Original Article

Evaluation of Pregnancy Rate in Polycystic Ovary Syndrome Patient with Effect of Letrozole Versus Clomiphene Citrate, Mirpur AJK

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ABSTRACT

Objective: The objective of this study to evaluate pregnancy rate in polycystic ovary syndrome patient with effect of letrozole versus clomiphene citrate, Mirpur AJK

Study Design: Cross-sectional study

Place and Duration of Study: This study was conducted at the Department of Obstetrics and Gynecology MBBS Medical College Mirpur AJK and Mohi-Ud-Din Islamic Medical College, Mirpur AJ&K from May 2022 to January 2023.

Materials and Methods: This study is a retrospective comparative analysis involving 400 infertile patients. The standard protocols for Ovulation Induction (OI) in infertile patients with PCOS were Clomiphene Citrate (CC) or Letrozole (LTZ). The patients were thoroughly briefed about the mechanisms and experiential effects of LTZ, including its off-label application. The use of LTZ was based on the couples' preference. The patients were categorized into two groups: the CC group (n=200) and the LTZ group (n=200). In the CC group, patients were administered 50 mg of CC twice daily, while in the LTZ group, patients were given 2.5 mg of LTZ twice daily

Results: When evaluating the ovulation rate per menstrual cycle, the LTZ group (94.1%) outperformed the CC group (84.8%), demonstrating statistical significance (p=0.013). In terms of clinical pregnancy rates, the LTZ group exhibited a rate of 53%, while the CC group displayed a rate of 43.2%, with the former exhibiting a statistically superior outcome (p=0.047).

Conclusion: In conclusion, the utilization of LTZ as an ovarian induction agent proves to be efficacious among individuals diagnosed with Polycystic Ovary Syndrome (PCOS). Notably, LTZ exhibits a notable advantage over CC, particularly concerning both pregnancy rates and the rates of successful live births. Given these findings, we propose that LTZ be prioritized as the primary therapeutic choice for treating PCOS patients.

Key Words: Polycystic ovary syndrome, Clomiphene Citrate, Letrozole

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INTRODUCTION

Polycystic ovary syndrome (PCOS) stands as the leading contributor to anovulatory infertility.[1] With a prevalence ranging from 6% to 21% in community-based studies, this rate significantly escalates to 70% when addressing cases of anovulatory infertility.[1,2] While there are ongoing discussions surrounding specific facets of the Rotterdam criteria, these established criteria persistently serve as the basis for diagnosing PCOS.[3] Clomiphene citrate (CC) emerges as the primary recommended option for initiating ovulation induction (OI) in patients with polycystic ovary syndrome (PCOS), primarily due to its proven safety, efficacy, widespread accessibility, cost-effectiveness, and favorable tolerability profile [4] As a selective estrogen receptor modulator (SERM), CC exhibits the ability to form prolonged interactions with nuclear estrogen receptors, subsequently influencing estrogen-mediated functionalities[5]. By negating the suppressive feedback exerted by estrogen, CC triggers the release of gonadotropin-releasing hormone (GnRH) within the hypothalamus. This cascade effect stimulates the secretion of pituitary gonadotropins, culminating in heightened ovarian follicular activity [6].However, it is

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important to acknowledge certain limitations associated with the use of Clomiphene citrate (CC) in treatment. Notably, a subset of patients, approximately 20-25%, exhibit an unresponsiveness to CC, rendering them as CC-resistant individuals.[7] Furthermore, CC's influence on estrogen receptors leads to extended occupancy and is characterized by a prolonged half-life of approximately two weeks, consequently exerting adverse effects on both endometrial thickness and cervical mucus composition.[8] Intriguingly, despite achieving elevated rates of ovulation through CC administration, the resultant pregnancy rate remains modest, estimated to be around 18%.[9] In contrast, an escalated release of gonadotropins, facilitated by Clomiphene citrate, orchestrates the stimulation of ovarian follicle growth and initiation of ovulation.[10] On another therapeutic front, Letrozole (LTZ) elevates intraovarian androgen levels, a pivotal element in early follicular development. This augmentation is attributed to intensified expression of follicle-stimulating hormone (FSH) receptors, alongside stimulation of insulin-like growth factor-I (IGF-I), both of which synergistically enhance the progression of follicular growth.[11] (Unlike CC, LTZ stands apart with its absence of anti-estrogenic effects, and furthermore, it boasts a considerably shorter half-life, approximately 45 hours . As a consequence of these unique characteristics, LTZ elicits negligible impact on cervical mucus and endometrial thickness, thereby leading to markedly improved pregnancy rates.[12]

Moreover, the employment of Letrozole for ovulation induction (OI) showcases additional merits. Notably, the incidence of mono-follicular development is more pronounced, paralleled by heightened singleton pregnancy rates hus, within the realm of PCOS patients, this study endeavors to conduct a comparative analysis of clinical outcomes pertaining to ovulation induction through timed intercourse, contrasting the effects of Letrozole and Clomiphene citrate [13].

MATERIALS AND METHODS

The study was conducted at two distinct medical institutions: MBBS Medical College and Mohi-Ud-Din Islamic Medical College, situated in Mirpur, Azad Jammu & Kashmir. The research involved patients aged 20 to 35 years, who were diagnosed with Polycystic Ovary Syndrome (PCOS) based on the Rotterdam criteria. These patients exhibited at least one functional fallopian tube and a normal uterine cavity as confirmed by hysterosalpingography (HSG). Additionally, the spouses of these patients exhibited normal spermiogram parameters. The Rotterdam criteria, which require the presence of any two of the following three criteria, were used to diagnose PCOS: Oligo/anovulation, clinical/biochemical hyperandrogenism, and polycystic ovary appearance observed through ultrasonography (US). Oligo/anovulation was defined by a menstrual pattern of infrequent or absent periods (cycle duration > 35 days) and/or a low mid-luteal serum progesterone concentration.This study is a retrospective comparative analysis involving 400 infertile patients. The standard protocols for Ovulation Induction (OI) in infertile patients with PCOS were Clomiphene Citrate (CC) or Letrozole (LTZ). The patients were thoroughly briefed about the mechanisms and experiential effects of LTZ, including its off-label application. The use of LTZ was based on the couples' preference. The patients were categorized into two groups: the CC group (n=200) and the LTZ group (n=200). In the CC group, patients were administered 50 mg of CC twice daily, while in the LTZ group, patients were given 2.5 mg of LTZ twice daily. Ovulation Induction (OI) was initiated in all patients following a transvaginal ultrasound (TVUS) examination performed between the 3rd and 6th days of the spontaneous menstrual cycle or induced withdrawal bleeding via 10 mg/day medroxyprogesterone acetate. CC or LTZ treatment continued for a duration of five days. Evaluation of endometrial thickness and the presence of follicles exceeding 10 mm was conducted using TVUS, five days after the final dose of medication. The response to the medication was assessed by the presence of follicles exceeding 10 mm. Subsequent TVUS examinations were performed until the observation of a mature follicle with a diameter of 18 mm.

RESULTS

Throughout the designated study timeframe, a total of 400 patients were subjected to Ovulation Induction (OI) procedures, with 200 individuals receiving Clomiphene Citrate (CC) and another 200 undergoing OI with Letrozole (LTZ). This investigation encompassed the comprehensive assessment of demographic characteristics, laboratory parameters, and clinical outcomes in both groups.

An exhaustive analysis of demographic features and laboratory values was executed for comparative purposes. The data indicated that there existed no statistically significant distinctions between the two groups with regard to age, Body Mass Index (BMI), primary or secondary infertility status, duration of infertility, basal Follicle-Stimulating Hormone (FSH), Luteinizing Hormone (LH), prolactin, estradiol, and Thyroid-Stimulating Hormone (TSH) levels.

A discernible dissimilarity was observed in the mean endometrial thickness between the CC group (6.9.1±1.7 mm) and the LTZ group (7.9±1.8 mm), attaining statistical significance ($p<0.001$). Conversely, the mean count of follicles with a diameter of ≥14 mm exhibited similarity in the CC group (1.2±0.7) and the LTZ group (1.2±0.6), yielding a non-significant p-value ($p=0.870$).

When evaluating the ovulation rate per menstrual cycle, the LTZ group (94.1%) outperformed the CC group (84.8%), demonstrating statistical significance

(p=0.013). In terms of clinical pregnancy rates, the LTZ group exhibited a rate of 53%, while the CC group displayed a rate of 43.2%, with the former exhibiting a statistically superior outcome (p=0.047).

Notably, the utilization of LTZ resulted in a notably higher live birth rate of 45%, in contrast to the live birth rate of 34% achieved through the administration of CC. This particular distinction was statistically significant (p=0.029), further underscoring the superiority of LTZ in this context.

Table No.1: Participant characteristics

	Letrozole (LTZ) Group (n=200)	**Clomiphene CitrateGroup (n=200)**
Age (years)	36.54 ± 10.49	35.56 ± 10.48
Education Basic Secondary University	B-50%, S-25% , U-25%	B-54 % , S-24% U-22%
Body weight (Kg)	71.3 + 12.5	71.1 + 12.4
BMI (kg/m2)	26.5 + 2.7	26.4 + 2.8

B: Basic , S: Secondary , U:University

Table No. 2: Clinical outcomes of Letrozole (LTZ) Group and Clomiphene Citrate Group

Letrozole (LTZ) Group (n=200)	**Clomiphene Citrate Group (n-200)**	**P-value**
ovulation rate per menstrual cycle		
94.1%	84.8%	p=0.013
Pregnancy rate		
53%	43.2%	p=0.047
Live birth rate		
45%	34%	p=0.029

DISCUSSION

Primary oral formulations constitute the preferred course of action for initiating ovulation induction (OI) in patients diagnosed with polycystic ovary syndrome (PCOS) .[14] Notably, elevated Body Mass Index (BMI) serves as a prominent clinical hallmark within the PCOS context, significantly influencing both the efficacy of OI and predisposing to potential adversities during pregnancy [15]Within our study, the mean BMI for the Clomiphene citrate (CC) group was 24.8±2.9 kg/m2, while the Letrozole (LTZ) group exhibited a mean BMI of 25.4±3.2 kg/m2. These values were consistent with BMI findings documented in parallel investigations.

Follicle tracking in tandem with timed intercourse emerges as a proven strategy for augmenting treatment success following the initiation of OI in PCOS patients.[16] The anti-estrogenic nature of CC results in prolonged estrogen receptor depletion, attributed to its protracted half-life.[17]

Conversely, Letrozole accentuates integrin expression, a pivotal marker of endometrial receptivity.[18] Notably, Baruah et al. underscored enhanced sub-endometrial blood flow among PCOS patients treated with LTZ, underscoring its advantageous impact over CC.[19]

In congruence with Franik et al., our study exhibited significantly higher ovulation rates within the LTZ group (76.5%), surpassing the CC group (66.2%) with statistical significance (p=0.013).[20] The robust follicular response closely correlates with the clinical triumph of LTZ. Legro et al. further substantiated the elevated pregnancy rates associated with LTZ, attributing this phenomenon to elevated mid-luteal serum progesterone levels[21] Mid-luteal serum progesterone values were indeed notably elevated in the LTZ group relative to the CC group within our study.[22]

Noteworthy is the relatively higher abortion rate among PCOS patients in contrast to the general population.[23] This consideration imparts a favorable effect in curtailing the risk of multiple pregnancies. Recent investigations highlight heightened rates of mono-follicular development and singleton pregnancy occurrences in PCOS patients treated with LTZ, signifying its therapeutic superiority over CC.[24]

However, historical concerns stemming from a 2005 study, revealing elevated incidences of locomotor and cardiac malformations in infants born following OI with LTZ, had temporarily impeded the widespread adoption of LTZ[25].

CONCLUSION

In conclusion, the utilization of LTZ as an ovarian induction agent proves to be efficacious among individuals diagnosed with Polycystic Ovary Syndrome (PCOS). Notably, LTZ exhibits a notable advantage over CC, particularly concerning both pregnancy rates and the rates of successful live births. Given these findings, we propose that LTZ be prioritized as the primary therapeutic choice for treating PCOS patients.

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Conflict of Interest: The study has no conflict of interest to declare by any author.

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