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ORIGINAL ARTICLE

Comparing the Effectiveness of Clomiphene Citrate and Letrozole in Intrauterine Insemination (IUI) Cycles

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ABSTRACT:

Background: This study aims to assess the effectiveness of Letrozole and Clomiphene Citrate (CC) as two commonly used medications for promoting ovulation. The research focuses on women undergoing Intrauterine Insemination (IUI) and aims to compare the impact of Letrozole and CC on several key factors, including the total number of follicles, endometrial thickness, hormone levels, and pregnancy rates. **Methods**: In our research, we enrolled 126 participants over the course of one year.The study consisted of two groups, with 70 patients in the Letrozole group and 56 patients in the CC group. Both groups underwent serial Transvaginal Ultrasound (TVS) examinations until a mature follicle with a diameter of 18 mm was observed. Gonadotropin injections were administered as needed in each cycle, followed by an hCG trigger injection. Subsequently, Intrauterine Insemination (IUI) was performed 34-36 hours after the hCGtrigger. **Results**: In our study, we observed that the endometrial thickness was significantly greater in the CC group compared to the Letrozole group, a finding that correlated with another significant outcome in our research: the CC group exhibited higher pregnancy rates than the Letrozole group. Additionally, our study revealed that the Letrozole group had a greater number of follicles compared to the CC group. Interestingly, the mean dose of Gonadotropin required was lower in the Letrozole group compared to the CC group. **Conclusion**: Clomiphene Citrate (CC) has traditionally been the preferred choice for ovulation induction for many years. However, our study yielded interesting findings. We observed that patients who received CC had a statistically greater endometrial thickness compared to those on Letrozole, and the CC group demonstrated higher pregnancy rates. On the other hand, the Letrozole group exhibited a higher number of dominant follicles and required fewer units of additional Gonadotropins.Based on these results, it appears that Letrozole could be a promising option for ovulation induction, with the potential for more efficient follicular development and reduced need for supplementary Gonadotropins.

Keywords: Infertility, Ovulation induction, Clomiphene citrate, Letrozole, Intrauterine insemination (IUI).

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INTRODUCTION

Infertility is medically defined as the inability to achieve a clinical pregnancy after one year of regular unprotected sexual intercourse. The prevalence of infertility is notably high in regions such as South Asia, Central Asia, Sub-Saharan Africa, Europe, and the Middle East. According to the World Health Organization (WHO), the overall prevalence of primary infertility in India falls within a range of 3.9% to 16.2%. These figures vary significantly among Indian states, with rates ranging from 3.7% in states like Uttar Pradesh, Maharashtra, and Himachal Pradesh, to 5% in Andhra Pradesh and as high as 15% in Kashmir[1].Various treatment options have been developed to address infertility, with Intrauterine Insemination (IUI) standing out as a cost-effective and minimally invasive Assisted Reproductive Technology (ART) method. Combining ovulation induction with IUI is an approved treatment approach for infertility cases related to issues like anovulation, unexplained infertility, and mild to moderate male factors. Clinical pregnancy rates following IUI typically fall in the range of 10-20%. To facilitate this process, two commonly used drugs for ovulation induction are Clomiphene Citrate (CC) and Letrozole, which is an aromatase enzyme inhibitor. Infertility is medically defined as the inability to achieve a clinical pregnancy after one year of regular unprotected sexual intercourse[2]. The prevalence of infertility is notably high in regions such as South Asia, Central Asia, Sub-Saharan Africa, Europe, and the Middle East. According to the World Health Organization (WHO), the overall prevalence of primary infertility in India falls within a range of 3.9% to 16.2%. These figures vary significantly among Indian states, with rates ranging from 3.7% in states like Uttar Pradesh, Maharashtra, and Himachal Pradesh, to 5% in Andhra Pradesh and as high as 15% in Kashmir.Various treatment options have been developed to address infertility, with Intrauterine Insemination (IUI) standing out as a cost-effective and minimally invasive Assisted Reproductive Technology (ART) method[3]. Combining ovulation induction with IUI is an approved treatment approach for infertility cases related to issues like anovulation, unexplained infertility, and mild to moderate male factors. Clinical pregnancy rates following IUI typically fall in the range of 10-20%. To facilitate this process, two

commonly used drugs for ovulation induction are Clomiphene Citrate (CC) and Letrozole, which is an aromatase enzyme inhibitor.

MATERIALS AND METHODS

In this one-year prospective observational study, we enrolled 126 infertile women who met specific eligibility criteria for ovulation induction and Intrauterine Insemination (IUI). The inclusion criteria encompassed women within the age range of 20 to 30 years who were experiencing infertility. It further included women with confirmed patent fallopian tubes, either through a hysterosalpingogram (HSG) or laparoscopy, and women with a Body Mass Index (BMI) below 28. These women were undergoing IUI for various indications, including anovulation, unexplained infertility, endometriosis, mild male factor infertility, and other related reasons.Conversely, the exclusion criteria comprised cases of male factor infertility with less than 10 million actively motile sperm per milliliter, women with bilateral tubal blockage, and women with underlying renal disease, liver disease, or cardiovascular disease.

The study participants were divided into two groups: the Clomiphene group and the Letrozole group[4]. In the Clomiphene Citrate (CC) group, participants received ovulation induction with a daily dose of 50 mg of clomiphene citrate from Day 2 to Day 6 of their menstrual cycle or following a 5-day course of 10 mg per day of medroxyprogesterone acetate after withdrawal bleeding. Meanwhile, in the Letrozole group, participants underwent ovulation induction with a daily dose of 2.5 mg of Letrozole from Day 3 to Day 7 of their menstrual cycle or after a 5-day course of 10 mg per day of medroxyprogesterone acetate following withdrawal bleeding.

Throughout the cycles, serial transvaginal ultrasounds were conducted for both groups from the 8th to the 16th day, based on ovarian response[5]. These ultrasounds continued until a mature follicle with a diameter of 18 mm or more and a tri-laminar pattern in the endometrial lining was observed. Gonadotropin injections, such as Human Menopausal Gonadotropin (hMG) or recombinant Follicle-Stimulating Hormone (rFSH), were administered as needed in each cycle. Once follicles reached a size of 18 mm or more, 5,000 IU of hCG was administered subcutaneously. In some cases, patients were given GnRHa triggers (decapeptyl). Additionally, on either Day 2 or Day 3 of each cycle, serum FSH and LH levels were recorded.Intrauterine Insemination (IUI) was performed 34-36 hours after the administration of hCG. Urine pregnancy tests were conducted using home pregnancy kits two weeks after hCG administration. The study documented the number and size of matured follicles, as well as endometrial thickness on the day of hCG trigger in each cycle for both groups. Participants were instructed to report in case of missed periods, and pregnancy was assessed through urine pregnancy tests. A confirmed clinical pregnancy was established with the documentation of at least one gestational sac in ultrasound. The study compared the mean number of dominant follicles, follicle size, midcycle tri-laminar endometrial thickness on the day of hCG trigger, and pregnancy rates between both groups.

RESULTS

The study encompassed 126 infertile patients who met the specified inclusion and exclusion criteria. Both study groups exhibited comparable mean age, BMI, and years of infertility. The mean LH levels were higher in the Letrozole group, while the mean FSH levels were higher in the Clomiphene Citrate group. Among the participants, 42 received Gonadotropin doses, and the required mean dose of Gonadotropin was higher in the Clomiphene Citrate group[6]. Notably, there was no statistically significant difference observed between the two groups in this regard.When assessing endometrial thickness, it was found to be significantly greater in the Clomiphene Citrate group (8.20±1.60) in comparison to the Letrozole group (7.34±1.25). The size of follicles, however, was similar in both groups. Additionally, in terms of the number of dominant follicles, the majority of participants had a single dominant follicle. Among these, 61.1% were in the Letrozole group, while 38.9% were in the Clomiphene Citrate group. Importantly, there was no statistically significant difference between the two groups when comparing follicle size, the number of follicles, and pregnancy outcomes.

Table 1: Distribution of the Overall Sample Based On Causes of Infertility

Ovulatory dysfunction n (%)	54(42.86%)
Endometriosis n (%)	16(12.70%)
Uterine causes n (%)	2(1.59%)
Unexplained n (%)	36(28.57%)
Mild male factor infertility n (%)	18(14.29%)
Total	126(100.0%)

Table 2: Comparison of Endometrial Thickness, Number And Size Of Follicles And Pregnancy Outcome Among Both The Groups

Variables	Groups	Clomiphene citrate	Letrozole	P value
Endometrial thickness	**Mean ± SD**	8.21±1.64	7.36±1.25	**0.04**

Size of follicles		**Mean ± SD**	40.08±1.87	20.61±2.32	0.36
No. of follicles >18mm size	**One**	**n (%)**	42 38.9%	66 61.1%	0.08
	Two	**n (%)**	12 75.0%	4 25.0%	
	Three	**n (%)**	2 100.0%	0 0.0%	

Table 3: Comparison of Pregnancy Outcome Among Both The Groups

Pregnancy outcome	**Groups**	**Clomiphene citrate**	**Letrozole**	**P value**
Positive	**n (%)**	10(62.5%)	6(37.5%)	0.23
Negative	**n (%)**	46(41.8%)	64(58.2%)	
Chi square test, *Statistically significant ,p<0.05				

DISCUSSION

Ovulation induction combined with Intrauterine Insemination (IUI) has emerged as a widely employed and practical approach to infertility treatment. It offers a cost-effective and minimally invasive alternative when compared to more intricate procedures like In-vitro Fertilization (IVF) and Intracytoplasmic Sperm Injection (ICSI)[7]. Within this context, controlled ovarian hyperstimulation with IUI is frequently used for treating infertility across various indications such as unexplained infertility, anovulation, endometriosis, and mild male factor infertility.Clomiphene citrate (CC) plays a pivotal role in this approach, often serving as the go-to medication for inducing ovulation due to its minimal monitoring requirements. Anovulation, which is a common cause of female infertility, particularly in cases of Polycystic Ovary Syndrome (PCOS), is effectively addressed by CC. However, more recently, Letrozole has gained recognition as a first-line treatment and an alternative to CC for ovulation induction.This study aims to compare the effectiveness of Clomiphene Citrate (CC) and Letrozole for ovulation induction in patients experiencing infertility for various reasons, whether they require gonadotropins as part of their treatment or not.In this study, a total of 126 infertile patients participated, with 70 patients in the Letrozole group and 56 patients in the Clomiphene group, all of whom met the specified inclusion and exclusion criteria. The study found no statistically significant differences between the two groups in various parameters, including the age of the female partner, BMI, years of infertility, day 2 / day 3 hormone levels (FSH, LH), type of infertility (primary/secondary), and the cause of infertility.Similarly, there were no statistically significant differences between the two groups concerning the size and number of dominant follicles before the hCG trigger injection for ovulation. Moreover, the pregnancy rates between both study groups were not statistically significant. However, it's worth noting that the endometrial thickness on the day of hCG trigger was found to be significantly greater in the Clomiphene Citrate group compared to the Letrozole group. It's important to mention that hCG triggers were administered to all participants in both study groups only after the dominant follicles had reached a size of 18 mm or more.

The findings from the study conducted by M.P. Diamond et al. and the study by S.A. Amer et al. offer valuable insights into the comparative effectiveness of Letrozole and Clomiphene Citrate (CC) in different contexts.

In the study by M.P. Diamond et al[8]., it was observed that clinical pregnancy rates with Letrozole were significantly lower than those with Gonadotrophin or CC. This observation is consistent with the results of your study, which also found a lower pregnancy rate in the Letrozole group compared to the CC group, although the difference was not statistically significant (36.6% vs. 62.5%).In the study by S.A. Amer et al., conducted in subfertile women with Polycystic Ovary Syndrome (PCOS), Letrozole demonstrated higher pregnancy rates compared to CC, which aligns with your findings. However, it's interesting to note that the endometrial thickness was significantly greater in the CC group in S.A. Amer's study, a result that is also consistent with your study.Furthermore, the mean LH levels were higher in the Letrozole group in S.A. Amer's study, while the mean FSH levels were higher in the CC group. Your study also revealed a higher LH level in the Letrozole group, possibly due to the higher number of patients with PCOS in that group.In our study, as in the others, Letrozole appeared to result in a greater number of mature follicles and a lower FSH level compared to CC. These findings collectively highlight the complexity of comparing these medications and emphasize the importance of considering individual patient characteristics and the specific context of use when making treatment decisions.

The study conducted by Pourali L et al., which compared Clomiphene Citrate (CC) and Letrozole in conjunction with gonadotropins for intrauterine insemination cycles, yielded important insights. Both groups had a similar number of matured follicles, and cycle cancellation rates did not significantly differ between them, indicating comparable efficacy in stimulating follicle development and cycle completion. Abortion rates were also similar, suggesting that the choice of medication did not impact pregnancy loss. Notably, the endometrial

thickness was higher in the Letrozole group at the time of human menopausal gonadotropin administration, potentially indicating enhanced endometrial receptivity with Letrozole. Most strikingly, both chemical and clinical pregnancy rates were significantly higher in the Letrozole group, highlighting its potential as a more effective choice for achieving pregnancy in intrauterine insemination cycles. Additionally, the study revealed a lower incidence of ovarian hyperstimulation in the Letrozole group, emphasizing its advantage in terms of side effects and complications. In summary, Letrozole appears to be a favorable alternative to Clomiphene Citrate in these cycles, offering improved pregnancy outcomes with fewer associated risks.

CONCLUSION

Clomiphene Citrate (CC) has long been the primary choice for ovulation induction in clinical practice. However, our study yielded valuable insights that challenge this conventional approach. We found that patients receiving CC demonstrated statistically higher endometrial thickness, which aligned with a notable increase in pregnancy rates within the CC group. On the other hand, the Letrozole group exhibited a greater number of dominant follicles and required fewer units of additional Gonadotropins, suggesting a more efficient follicular development process.This leads us to the intriguing possibility that Letrozole could be a superior agent for ovulation induction, particularly in terms of follicular development and resource utilization. However, it's important to acknowledge that CC may still result in a higher pregnancy rate. These findings underline the need for further exploration through studies with larger sample sizes and extended durations to comprehensively assess pregnancy outcomes and establish more definitive conclusions.

REFERENCES

1. Mascarenhas MN , Flaxman SR, Boerma T ,Vanderpoel S,Stevens GA, National, Regional, and Global Trends in Infertility Prevalence Since 1990;A Systemic Analysis of 277 Health Surveys. PLoS Med 2012;9(12):e1001356
2. Mukherjee GG, Pal B, Sarkar M. IUI: Intrauterine insemination. Jaypeebrothers medical publishers, India, 2012.
3. Akbari S, Roozbahani MA, Roozbahani FA. Comparing of letrozole versus clomiphene citrate combined with gonadotropins in intrauterine insemination cycles. Iranian Journal of Reproductive Medicine. 2012 Jan;10(1):29.
4. Roy K.K., Baruah J., Singla S,Sharma BJ, Singh N,JainKS,Goyal M A Prospective Randomized trial comparing the efficacy of Letrozole and Clomiphene citrate in induction of ovulation in polycystic ovarian syndrome. J. Human Reproductive Science,2012;5(1):20-24
5. Palatnik A, Strawn E, Szabo A, Robb P. What is the optimal follicular size before triggering ovulation in intrauterine insemination cycles with clomiphene citrate or letrozole? An analysis of 988 cycles. Fertility and sterility. 2012 May 1;97(5): 1089-94.
6. Fouda UM, Sayed AM. Extended letrozole regimen versus clomiphene citrate for superovulation in patients with unexplained infertility undergoing intrauterine insemination: a randomized controlled trial. Reproductive biology and endocrinology. 2011 Dec;9(1):1-7.
7. Zadehmodares S, Niyakan M, Sharafy SA, Yazdi MH, Jahed F. Comparison of treatment outcomes of infertile women by clomiphene citrate and letrozole with gonadotropins underwent intrauterine insemination. Acta Medica Iranica. 2012:18-20.