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Original Article

A STUDY OF EFFICACY AND SAFETY OF DRUGS USED FOR INFERTILITY AT A TERTIARY CARE CENTER-A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Objective: To assess the efficacy and safety of drugs used for infertility with respect to ovulation induction and conception.

Methods: A prospective observational study was conducted in gynaecology Out Patient Department (OPD) of a tertiary care hospital from June 2019 to November 2019. 45 women who presented with history of infertility were included. Details of socio-demographic factors, treatment, investigations, efficacy and safety parameters were collected. Efficacy parameters considered were mature follicle ≥18 mm, endometrial thickness of ≥7 mm, occurrence of ovulation and pregnancy. Safety parameters included any adverse effects encountered during drug therapy.

Results: Out of 45 patients, 24 were treated with Clomiphene citrate and 21 with Letrozole. The two groups had similar baseline characteristics. Mature follicular size was attained in 83.3% of Clomiphene citrate group and 61.9% of letrozole group. Mean endometrial thickness was 7.6 mm in Clomiphene citrate while 8.3 mm in letrozole group. Ovulation occurred in 45.8% of patients in Clomiphene citrate group and 47.6% of letrozole group. 41.7% of patients in Clomiphene citrate group and 28.6% of letrozole group conceived. However, there was no significant difference between the two groups in the above parameters. No serious adverse effects were observed.

Conclusion: Both letrozole and clomiphene citrate were equally efficacious in ovulation induction and did not cause any serious adverse effects.

Keywords: Infertility, Clomiphene citrate, Letrozole, Efficacy, Safety

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INTRODUCTION

Infertility is a unique disorder involving a couple rather than an individual. Infertility refers to the inability to conceive after unprotected intercourse for one year. It can be either primary or secondary [1]. In primary infertility, there is no history of previous conception while in secondary infertility, there is inability to conceive after having a successful conception [2]. Globally about 15% of reproductive-age couples are infertile. The overall prevalence of primary infertility in India is between 3.9 to 16.8% as per World Health Organization estimate [3]. Female factors, male factors and unknown factors contribute equally to infertility [4]. Among the infertile patients, approximately 40% fail to ovulate, 30-50% have tubal pathology and ≤ 10% have some cervical barrier [5].

Human Menopausal Gonadotropin (hMG), Follicle Stimulating Hormone (FSH), Gonadotropin Releasing Hormone (GnRH) agonists, Clomiphene Citrate (CC) and letrozole are the various drugs used for ovulation induction [5]. Infertility treatment with gonadotropins is expensive and associated with adverse effects like ovarian hyperstimulation syndrome and multiple gestations [6]. GnRH agonists are used along with gonadotropins in *in vitro* fertilisation (IVF) regimens to prevent premature ovulation and increase the success rate [7]. CC is an anti-estrogen which is most widely used for ovulation induction. However, CC has poor efficacy, high rate of multiple-pregnancy and causes mood changes and hot flushes. Many patients fail to respond to CC [8]. In such CC resistant cases, metformin can be combined with it before trying alternative therapies [9]. Letrozole, an aromatase inhibitor, is increasingly being used to induce ovulation [7, 10]. Although it is superior to CC in some ways-like has lesser rates of multiple pregnancies and more favorable side-effect profile, there is a concern about its teratogenic potential [8]. Hence, this study was planned to assess the efficacy and safety of the various infertility treatments given at our tertiary care hospital.

MATERIALS AND METHODS

This was a prospective observational study which was carried out in the outpatient department of Obstetrics and Gynaecology (OBG) between June 2019 to November 2019. The study was approved by institutional ethics committee (Reference no.- IEC/KRIMS/O/39/2019). Sample size was calculated as below;

Group 1 (Letrozole): $\mu_1 = 8.44$, S1= 0.73, $n_1 = 50$

Group 2 (Clomiphene citrate): $\mu_2 = 7.86$, S2= 0.67, $n_2 = 50$

$$\text{Sample size}^{11}\ (n) = \frac{[Z_{1-\alpha/2} + Z_{1-\beta}]^2\,(S1^2 + S_2^2)}{(\mu_1 - \mu_2)^2}$$

Where, $Z_{1-\alpha/2} = 1.96$ at 5% level of significance

$Z_{1-\beta} = 0.84$ at 80% power

n = 23

23 subjects should be included in each group, total sample size = 46.

Forty five patients with infertility were included after obtaining written informed consent. Women between 21 and 40 y of age with normal pelvic ultrasound and patent fallopian tubes and normal semen analysis of husband were included. Women with thyroid disorders, abnormal blood sugars, impaired hepatic or renal function, gynaecological disorders such as pelvic inflammatory disease and previous genital tract surgeries were excluded.

Infertility workup was done on all the patients – tubal patency test, pelvic USG, serum hormones like Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), Prolactin, Thyroid Stimulating Hormone (TSH) and semen analysis of husband. Patients received either clomiphene citrate (CC) 50 mg or letrozole 2.5 mg from day 3 of their cycles for 5 d. The dose was increased to 100 mg for CC and 5 mg for letrozole in case of non-response. Serial transvaginal Ultra SonoGraphy (USG) was done in all patients from day 12 to day 16 to observe the presence of mature follicle of ≥18 mm and endometrial thickness. When a mature follicle was present, injection hCG 10,000 IU was administered intramuscularly. Occurrence of ovulation was confirmed by observing the rupture of the follicle by transvaginal USG.

The data was collected from the OPD files of the study participants as per the study proforma. Proforma consisted of details of socio-demographic factors, investigations, treatment details, efficacy and safety parameters. Efficacy parameters included mature follicle≥18 mm, endometrial thickness of ≥7 mm, occurrence of ovulation and pregnancy. Safety parameters such as occurrence of polycystic ovaries, gastric upset, multiple pregnancy, hot flushes, allergic dermatitis, nausea, diarrhoea, vaginal dryness, joint pain, stiffness and Ovarian Hyper Stimulation Syndrome (OHSS) if any were noted.

Statistical analysis

Sample t-test and z test of proportions were used to compare letrozole and clomiphene citrate treated patients. P value<0.05 was considered to be significant.

RESULTS

In the present study, 45 women with history of infertility visited the OBG OPD during the study period of 6 mo. Among them, 24 were treated with CC and the remaining received letrozole. Their baseline characteristics are tabulated in table 1. The two groups were similar at baseline and there was no statistically significant difference among them.

Mature follicle of ≥18 mm was seen in 83.3% cases of CC treated patients and 61.9% in letrozole treated patients. However the difference seen was not statistically significant. 41.7% patients who were on CC conceived while 28.6% conceived in letrozole group. This difference was not statistically significant (table 2). The adverse effects encountered with the use of CC and letrozole are tabulated in table 3.

Table 1: Baseline characteristics of the patients

Parameter	Group	Mean±Std. deviation	p-value
Age (y)	Clomiphene Citrate	31.8±5.2	0.65
	Letrozole	32.5±4.2	
Body Mass Index (kg/m^2)	Clomiphene Citrate	23.3±3.7	0.75
	Letrozole	23.7±4.4	
Period of Infertility (y)	Clomiphene Citrate	4.2±2.3	0.11
	Letrozole	3.2±1.7	
Hemoglobin (g/dl)	Clomiphene Citrate	11.6±1.2	0.85
	Letrozole	11.7±1.3	
Random Blood Sugar (mg/dl)	Clomiphene Citrate	88.1±6.9	0.34
	Letrozole	91±11.9	
Follicle Stimulating Hormone (mIU/l)	Clomiphene Citrate	7.6±2.3	0.62
	Letrozole	7.9±1.6	
Luteinizing Hormone (IU/l)	Clomiphene Citrate	5.6±3.7	0.10
	Letrozole	7.3±3.2	
Thyroid Stimulating Hormone (mIU/l)	Clomiphene Citrate	3.2±3.5	0.19
	Letrozole	2.2±0.9	

P<0.05-significant

Table 2: Efficacy parameters of drugs for infertility

Parameter		Clomiphene citrate (24)	Letrozole (21)	p-value
Follicle size (≥18 mm)		20 (83.3%)	13 (61.9%)	0.10
mean Endometrial thickness (mm)		7.6±1.3	8.3±2.1	0.18
Ovulation		11 (45.8%)	10 (47.6%)	0.90
Pregnancy		10 (41.7%)	6 (28.6%)	0.36
Cycle of conception	Cycle 1	2 (20%)	3 (50%)	0.53
	Cycle 2	2 (20%)	1 (16.7%)	0.63
	Cycle 3	2 (20%)	1 (16.7%)	0.63
	Cycle 4	4 (40%)	1 (16.7%)	0.20

P<0.05-significant

Table 3: Safety parameters of drugs for infertility

Parameter	Clomiphene citrate (24)	Letrozole (21)	p-value
Polycystic ovaries	3 (12.5%)	0	0.09
Gastric upset	5 (20.8%)	2 (9.5%)	0.30
Multiple pregnancy	1 (4.2%)	0	0.34
Hot flushes	6 (25%)	1 (4.8%)	0.06
Nausea	2 (8.3%)	5 (23.8%)	0.15
Diarrhoea	3 (12.5%)	6 (28.6%)	0.18
OHSS	0	0	0

P<0.05-significant

DISCUSSION

Infertility is a global issue that has an impact on many elements of life of both genders [12]. Among various causes of infertility, anovulatory dysfunction accounts for about 40% of female infertility [11]. A well-coordinated hypothalamo-pituitary ovarian axis is essential for normal ovulation [13]. Anovulatory dysfunction is amenable to treatment by drugs such as gonadotropins, GnRH agonists, clomiphene citrate and letrozole [5]. Outcome of any infertility treatment is dependent on various prognostic factors like maternal age, duration of infertility, primary infertility, number of mature follicles, endometrial thickness, mature follicle size, sperm motility, the drug type and estrogen level on the day of hCG administration [14].

Women's fertility declines as they get older. Rising maternal age and declining success in conceiving, both naturally and following IVF, are clearly correlated [15, 16]. Oocyte competence and ovarian reserve both deteriorate with Advanced Maternal Age (AMA) (age>35 y) [17]. In our study, mean maternal age and period of infertility in CC group were 31.8 y and 4.2 y, while in letrozole group were 32.5 y and 3.2 y respectively. There were a total of 10 women with advanced maternal age in this study. Out of which 4 were treated with CC and the remaining 6 were given letrozole. Among them 2 conceived in CC while 1 conceived in letrozole group.

Clomiphene citrate has been the most commonly used drug for ovulation induction [18]. It is an antiestrogen, which causes an increase in the pulsatile production of LH and FSH in anovulatory individuals by suppressing the negative feedback on endogenous oestrogen at the level of the hypothalamus-pituitary [19]. However, 15-20% patients are resistant to CC [1]. Also it has a negative impact on the endometrium and may cause a reduction in endometrial thickness [20]. Low implantation rates and early pregnancy loss due to luteal phase defect are both linked with the improper development of the endometrium [21].

Letrozole is a highly potent aromatase inhibitor which has selective and competitive action [5]. It inhibits the rate-limiting step of oestrogen synthesis which is catalysed by a cytochrome P-450 hemoprotein-aromatase [12]. It was postulated that the hypothalamo-pituitary axis would be freed from estrogenic negative feedback by inhibiting aromatization, the conversion of androstenedione and testosterone into estrogen in the ovary. As a consequence of which, there is increased FSH release which in turn stimulates the growth of ovarian follicle [1].

Ovulation cannot occur if follicle size is too large or too small. Optimum follicle size which results in ovulation is 16-22 mm as per the existing data [23]. In our study, Clomiphene citrate treated patients had higher number of mature follicles (≥18 mm) than letrozole treated patients. However the difference seen was not statistically significant. Study by Badawy *et al.* [10] reported similar findings while study by Pandya and Patel [24] reported significantly higher number of mature follicles in letrozole group.

We observed a higher ovulation rate in letrozole (47.6%) treated patients compared to the CC(45.8%) group, which was not significant. This is similar to the study by Jain S *et al.* [5] who reported better ovulation rates in letrozole group (81.65%) than clomiphene group (65.5%). This was in contrast to a study by Badawy *et al.* [10] who reported a higher ovulation rates in CC group (70.9%) than letrozole group (67.5%). Higher ovulation rate seen in letrozole treated patients is because of the fact that letrozole by preventing the conversion of androgens to estrogens, produces an environment that lacks estrogen and hence the pituitary is freed from negative feedback by estrogen [25].

For a successful implantation after ovulation induction by CC or letrozole, optimum endometrial thickness (ET) is a must [26]. There is no consensus about the minimum endometrial thickness which results in pregnancy. However, various studies have reported higher success rates when the ET is>7 mm [27]. In this study, endometrial thickness was greater in letrozole treated patients; however the difference was not statistically significant. This was similar to the observations of Ghomian *et al.* [28]. Khan S *et al.* [29] and Maji A *et al.* [11] reported greater endometrial thickness in letrozole group while Badawy *et al.* [10] reported greater ET in CC group. This may be explained by the fact that CC produces sustained depletion of endometrial estrogen receptors which did not improve even by supplementing estrogen [5, 30].

In our study, Clomiphene citrate treated patients had higher conception rate than letrozole treated patients. However the difference seen was not statistically significant. Pandya and Patel [24] also reported a higher conception rate in letrozole group but the difference was not statistically significant. Generally, conception should result within five treatment cycles. Beyond that, pregnancy rate is lower because the cohort of women remaining represents the harder to obtain pregnant cases [26]. In general, women undergoing infertility treatment with ovulation inducing agents are supposed to conceive within five treatment cycles, otherwise there will be poorer response in later cycles. Majority of CC treated patients (40%) conceived in cycle 4 while majority of letrozole treated patients (50%) conceived in cycle 1. Jain S *et al.* [5] reported that 50% patients each in letrozole and CC groups conceived in cycle 3.

Gastric upset and hot flushes were more common in patients who received CC. Nausea and diarrhoea were more common in patients who received letrozole. 12.5% patients developed polycystic ovaries in CC treated patients while none in letrozole group. Multiple pregnancies and ovarian hyperstimulation syndrome were not encountered in any of the patients treated with either CC or letrozole.

The limitations of the study was that, the study was conducted at a single tertiary care centre with limited sample size. Hence the results of the study cannot be generalized.

CONCLUSION

From our study we found that, letrozole produced less number of mature follicles than clomiphene citrate but it had a much better effect on endometrial thickness and a higher ovulation rate than clomiphene citrate. But the differences observed were not statistically significant. Thus we conclude that both letrozole and clomiphene citrate were equally efficacious in ovulation induction and did not cause any serious adverse effects. Yet, in order to prove the letrozole's benefit over CC, we need to conduct larger, well designed, randomised multicentric trials involving diverse populations.

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AUTHORS CONTRIBUTIONS

The authors confirm contribution to the paper as follows: study conception and design: Swetha K and Manasa M. R; data collection: Swetha K, Manasa M. R, Naresh T Pawaskar, and Amruta C; analysis and interpretation of results: Swetha K and Manasa M. R; draft manuscript preparation: Swetha K and Manasa M. R. All authors reviewed the results and approved the final version of the manuscript.

CONFLICT OF INTERESTS

Declared none

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