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Efficacy of clomiphene citrate versus letrozole in attaining optimum follicular growth.

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ABSTRACT... Objectives: To compare the efficacy of clomiphene citrate versus letrozole in attaining optimum follicular growth among infertile women of reproductive age group in Isra University Hospital Hyderabad. **Study Design:** Randomized Controlled trial. **Setting:** Department of Obstetrics and Gynecology, Isra University Hospital Sindh, Pakistan. **Period:** May 2016 to November 2016. **Material & Methods:** A total of 128 women with anovulation due to known endocrine disorders were included in this study. These were randomly allocated in group 1 and 2. Group 1 consisted of 64 women received 50mg of clomiphene citrate and 64 in group 2, treated with letrozole. Proformas were filled and results regarding the drug achieving follicular diameter of >18mm by Trans abdominal Ultrasound in maximum number of women in any of the group was supervised by consultant gynecologist practicing for more than 10 years. Stastical analysis was done using SPSS version 19.The average age of women was 27.21+3.21. Number of patients with primary infertility were 60 (93.8%) and 57 (89.1%) in group 1 and 2 respectively while secondary infertility was observed in 4 (6.3%) and 7(10.9%) in group 1 and 2 respectively. Regarding endocrine disorders, 34 (26.6%) were polycystic ovaries and 35(27.3%) hypothalamic. **Results:** The average age of women was 27.21±3.21 years. Efficacy was significantly high in clomiphene citrate (group 1) as compared to letrozole (group 2) [92.19% vs 79.69%; p=0.042]. **Conclusion:** This study demonstrates that clomiphene citrate is superior to letrozole as an inducer of ovulatory cycles. However there is need for larger well designed randomized trials to generate robust data in order to establish the true potential of clomiphene.

Key words: Clomiphene Citrate, Infertile Women, Letrozole, Optimum Follicular Growth.

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INTRODUCTION

Infertility is defined as inability of the couple to conceive atleast 12 months after unprotected sexual intercourse that is without using any birth control methods. As per study, published at the end of 2012 by WHO, one in every four couples in developing countries had been found to be affected by infertility.[1] Primary infertility is defined as couples unable to conceive after at least 1 year regular intercourse during fertile days without using any birth control methods. The term secondary infertility is for couples who have been able to conceive at least once whatever is the outcome of pregnancy but now are unable. Infertility is of concern since ages as it affects 10_15% of reproductively active couples despite rapidly growing world population. The causes of primary infertility are mainly male factors either due to ejaculatory problems, autoimmune and endocrinological disorders or chromosomal anomalies (20%-25%), anovulation (15%-20%) and endometriosis (5_10%). The causes of secondary infertility are tubal defects (15%-40%), endometriosis and unknown etiology in most of the cases despite all normal clinical findings and laboratory investigations (20%-30%).[2] Pakistan is one of the most populous country of the world with a high fertility rate, still infertility affects 30% of Pakistani population with prevalence of primary and secondary infertility 5% and 18% respectively.[3] The higher prevalence of secondary infertility in Pakistan is due to early marriages, malnourishment, unsafe obstetric practices and higher prevalence of anaemia.

Identifiable factors affecting female infertility include hormonal or endocrine disturbances including polycystic ovaries, diabetes, subclinical and clinical thyroid disorders and obesity, distorted tubes due to endometriosis and pelvic inflammatory disease, mullerian agenesis or malformation including unicornuate uterus and uterine didelphys, sexual dysfunction due to vaginismus and vulval problems, imperforate hymen and transverse vaginal septum.[4] While infections are the leading cause of secondary infertility among woman in developing countries. Being a third world country Pakistani women get most of the infections by unsafe methods of termination of pregnancy, unsterilised instruments used during labour and delivery as well as sexually transmitted infections.[5]

Clomiphene citrate is an oldest drug used for induction of ovulation. It is the treatment of first choice in women with ovulatory disorders and in woman with unidentifiable cause of infertility as it is easily available and cost effective. It has central action on hypothalamus with both oestrogenic and anti-oestrogenic properties.[6] Aromatase is a member of the cytochrome P450 haemoprotein containing enzyme complex super family. It catalysis the rate-limiting final step in oestrogen production and the hydroxylation of androstenedione to oestrone and testosterone to oestradiol.[7] Approximately 60_ 80% of women ovulate while using clomiphene however, only 40% of women achieved pregnancy.[8] Letrozole has a pregnancy rate of 80%, which is due to its less anti estrogenic effect on endometrium that is it does not causes endometrial atrophy as its action is more specific.[9]

Other rare causes of infertility like hypogonadotrophic hypogonadism and uterine congenital Anomalies have other treatment modalities.

The aim of my study was to compare the efficacy of clomiphene citrate and letrozole in attaining optimum follicular growth in infertility associated with anovulation and endocrine disturbances.

MATERIAL & METHODS

This study was done in outpatient department of Isra hospital Hyderabad from May to November 2016.After taking approval from ethical committee, patients fulfilling the criteria were included in the study after taking informed consent. A detailed history was obtained from the infertile couple at first visit and couples not fulfilling inclusion criteria were excluded. Group 1 consisted of 64 women was received 50mg of clomiphene citrate from day 3 to day 7. Women who did not show optimum follicular growth, received 100 and 150mg of clomiphene citrate in subsequent cycle. In group 2, letrozole 2.5mg was used from day 3 to day 7 and followed similarly to group 1. Those, not showing optimum follicular growth was received 5 and 7.5mg of letrozole in subsequent cycles. Women were monitored by transabdominal ultrasound five days after the last dose. Both the groups were followed up for number of follicles, diameter of large follicle, endometrial thickness and serum estradiol levels. Data was entered and analyzed by using SPSS version 19. Mean and standard deviation were calculated for quantitative variables like age, height, weight, number of follicles, diameter of follicles, endometrial thickness and serum estradiol levels. Frequency and percentages were calculated for qualitative variables like smoking, hypertension, diabetes, endocrine disorders and efficacy.

RESULTS

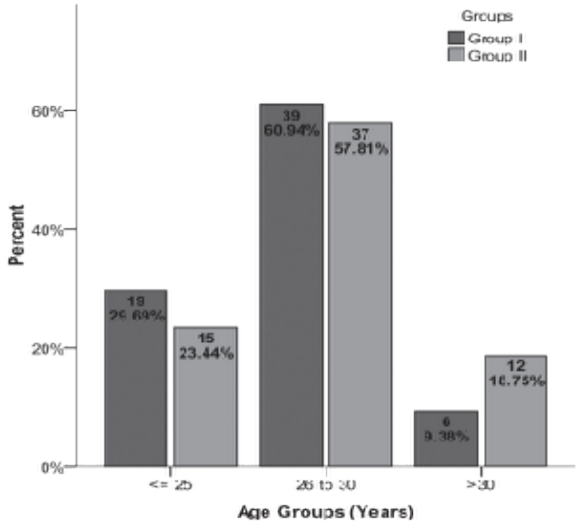
A total of 128 women with anovulation due to known endocrine disorders were included in this study. These were randomly allocated into group I and II. Group 1 consisted of 64 women, received 50mg of clomiphene citrate and 64 in group 2, treated with letrozole. The average age of the women was 27.21±3.21 years. The number of patients with primary infertility were 60(93.8%) and 57(89.1%) in group I and group II respectively while secondary infertility was observed in 4(6.3%) and 7(10.9%) in group I and II respectively as shown in Figure-1. Mean number of follicles was not significant between groups while mean diameter of follicles, endometrial thickness, serum estradiol levels was significant between groups as shown in Table-I. Comparison of efficacy of clomiphene citrate versus letrozole in attaining optimal follicular growth (>18mm) among infertile women of reproductive age group

is presented in Figure-2.

Efficacy was significantly high in clomiphene (group-I) as compared to letrozole (Group –II) [92.19% vs. 79.69%; p=0.042].

DISCUSSION

Clomiphene citrate is an oldest and long-standing, standard drug for ovulation induction and is still considered as first-line option in women with anovulation, endocrinological disorders and in unexplained infertility.[10] Mode of action of clomiphene citrate is to act on hypothalamus where it blocks oestrogen receptors, stimulates FSH and LH secretion thus increases formation of ovarian follicles.



Figur-1. Age distribution of the patients with respect to groups [n=128].

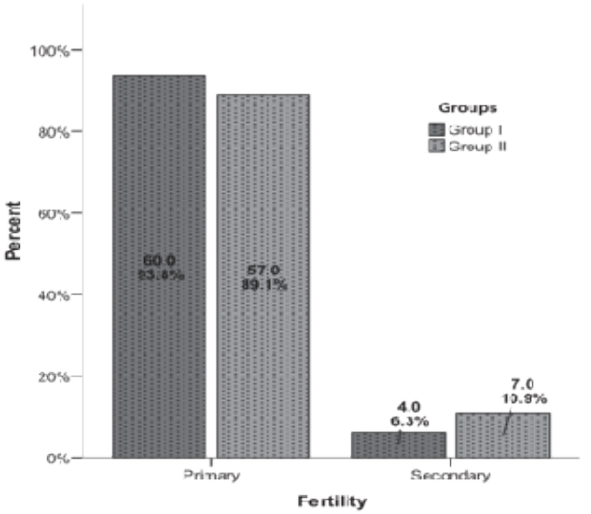


Figure-2. Fertility distribution of the patients with respect to groups [n=128].

	Group I n=64	Group II n=64	P-Value		
	Mean	Std. Deviation	Mean	Std. Deviation	
Number of follicles	1.98	0.724	1.77	0.66	0.076
Diameter of follicles (mm)	21.59	2.62	20.59	2.34	0.024
Endometrial thickness (mm)	7.16	1.275	8.44	1.05	0.0005
Serum estradiol levels	476.23	197.97	271.72	44.03	0.0005

Table-I. Comparison of response to ovulation between groups.

Age Groups (Years)	Efficacy	Group I	Group II	P-Value		
		n	%	N	%	
≤25	Yes No Total	18 1 19	94.7% 5.3%	13 2 15	86.7% 13.3%	0.571
26 to 30	Yes N Total	36 3 39	92.3% 7.7%	30 7 37	81.1% 18.9%	0.186
>30	Yes No Total	5 1 6	83.3% 16.7%	8 4 12	66.7% 33.3%	0.615

Table-II. Compare the efficacy between groups in attaining optimal follicular growth (>18mm) stratified by age of the women [n=128].

Endocrine Disorder	Efficacy	Group I	Group II	P-Value		
		n	%	N	%	
Polycystic ovaries	Yes No Total	11 1 12	91.7% 8.3%	18 4 22	81.8% 18.2%	0.635
Hypotha lamic	Yes No Total	14 2 16	87.5% 12.55	16 3 19	84.2% 15.8%	0.99
Pituitary	Yes No Total	15 0 15	100% 0%	11 3 14	78.6% 21.4%	0.100
Thyroid disor-der s	Yes No Total	19 2 21	90.5% 9.5%	6 3 9	66.7% 33.3%	0.143

Table-III. Compare the efficacy between groups in attaining optimal follicular growth (>18mm) stratified by endocrine disorder [n=128].
Fisher Exact test used

Multiple follicles can lead ta women to have multiple pregnancies and its antiestrogenic effects cause's endometrial atrophy. It is also used in artificial reproductive procedures during follicular phase. Letrozole is an orally-active aromatase inhibitor. It prevents aromatase from producing oestrogen by binding to the heme of its cytochrome P450. Letrozole is mainly used after failure of clomiphene citrate to induce ovulation post 3 or 6 months use. It has specific action hence endometrium and cervical mucus production is not affected. Letrozole has been shown to have good ovulation rate in woman with endocrinological disorders.[11] Side effects of letrozole includes hot flashes, joints and bone pain, tiredness and night sweats.

In present study mean **n**umber of follicles was not significant between groups while mean diameter of follicles, endometrial thickness, serum estradiol levels were significant between groups. According to Badawy et al. letrozole has an ovulatory rate of 62%.[12] In another trial, Mitwally and Casper shows letrozole ovulatory rate of 75%.[13] Al- Omari et al defines an ovulatory rate of 87.5%[14], whereas Elnashar et al reported an ovulation rate of 54.6%.[15]

This may be explained by the small sample size in present study. Pregnancy was achieved in 53% in group A and 58% in group B, which is not comparable to 12.2% reported by Badawy et al. for letrozole; the miscarriage rate was similar in both of groups. In this study efficacy was significantly high in clomiphene (group I) as compare to letrozole (Group –II) [92.19% vs. 79.69%; p=0.042]. Requena et al[16] in their literature review looked at randomized trials comparing letrozole versus clomiphene as first line therapy and included four studies.[17] The ovulation rate for letrozole in comparison with clomiphene did not differ significantly (OR 1.7; 95% CI 0.66 - 2.09) nor did the pregnancy rate per patient (OR 1.37; 95% CI 0.70 - 2.71).

CONCLUSION

Our study showed statistically significantly higher pregnancy rates when clomiphene was used as ovulation induction drug in infertile women. Letrozole leads to production of monofollicles and hence here are less chances of having multiple pregnancy as compared to Clomiphene citrate. Overall, this study demonstrates that Clomiphene is superior to Letrozole as an inducer of ovulation cycles.

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