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Comparison of Letrozole with Clomiphene Citrate as a First Line Treatment for Ovulation Induction in PCOS Patients

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ABSTRACT

Background: The polycystic ovarian syndrome is a common cause of anovulation leading to female infertility. Treatment given classically was Clomiphene citrate. New therapy available is Letrozole, a third-generation aromatase inhibitor. It is more effective in induction of ovulation in PCOS compared to Clomiphene citrate & has minimal side effect, no teratogenicity & is cost-effective.

Objective: To assess the effectiveness of letrozole in comparison to Clomiphene citrate as the initial therapeutic approach for stimulating ovulation in women diagnosed with Polycystic Ovary Syndrome (PCOs).

Material and Methods: This experiment, which was both randomized and controlled, occurred from January 2017 to June 2017 at Unit III of the Department of Obstetrics & Gynaecology, Sheikh Zaid Women Hospital in Larkana. A total of 100 participants (50 in each category A & B), aged between 20 and 38 years, experiencing polycystic ovary syndrome (PCO) with anovulatory infertility were chosen. Individuals with uterine and adnexal abnormalities, ovarian cysts, hyperprolactinemia, and prior surgeries related to the genital tract were excluded. Category A received treatment with Clomiphene citrate, while category B received Letrozole.

Results: The average age with standard deviation (SD) in group-A was 28.28 ± 5.91 years, whereas in group-B, the mean age ± SD was 29.06 ± 4.94 years. The age range was 20-38 years. In terms of body mass index (BMI), the mean ± SD for group-A was 30.10 ± 4.45, and for group-B, it was 31.27 ± 4.69 Kg/m2. Letrozole demonstrated greater efficacy, with a pregnancy rate of 22%, compared to only 08% with Clomiphene citrate. The effectiveness of both drugs was influenced by the age and BMI of the patients. In younger and overweight women, the efficacy of both drugs was lower (P values = 0.219 & 0.560).

Conclusion: Letrozole exhibits a greater success rate than Clomiphene when addressing infertility in individuals with polycystic ovarian syndrome. It is advised to employ Letrozole specifically for this objective.

Key words: Letrozole, Clomiphene citrate, Infertility, Ovulation.

INTRODUCTION

Infertility is characterized by the inability to achieve pregnancy after unprotected intercourse for a period of one or two years. On the other hand, subfertility is a type of diminished fertility leading to an extended period of undesired absence of conception.[1,2] In the United States, around 10-15% of couples of reproductive age experience the occurrence of infertility.[3,4] In Pakistan, the occurrence of infertility stands at 22%, wherein primary infertility makes up 4%, and secondary infertility accounts for 18%.[5,6] Not having children and facing diverse approaches to fertility, the infertile couple is prone to encountering a range of psychosexual issues. Causes of female infertility could stem from physical factors (such as tubal issues), hormonal imbalances (like anovulation), and occasionally remain unexplained.[7,8]

Ovulation is reliant on hormones discharged from the hypothalamic pituitary axis. Consequently, any element influencing this process results in a failure of ovulation. Polycystic ovarian syndrome stands out as the most prevalent endocrine factor leading to ovulatory failure. [9,10]

Polycystic Ovary Syndrome (PCOS) was initially delineated by Stein and Leventhal in 1935.[11] It is identified by the existence of two criteria among three. Initially, the presence of biochemical or clinical features indicative of hyperandrogenism. Secondly, oligoovulation or anovulation, and the third criterion is the manifestation of a polycystic appearance of ovaries during ultrasound. This is a prevalent condition impacting 10% to 15% of women in their reproductive age and is linked to issues such as obesity and insulin resistance.[12] Despite its diverse characteristics, the disease is characterized by hyperandrogenism and either infrequent or absent ovulation. Hormonal irregularities in PCOS hinder the development of follicles in the ovaries, leading to anovulation. Additional clinical manifestations include excessive hair growth, acne, and/or male-pattern baldness.[13,14]

Infertility arising from PCOS is addressed through diverse treatment approaches. The predominant method involves the utilization of Clomiphene citrate (CC), a medication also employed in addressing unexplained infertility. For individuals resistant to clomiphene, alternative strategies are implemented to stimulate ovulation..[13,1 5] Clomiphene, an antiestrogen, operates by obstructing the estrogen receptors in the hypothalamus, leading to the hypothalamus-pituitary axis becoming insensitive to naturally occurring circulating estrogen.[16,17] Clomiphene citrate has served as the cornerstone for promoting ovulation in women facing infertility. The likelihood of achieving pregnancy is highest during the initial 3 to 6 cycles, with a success rate ranging from 55% to 73%.[18] Treatment beyond 6 cycles is not advisable. Clomiphene citrate exhibits minimal side effects such as emotional fluctuations, vasomotor flushes, and visual disturbances, and is well received by women.[19] Adverse outcomes associated with Clomiphen citrate encompass multiple gestations, miscarriage, ovarian hyperstimulation syndrome, and so forth.[13-16]

On the flip side, a newer and perceptive aromatase inhibitor drug (Letrozole) is utilized for instances of fertility issues linked to polycystic ovary syndrome (PCOS). [16,20] It operates by hindering the transformation of androgens into estrogen, consequently modifying the adverse feedback loop of the hypothalamic-pituitary axis, leading to heightened secretion of FSH. Elevated androgen levels in the ovary additionally amplify the follicles' responsiveness to FSH. In contrast to clomiphene, letrozole lacks an antiestrogenic impact on the endometrium and cervical mucus. It has a brief half-life (48 hours), allowing for rapid elimination from circulation, while Clomiphene citrate, owing to its lengthier half-life, necessitates two months for clearance.[14,16,21]

Letrozole has been identified as highly efficacious and secure in numerous investigations. Even individuals who experienced failure with Clomiphene Citrate (CC) achieved successful pregnancies through the administration of Letrozole. [22,23,24,25]

Letrozole has received approval from the FDA as well. It is noted that Letrozole may lead to the occurrence of birth defects or congenital anomalies, although the incidence is reportedly quite minimal (less than 8%).[23,24]

Even though Polycystic Ovarian Syndrome (PCOS) is a frequently diagnosed condition among our local patients, there is a lack of research-backed evidence regarding a more potent treatment

in the local context. The primary aim of our investigation was to assess and contrast the effectiveness of Letrozole and Clomiphene citrate concerning inducing ovulation.

PATIENTS AND METHODS

A randomized controlled experiment took place at Unit III of the Obstetrics and Gynecology division in Sheikh Zaid Women Hospital, Larkana, spanning from January 2017 to June 2017. Structured as a trial with single-blinded design, the research sought to assess the effectiveness of Letrozole and Clomiphene citrate in stimulating ovulation and fostering pregnancy among patients with polycystic ovary syndrome (PCOS). The hypothesis posited that Letrozole would be more effective, with an anticipated 20.4% difference. The significance level was set at 5%, and the test's power was 80%. The study included a total of 100 infertile women, with 50 patients allocated to each group. The participants, aged 20-40 years, met standard criteria for PCO and anovulatory infertility. Exclusion criteria encompassed hyperprolactinemia, FSH >9ml U/ml (during the early follicular phase), and the presence of uterine or adnexal pathology such as leiomyomata. Individuals with a history of surgery related to the genital tract were also excluded.

Anovulation was characterized as a serum progesterone level below 30nmol/L on day 21 of a standard 28-day cycle or a failure of basal body temperature to increase by more than 0.4 degrees Celsius for a duration of 10 days or longer.

The allocation of groups was carried out randomly by instructing the patient to select an opaque envelope from a jar. Patients in Group A were administered Clomiphene citrate, starting at 50mg with the possibility of increasing up to 200mg. In Group B, Letrozole 2.5mg was administered. Both treatments commenced from the 3rd to the 7th day of the menstrual cycle. Patients attended the outpatient department for follicular tracking through transvaginal ultrasound. Subcutaneous HCG 10,000 IU was administered to induce ovulation upon the observation of a follicle with a diameter of 18mm.

Positive drug efficacy was determined when progesterone levels exceeded 30 nmol/L on day 21 of the 28-day cycle or when there was a rise in basal body temperature of more than 0.4 degrees Celsius for 10 days or more. If patients were ovulating normally, the drug administration continued for a total of 6 treatment cycles. Demographic information and comprehensive laboratory tests were recorded using a pre-established form. The research obtained authorization from the Ethical Review Board of the institution, and a detailed, well-informed, written agreement was directly secured from the individual.

Statistical Analysis

The analysis of data involved the utilization of SPSS software, specifically version 15. Calculations were executed to ascertain the average and deviation from the norm for numerical factors like age, weight, height, body mass index, progesterone level, and basal body temperature. Meanwhile, qualitative variables like efficacy in groups A and B were assessed through the computation of frequency and percentage.

A comparison of efficacy between the two groups was conducted, and the hypothesis was subjected to testing using the Chi-square test. To assess the impact of age and BMI on the outcome variable, a stratification approach was employed, followed by the application of the Chi-square test. P value <0.05 was considered as significant level.

RESULTS

Table #1 displays the average ± standard deviation and the minimum/maximum values of essential demographic factors such as age, body mass index (BMI), serum concentrations of follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, and free testosterone within the two specified groups of patients. These variables exhibited resemblance. In class-A, the average age accompanied by a standard deviation was 28.28 ± 5.91 years, whereas in class-B, it registered at 29.06 ± 4.94 years (refer to Table 1). The mean ± standard deviation for the number of ovarian follicles (>18 mm) in class-A was 19.04 ± 2.42, while in class-B, the average ± standard deviation for the quantity of follicles in the ovary (>18 mm) was 25.62 ± 7.24 (see Table 1). The dependent variable (effectiveness) was assessed, revealing a highly significant difference indicating that Letrozole (Group-B) exhibited greater effectiveness (Figure: 1; P value < 0.001). At the conclusion of the study, approximately 22% (n = 11) of women who used Letrozole achieved pregnancy, while only 08% (n = 4) of those who utilized Clomiphene citrate experienced the same outcome.

Stratified examination revealed that age did not act as a significant modifier, and the effectiveness of Clomiphene citrate was higher in women of advanced age (P value = 0.219). In contrast, the effectiveness of Letrozole remained nearly consistent across all age groups of patients (Table: 2; P value = 0.560). Furthermore, Clomiphene citrate and Letrozole exhibited notably higher effectiveness in women with a standard BMI in contrast to individuals who were overweight or obese (Table: 3; P value = 0.054 & 0.022 correspondingly).

Table: 1. Descriptive statistics of different variables.
Group- A: Clomiphene & Group- B: Letrozole

variable	Group	Minimum	Maximum	Mean	SD
Age (Years)	**A**	20	38	28.28	5.914
	B	21	37	29.06	4.94
FSH (mIU/mL)	**A**	2	9	5.25	1.93
	B	3	8	5.40	2.03
LH (mIU/mL)	**A**	5	18	9.94	4.19
	B	6	18	9.49	3.94
Progesterone (nmol/L)	**A**	3	45	14.71	10.58
	B	8	85	25.91	17.09
PRL (mIU/ml)	**A**	3	25	15.37	6.86
	B	3	26	17.05	6.03
Basal body temperature (^{0}C)	**A**	0.15	1.17	0.31	0.19
	B	0.21	1.50	0.45	0.33
Free testosterone (pg/mL)	**A**	0.3	9.1	3.14	2.28
	B	0.7	9.4	2.93	2.52
Number of follicles (>18 mm)	**A**	12	25	19.04	2.42
	B	13	33	25.62	7.24
Body Mass Index	**A**	27.75	38.91	30.10	4.45
	B	25.50	39.91	31.27	4.69

Figure: 1. Percentage of efficacy among between groups.
(n= 50 in each group)

P value < 0.049

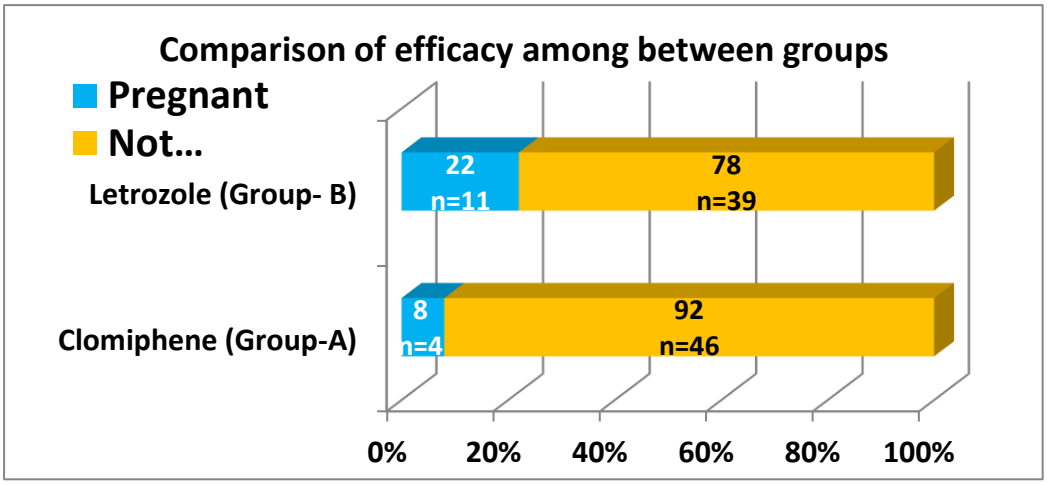

Table: 2. Comparison of effect of age on efficacy of two treatment options among two groups.

Group- A: Clomiphene & Group- B: Letrozole

Group	Age	Efficacy			*P*-value
		Pregnant	Not pregnant	Total	
A	20 -30 Years	1 (3.6%)	27 (96.4%)	28	0.219
	31-38 Years	3 (13.6%)	19 (86.4%)	22	
	Total	4 (8%)	46 (92%)	50	
B	20 -30 Years	5 (20.8%)	19 (79.2%)	24	0.560
	31-38 Years	6 (923.1%)	20 (76.9%)	26	
	Total	11 (22%)	39 (78%)	50	

Table: 3. Comparison of effect of BMI on efficacy of two treatment options among two groups.

Group	BMI	Efficacy			*P*-value
		Pregnant	Not pregnant	Total	
A	Normal weight	3 (11.5%)	23 (88.5%)	26	0.054
	Overweight	1 (12.5%)	7 (87.5%)	8	
	Obese	0 (00%)	16 (100%)	16	
	Total	4 (8%)	46 (92%)	50	
B	Normal weight	8 (29.6%)	19 (70.4%)	27	0.022
	Overweight	2 (25%)	6 (75%)	8	

	Obese	1 (6.7%0)	14 (93.3%)	15	
	Total	11 (22%)	39 (78%)	50 (100%)	

DISCUSSION

The incapacity of a pair to conceive is linked to deep psychological and societal concerns. For women who have already experienced motherhood, the situation of being unable to conceive again despite the wish and consistent unprotected intercourse can be quite distressing. In many instances, primary and secondary infertility resulting from PCOS can be addressed.[12-16,26,27]

The glimmer of optimism for such women lies in Clomiphene citrate, succeeded by Letrozole, the latter being reportedly more potent than the former. This investigation aimed to evaluate the disparity in effectiveness between the two medications within the local population.

The present study observed that Letrozole exhibits significantly higher efficacy than Clomiphene citrate among women with polycystic ovary syndrome (PCOs). In this study, women undergoing Letrozole therapy experienced a tenfold increase in ovulation and a threefold rise in pregnancy rates compared to those using Clomiphene. Despite Clomiphene citrate serving as a crucial initial treatment for the majority of women facing anovulatory infertility, Letrozole emerges as a more efficacious option, as per the findings of this study.[12-16] However, when paired with sexual activity, it fails to enhance reproductive success in couples grappling with infertility linked to polycystic ovary syndrome (PCOs), as evidenced by the present investigation. In such instances, the potential of letrozole appears more auspicious than that of Clomiphene. Additionally, there was a higher occurrence of follicles surpassing 18mm in the Letrozole group. A recent investigation closely examined the efficacy of Letrozole and Clomiphene citrate in women facing unexplained infertility. The findings revealed that the Letrozole group exhibited higher pregnancy rates at 58%, surpassing both the Clomiphene group at 53.6% and the control group at 46%.[28] A different investigation conducted in Massachusetts, USA, revealed that women administered with Clomiphene citrate experienced a lower overall occurrence of successful live births compared to those given letrozole (19.1% as opposed to 27.5%, with a P value of 0.007).[29]

These results align with the present investigation and substantiate the superior effectiveness of Letrozole. The average ages of our subjects mirrored those of participants in other research. The mean age in our study was 28.28 ± 5.91, whereas other research proposed an average age of 26.4 ± 3.2 (Range: 20-33 years).[29]

The present investigation also assessed how age impacts the effectiveness of treatments for ovulation induction. It was observed that older women exhibited higher efficacy in both treatment categories (A and B). This contrast was more pronounced in the case of Clomiphene compared to Letrozole. (P values = 0.219 & 0.560).

Similarly, another factor influencing the effectiveness of the two treatments was body mass index (BMI). In the present investigation, the average ± standard deviation of BMI was approximately 30 ± 4 Kg/m2, slightly elevated compared to the figures reported by Sakhavar et al., where the mean BMI was 26.3 ± 3.2 Kg/m2.[29]

During the continuous inquiry, it was noted that the efficiency of both therapeutic categories (A and B) declined in women with increased BMI (those identified as overweight or obese with a BMI >30 Kg/m2).These results demonstrated significant statistical significance (P value = 0.054 & 0.022, respectively).

During this investigation, it was found that FSH levels in the mid-luteal phase were lower with Letrozole in comparison to Clomiphene. This reduction is linked to either the presence of PCOs

or the therapeutic procedures involved. Despite certain drawbacks such as a smaller sample size and limited follow-up duration, the study as a whole has presented compelling evidence. This evidence can aid infertility specialists in making more informed decisions for their patients, ultimately enhancing success rates and patient satisfaction.

The present investigation also proposes conducting additional research on the effectiveness, adverse reactions, and acceptability of Letrozole, employing more extensive samples and placing particular focus on women with obesity.

CONCLUSION

Barrenness is considered a bane in our region and warrants prompt attention. Medical professionals ought to select the most optimal treatment. Recent studies suggest that Letrozole outperforms Clomiphene Citrate concerning inducing ovulation, attaining conception, and aiding pregnancy in women with a diagnosis of polycystic ovary syndrome. The ongoing inquiry supports the use of Letrozole for treating infertility linked to polycystic ovary syndrome.

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