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ORIGINAL ARTICLE

Unexplained Infertility: Comparison of Efficacy of Letrozole and Clomiphene Citrate

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ABSTRACT

Background: Infertility is always been considered as social issue because of its impact on individuals as well as on families. Unexplained infertility defined as inability of a couple to conceive after one year of unprotected intercourse even in the absence of any specific reason for it.
Aim: To compare the efficacy of letrozole and clomiphene citrate among patients presenting with unexplained infertility
Study design: Prospective observational study.
Place and duration of study: Department of Obstetrics & Gynecology, Sheikh Zayed Women Hospital Larkana from 1st January 2020 to 31st December 2020.
Methodology: Three hundred and thirty six women having unexplained infertility were randomly allocated into two groups. One hundred and sixty eight patients in group A were given letrozole 2.5mg and 168 women in group B received clomiphene citrate 50mg for three months with successive increase in dose up to 3 cycles, if not conceived in first cycle. They were assessed for pregnancy after 4, 8 and 12 weeks of treatment.
Results: The average age of the patients was 27.01±2.53 years. Efficacy of letrozole was significantly high as compare to clomiphene citrate [82.1%vs.62.5%;p=0.0005].
Conclusion: The efficacy of letrozole was significantly high as compared to clomiphene citrate. Letrozole is a better alternative for ovulation induction in anovulatory women because it has high pregnancy rates with shorter time to pregnancy and chances of multiple pregnancies are less because of high monofollicular growth.
Keywords:-Infertility, Clomiphene citrate, Letrozole, Unexplained infertility.

INTRODUCTION

Infertility is a global problem which creates intense societal and fanatical repercussions for the couples experiencing. In fertility is defined as inability of a couple to conceive after one year of unprotected intercourse, which is prevalent in about21.9% in Pakistan.[1]

Unexplained infertility refers to the absence of a definable cause for a couple's failure to achieve pregnancy after 12 months of attempting conception (despite a thorough evaluation), or after six months in women 35 and older.[2] Infertility is usually caused by either problem with ovulation or due to semen abnormalities but there are around 10% and 30% of infertile couples diagnosed with unexplained infertility, but no proper protocols of treatment are opted for them yet so far.[3]Desperate infertile couples frequently change physicians in order to achieve pregnancy by any medicine whatever they are prescribed, especially when they are diagnosed to have unexplained infertility. In women in their late reproductive age, infertility is possibly caused by availability of either the less number but also poor quality follicles. Therefore, based on certain experiences, induction of ovulation has been giving good results in not only achieving pregnancy but also has impact on improving cumulative live birth rates[4].

Clomiphene citrate (CC) has been used as easily available oral drug since years for induction of ovulation which acts by blocking estrogen receptors and thus enhancing follicle stimulating hormone and subsequently ovulation. Another salt which was initially used for treating women with breast cancer, letrozole has also been found safe and useful agents for ovulation induction in patients with unexplained infertility.[5] Letrozole belonging to aromatise inhibitor family has been introduced as a new choice for ovulation induction in the recent past and is being used for ovarian stimulation in women with unexplained infertility as it has fewer side effects in comparison to clomiphene citrate and also there are less chance of multifetal gestations.[6] Letrozole is seen with promising results in pregnancy rates when compared to injectable gonadotropins equivalent to, at lower cost and with fewer adverse effects[7,8]. As infertility is a condition which is multi-faceted and has many effects not only on couple, but whole of the family. Therefore, determining the best efficacious medicine as its treatment is need of the hour. This study will help us to find better drug for patients within fertility in our population. Also there is minimal literature available on this topic in Pakistan, so our study results will add on evidence for treatment of infertility. If one drug is found better than the other, we may use it regularly in our population even in age group of21-30 years because this is the potential age mostly presenting to us. Previously, no study has particularly considered this age for treatment modalities of unexplained infertility.

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MATERIALS AND METHODS

We conducted descriptive study after permission from IRB in OPD of Obstetrics & Gynecology Sheikh Zayed Women Hospital Larkana from 1st January 2020 to 31st December 2020. A sample size of 336 patients (168 in each group) calculated taking level of significance as 5%, power of test as 90% through non-probability, consecutive sampling. All women attending outpatient department, who had all clear test as per record and declared as having unexplained infertility were taken for study after Informed consent. Approval from Ethical Review Board of the hospital was obtained. Their demographic details including age, BMI (weight(kg)/ height (meters), socioeconomic status and family history of infertility in siblings was obtained. Patients were kept into two groups: group A (Letrozole) and groupB (Clomiphene Citrate). They were assured regarding confidentiality and expertise of the physician and educated for an anticipated better outcome. Patients in group A received Letrozole starting from 2.5 mg reaching maximum to 7.5mg, while patients in group B received maximum of 150 mg of CC daily (started from 50 mg) for 5 days taken from day 3 of the menstrual cycle for three cycles. They were assessed for pregnancy after 4 weeks of treatment 8 weeks and 12 weeks. Treatment was given for 3 consecutive cycles, but they were followed till six months because few patients even reported after six months of treatment. All data was recorded

The collected data was entered and analyzed accordingly using SPSS-21. Efficacy was compared in both groups using Chi-square test. P-value ≤0.05 was considered as significant.

RESULTS

The average age of the patients was 27.01±2.53 years. Mean age, weight, height and BMI of the women according to groups are reported in Table 1. More than half of the women were belonged to lower middle socio economic status in both groups. Family history of infertility in siblings was noted in16.07% and 23.21% in group A and group B respectively.

Comparison of the efficacy of letrozole and clomiphene citrate among patients presenting with unexplained infertility is shown in table 2. Efficacy of letrozole (groupA) was significantly high as compare to clomiphene citrate (group B) [82.1%vs.62.5%;p=0.0005]. Stratification analysis according to age groups, BMI, socioeconomic status and history of infertility in sibling were observed but efficacy of letrozole (group A) was significantly high as compare to clomiphene citrate (group B) in obese as presented in Figure 1.

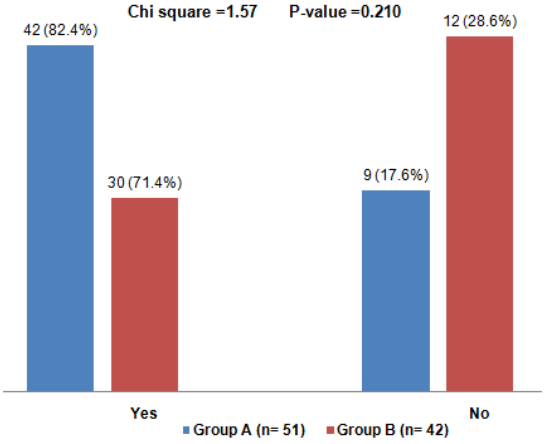
Table 1: Demographic characteristics according to groups

Variable	Group A	Group B
Age (years)	26.64±2.66	27.38±2.35
Weight (kg)	74.29±17.34	75.40±19.29
Height (cm)	164.37±10.43	163.46±9.59
BMI (kg/m^2)	27.47±5.52	28.07±6.11

Table 2: Comparison the efficacy of letrozole and clomiphene citrate among patients presenting with unexplained infertility

Efficacy	Group A	Group B	P value
Yes	138(82.1%)	105(62.5%)	0.0005
No	30(17.9%)	63 (37.5%)	

Fig. 1: Comparison the efficacy of and clomiphene citrate and letrozole among patients presenting with unexplained infertility in obese women



DISCUSSION

Unexplained infertility (UI) is the type of infertility which is affecting around 15-30% of all cases and the diagnosis is declared when both partners show no abnormality in their required parameters, thus the treatment is usually based on rationale basis addressing couples at a time.[9]

Since long time, clomiphene citrate (CC) had been used as the first line of treatment for ovulation induction in these infertile women but most of the time it has been found as having chances of multiple pregnancy and hyper stimulation of ovaries[10] Letrozole (LE), works in a way to decrease estrogen synthesis is used as effective as injectable gonadotrophins and traditional clomiphene citrate. Therefore letrozole is found with desirable effect on endometrium promoting implantation and improving pregnancy rates[11-13].

In this study, we comparatively observed efficacy of letrozole with clomiphene citrate in women with unexplained infertility when they were prescribed both drugs. In our study, the average age of the patients was 27.01±2.53 years and BMI was also 27 which is comparable to study done by Sakhavar et al[14] where mean age was 26.4±3.2 (20-33) and mean BMI 26.3±3.2 while study done by Eskew et al study[15] the mean age of patients was between 23.5 and 33.4 years, and mean BMI was between 23.8 and 30.

Compared with CC, LE is involved in a thickerendometrium[12] which promotes implantation successfully. In this study, efficacy of letrozole was significantly high as compared to clomiphene [p=0.0005]. The same result is reported in one study done Atay et al[16] on their patients, where they also found high pregnancy rates in letrozole group than the clomiphene group. Another trial study done by Kamath[17] favoured the use of letrozole due to its better efficacy. However, in Badawy[18] and Qin et al study[19] found no significant difference between CC group and LE group as far as ovulation is concerned but he concluded favoring letrozole in monofollicular growth which optimally result in prevention of higher order multifetal pregnancies. Further larger multicentric trials are required to comprehend the results.

Although in our study, women denied having taken previously any medicine for ovulation induction but there are studies done, where women resistant to clomiphene citrate 100mg were given high dose of letrozole 7.5mg and amazingly 62.5% women responded with ovulation in comparison to control group who were given 150mg of clomiphene (37.5%) begum et al[20] We noticed in our study, successively increased the dose of both drugs but one study has even supported use of 2.5mg as achieving high pregnancy rate.[21] Mono ovulation is far better in many patients specially in women with polycystic ovarian syndrome and this was also one of many reasons to prefer letrozole over clomiphene citrate.

CONCLUSION

The efficacy of letrozole was significantly high as compared to clomiphene citrate. Letrozole is an empirical better option for ovulation induction in women with unexplained infertility and it works amazingly in achieving pregnancy. There are very less chance of multiple pregnancies because of high monofollicular growth. Trials with letrozole in patients with unexplained infertility should be done in low resourced cities and in those who cannot afford the cost incurred on assisted reproduction techniques.

Conflict of interest: Nil

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