18.1-20	22 (36%)	33 (53%)
	>20	39 (64%)	27 (43%)
Endometrial thickness (mm)	≤7	2 (3%)	8 (13%)
	7.1-10	48 (79%)	50 (81%)
	>10	11 (18%)	4 (6%)

Table 4: Various mean values of Group A and Group B

	Mean		P value
	Group A	Group B	
Duration of stimulation	13.1±6.1	13.7±4.7	0.517
Number of follicles	67(100%)	67(100%)	0.951
Lead follicle size (mm)	18.4±7.9	19.2±5.8	0.464
Endometrial thickness (mm)	8.3±3	7.8±2.5	0.354

Table 5: Various other parameters of groups A and B

	Group A	Group B	P value
Ovulation rate	61(91%)	62(92.5%)	0.753
Cancellation of cycle	6(9%)	5(7.5%)	0.753

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DISCUSSION

The mean duration of infertility in our study was 4 years, while it was 3.5 years in the studies by Badawy et al. and Rahmani et al.[6,7] The main reason for the increased duration of infertility in our study may be the delay in seeking treatment by Indian women for social reasons. In our study population, 63% had female factors and 88% had PCOS. The prevalence of PCOS is increasing in our population, probably because of lifestyle changes. In a study by Fouda et al., 50% of patients had unexplained infertility.8 A study by Zhu et al. included only PCOS patients with letrozole resistance as the study population.9 A study by Badawy et al. included only PCOS with clomiphene resistance.[6]

In our study, the mean BMI was 27 kg/m2 which was comparable to the studies by Badawy et al., Rahmani et al., Fouda et al., and Zhu et al. which had a mean BMI of 33.9 kg/m2, 25.8 kg/m2, 26 kg/m2, 24.8 kg/m2, respectively.[6-9] The BMI in a study by Badawy et al. was higher as compared to other studies because the average BMI in the European population is high due to high socioeconomic status and educational status.[6]

In our study, the mean duration of stimulation was 13.1 days in the extended letrozole group which is comparable to the studies by Fouda et al. and Zhu et al. which had 12.3 and 17.4 days mean duration of stimulation respectively.[8,9] In our study, the mean number of follicles greater than 14 mm was comparable in both groups. The mean number of follicles was 2–3 in our study which might be due to PCOS being more common in our study population. The mean number of follicles in other studies by Badawy et al., Fouda et al. and Zhu et al. were 3,2,1 respectively.[6,8,9] The number of follicles was more in the study by Badawy et al. when compared to other studies because it included CC-resistant PCOS.[6] The mean number of follicles was higher in the study by Fouda et al. because of unexplained infertility.[8] There was a lesser number of follicles in a study by Zhu et al. because of letrozole resistance.[9]

In our study, the mean diameter of the dominant follicle was 19 mm in the extended letrozole group, and both groups were comparable in terms of lead follicle size. The mean follicle size was 20.3 mm in a study by Rahmani et al. and 21.5 mm in a study by Zhu et al.[7,9] This difference in our study might be due to better folliculogenesis which was also reflected by good pattern and thickness of endometrium. The mean endometrial thickness in our study was 8 mm with extended letrozole. In other studies, by Badawy et al., Fouda et al. and Zhu et al. the mean endometrial thickness was 11.2 mm, 9.1 mm, and 10.58 mm respectively.[6,8,9] Our study is comparable with the study by Fouda et al.[8] However endometrial thickness was less in our study when compared to studies by Badawy et al. and Zhu et al.[6,9]

This may be due to early rupture of follicles, probably due to premature LH surge on or before day 12 in 7% of the patients in our study. However, the number of cases with thin endometrium was lower in the extended letrozole group (3%) than in the conventional letrozole group (13%). Ovulation and cycle cancellation rates were similar in both groups. No OHSS was observed in either group in the present study.

CONCLUSION

The extended letrozole regimen for ovulation induction showed better follicular development and endometrial thickness than the conventional regimen.

Strengths

This prospective observational study design strictly adhered to the enrolment criteria, ensuring consistency in the study population across both groups. In addition, all causes of infertility were included in this study.

Limitations

The limited sample size and short study duration prevented the analysis of stimulation outcomes.

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