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Original Research Article

Letrozole and Clomiphene Citrate Alone and Combine with Gonadotropins in Infertile Women – A Prospective Randomized Study

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Abstract:

Introduction: Polycystic ovarian syndrome (PCOS) PCOS is a prevalent ovarian endocrinopathy that causes anovulatory infertility in over 80% of cases. Standard first-line ovulation induction drug clomiphene citrate (CC) has a pregnancy rate of 35%-40% with specific adverse effects. Letrozole, an aromatase inhibitor that lowers oestrogen production, may be a preferable option to CC. This research examined the efficacy of clomiphene citrate and Letrozole alone and with gonadotropins in infertile women.

Materials and methods: A total of 180 women with infertility attending outpatient department of obstetrics and gynaecology between 18-35 years of age were considered. Cases were randomly allocated to 100 mg of clomiphene citrate daily group, 2.5 mg of letrozole twice daily, 100 mg of clomiphene citrate with gonadotropins and 2.5 mg of letrozole with gonadotropins. The details of number of follicles, endometrium thickness, ovulation rate, monofollicular development were recorded and analysed.

Results: Polycystic ovary syndrome (PCOS) was found in 37.78% of individuals in group A and 33.33% of participants in group B. The endometrial thickness was 7.04mm and 7.66mm, in clomiphene citrate alone and with gonadotropins and 8.58mm and 9.12mm in letrozole alone and with gonadotropins respectively. Treatment with 2.5mg of letrozole alone or combined with gonadotropins resulted in significantly higher rates of ovulation and single follicle formation compared to 100 mg of clomiphene citrate alone or combined with gonadotropins ($p<0.05$)

Conclusion: Letrozole and gonadotropin together was shown to be effective in triggering ovulation, facilitating the formation of a suitable endometrium, obtaining an optimal size for the dominant follicle, and inducing ovulation from a single follicle.

Keywords: Polycystic ovarian syndrome, Letrozole, clomiphene citrate, Infertility, Endometrium.

Introduction

Polycystic ovarian syndrome (PCOS) is a prevalent hormonal illness that is characterised by irregular ovulation, hyperandrogenism, and the presence of many cysts on the ovaries as determined by ultra-sound according to the Rotterdam criteria. PCOS is responsible for 80% of cases of infertility caused by lack of ovulation in women.

Clomiphene citrate (CC), a medication that specifically targets oestrogen receptors, has been widely used as the first therapy for inducing ovulation in individuals with polycystic ovary syndrome (PCOS) for many years. Clomiphene is associated with several limitations, such as its generally low effectiveness and an unfavourable range of adverse effects [3]. Clomiphene resistance, seen in 25% of instances, or clomiphene failure often necessitates the use of costlier therapy alternatives for infertility [4]. Third-generation aromatase inhibitors, such as letrozole, have shown to be more effective than other hormone treatments in treating early and metastatic breast cancer in post-menopausal women [5]. Letrozole, a very effective aromatase inhibitor taken orally, was often used for the purpose of inducing ovulation.

A multitude of primary papers, evaluations, and meta-analyses have been published. Letrozole has been shown to be very successful in increasing both ovulation rate and live birth rate, particularly in women who have had failure or resistance to CC. The pharmacodynamics of letrozole result in

enhanced endometrial thickness, cervical mucus quality, the development of a single dominant follicle, and increased folliculogenesis. Consequently, these circumstances may result in increased conception rates and a higher probability of having a single pregnancy [7].

Combining gonadotropins (FSH/hMG) with CC reduces the necessary dosage for optimal stimulation and increases cost-effectiveness in women who do not react to CC therapy [8]. The distinct modes of action of CC and letrozole suggest that their concurrent use may enhance the ovulation rate via a synergistic effect. Nevertheless, there is a scarcity of research that has conducted a comparison between the combined use of CC and letrozole and a single ovulation induction drug. A study comparing the use of CC and letrozole together vs letrozole alone for stimulating ovulation discovered that the combination group had a considerably greater rate of ovulation compared to the letrozole-alone group (77% vs. 42.9%, respectively). This finding indicates that CC improves the efficacy of letrozole for inducing ovulation [9].

Therefore, it is important to investigate the possible synergistic impact of CC in a group that combines many factors. The current research aimed to assess the effectiveness of ovulation induction medicines used alone vs ovulation induction drugs combined with gonadotropins in women with infertility.

Materials and Methods

The present prospective study was conducted in the Department of Obstetrics and Gynaecology at Maheshwara Medical College and Hospital, Isnapur from January 2022 to December 2023. A total of 180 women attending outpatient department of obstetrics and gynaecology aged between 18-35 years were recruited. Cases with infertility, ≥1 year with regular unprotected sexual intercourse, patent fallopian tubes on both sides, normal pelvic anatomy, normal semen analysis, without history of exogenous gonadotropin treatment and willing to participate were included. Cases with immunological basis for infertility, uterine cyst, ovarian cyst, surgical history to genital tract, premature ovarian failure, cardiovascular and renal complications, hyperprolactinemia and not willing to participate were excluded. Written informed consent was obtained from all the study participants and study protocol was approved by institutional ethics committee.

Two study groups were randomly formed from the participants. The only medication given to Group A (n=90) was medication to induce ovulation. From the third to the seventh day of their menstrual cycles, individuals in group A were randomly assigned to one of two groups: A1 and A2. Group A1 received 100 mg of clomiphene citrate daily, while group A2 received 2.5 mg of letrozole twice daily. Ovulation induction medications with gonadotropins were given to Group B (n=90).

For group B, we randomly assigned some participants to receive 100 mg of clomiphene citrate daily with gonadotropins (group B1), while others received 2.5 mg of letrozole twice daily (group B2), also with gonadotropins. Detailed clinical examinations were conducted on participants, noting conditions such as hirsutism, acanthosis nigricans, thyroid problems, and body mass index (BMI). The purpose of the hysterosalpingography was to detect any abnormalities or problems with the uterus.

The number of follicles, their size, and the thickness of the endometrium were all measured using transvaginal ultrasound. We performed a battery of biochemical testing, including CBP, random blood glucose, liver function tests, and kidney function tests. When a patient stopped having menstrual periods and a USG confirmed pregnancy, a urine pregnancy test (UPT) was immediately administered. We used SPSS 26.0 to evaluate the data that we obtained. Percentages and frequencies were used to depict categorical variables.

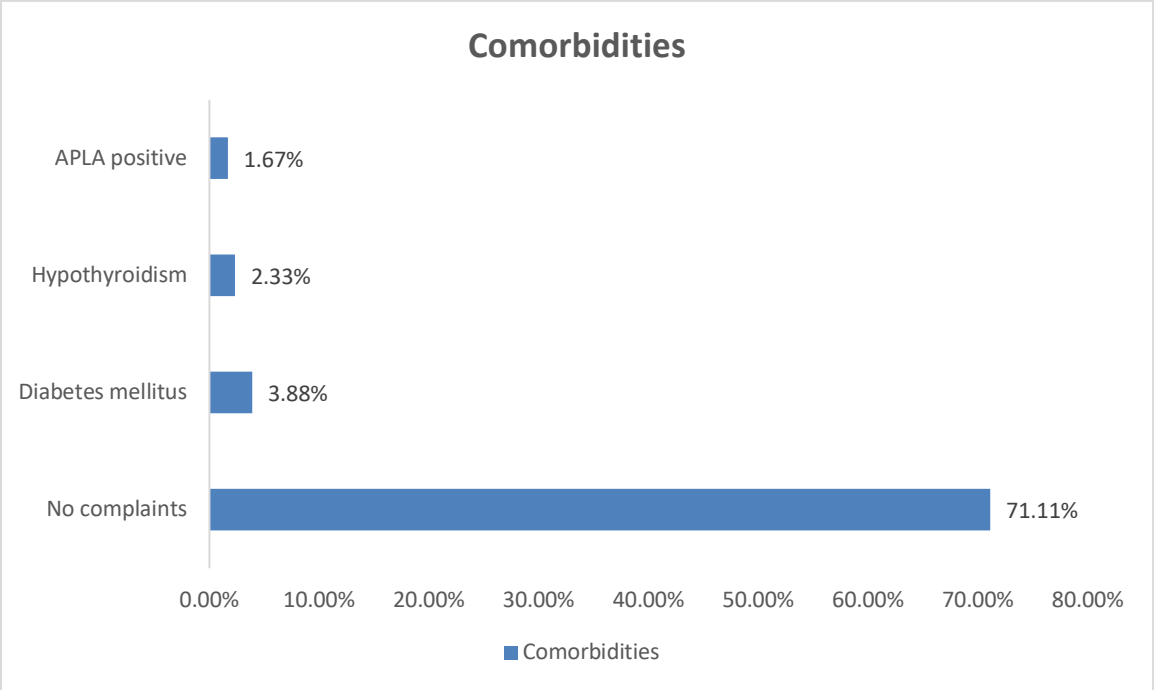
Results

Table 1: Sociodemographic details of study participants

Demographic data	Group A (n=90)		Group B (n=90)	
	Frequency	Percentage	Frequency	Percentage
Age (In years)				
18-24	27	30%	24	26.67%
25-30	47	52.22%	46	51.11%
31-35	16	17.78%	20	22.22%
Duration since marriage				
<5 years	78	86.67%	76	84.44%
>5 years	12	13.33%	14	15.56%
Weight (Mean±SD)	63.8±7.24		65.12±10.02	
BMI (Kg/m^2)	25.89±4.67		26.42±2.18	

Table 2: Menstrual and obstetric history of study participants

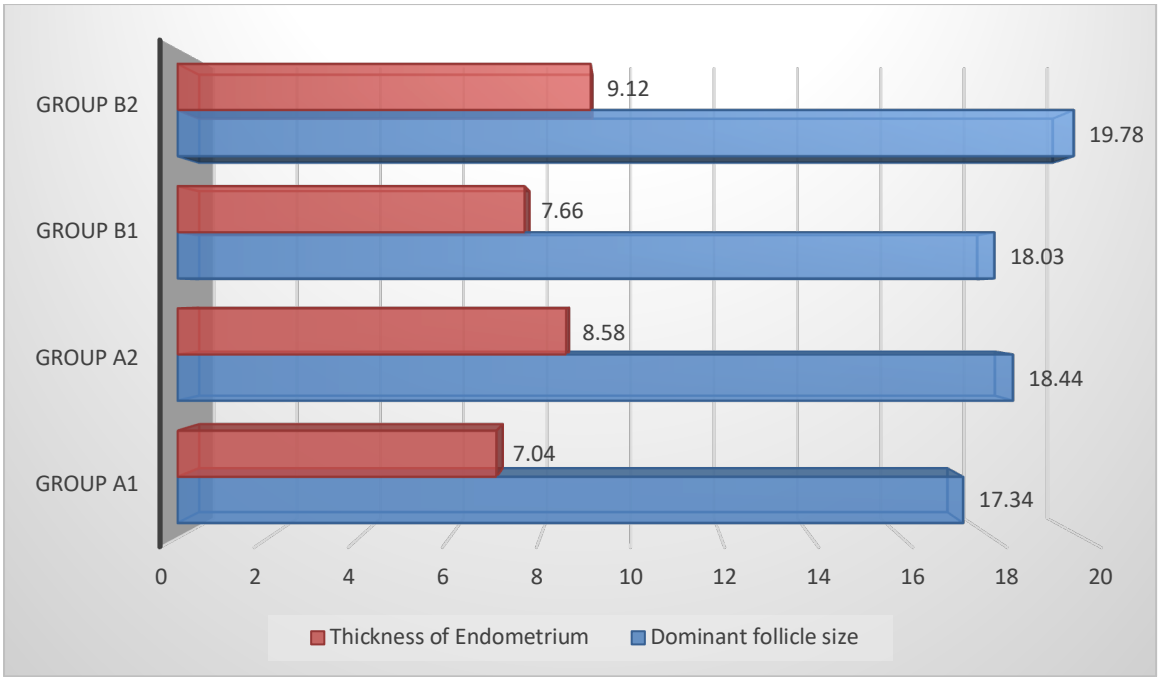
Parameters	Group A (n=90)		Group B (n=90)	
	Frequency	Percentage	Frequency	Percentage
Menstrual cycles				
Regular	29	32.22%	37	41.11%
Irregular	61	67.78%	53	58.89%
Status of infertility				
Primary	56	62.22%	49	54.44%
Secondary	34	37.78%	41	45.56%
PCOS				
Present	34	37.78%	30	33.33%
Absent	56	62.22%	60	66.67%



Graph 1: Associated comorbidities in study participants

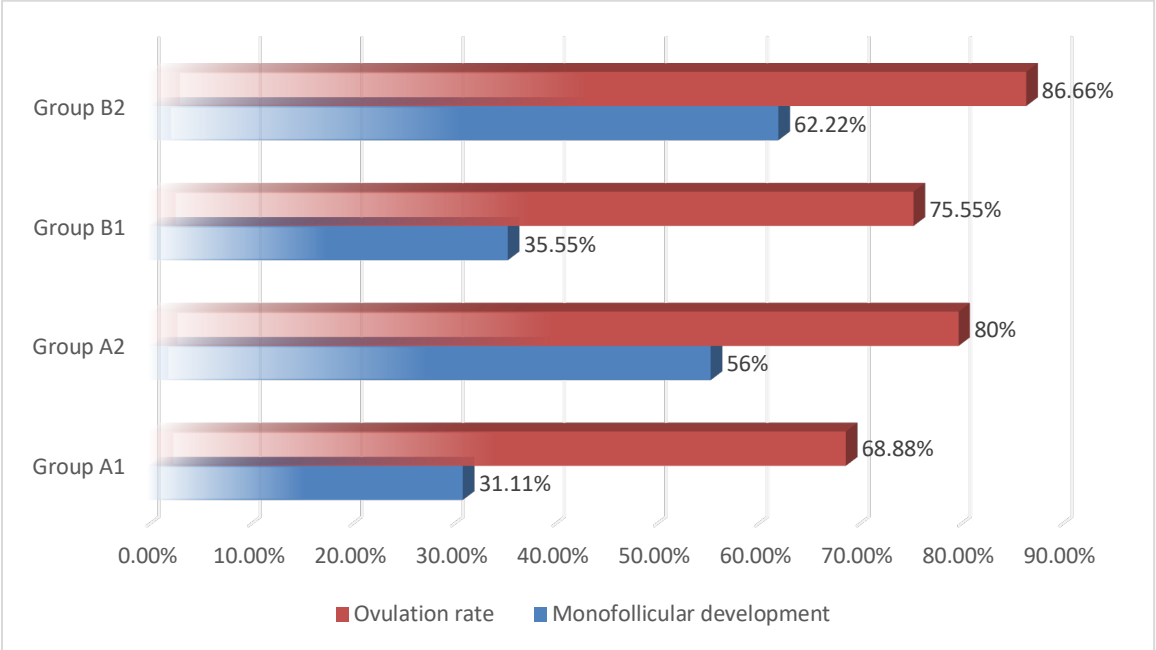
Table 3: Outcome comparison of ovulation induction drugs among study participants

Parameters	Group A		Group B		p-value
	100 mg clomiphene citrate +100 mg clomiphene citrate with gonadotropins		2.5 mg letrozole + 2.5 mg letrozole with gonadotropins		
Number of dominant follicles					
Nil	20	22.22%	22	24.44%	0.001
1	24	26.67%	49	54.44%	
2	30	33.33%	16	17.78%	
3	16	17.78%	03	3.33%	
Incidence of pregnancy					
Positive	19	21.11%	22	24.44%	0.001
Negative	54	60%	42	46.67%	
No growth	17	18.89%	26	28.89%	
Conception method					
Intra uterine insemination	07	36.84%	06	27.28%	1.458
Natural conception	12	63.15%	16	72.72%	



Graph 2: Comparison of thickness of endometrium and size of dominant follicle among study groups

*Group A1:100 mg clomiphene citrate, Group A2: 2.5 mg letrozole, Group B1: 100 mg clomiphene citrate with gonadotropins, Group B2: 2.5 mg letrozole with gonadotropins.



Graph 3: Comparison of ovulation rate and monofollicular development among study groups

Discussion

The majority of participants in both groups, A and B, were between the ages of 25 and 30, with 52.22% in group A and 51.11% in group B. The next largest age group was 18-24 years. The majority of individuals indicated a length of less than 5 years since their marriage, with 86.67% in group A and 84.44% in group B. The average weight in group A was 63.8 kg, whereas in group B it was 65.12 kg. In group A, the average BMI was 25.89 Kg/m2, whereas in group B, it was 26.42 Kg/m^2 (Table 1).

In group A, irregular menstrual periods were detected in 67.78% of patients, whereas in group B, they were observed in 58.89% of cases. In group A, primary infertility was seen in 62.22% of cases, while secondary infertility was observed in 37.78% of instances. In group B, primary infertility was

observed in 54.44% of cases, while secondary infertility was observed in 45.56% of cases. Polycystic ovary syndrome (PCOS) was found in 37.78% of individuals in group A and 33.33% of participants in group B (Table 2).

The study population had the following comorbidities: diabetes mellitus (3.88%), hypothyroidism (2.33%), and APLA positive (1.67%). The majority of individuals (71.11%) reported no relevant comorbidities (Graph 1). In instances where 100 mg of clomiphene citrate was taken alone or in combination with gonadotropins, the findings showed that 26.67% of cases had one dominant follicle, 33.33% had two follicles, and 17.78% had three. The prevalence of successful pregnancy was reported in 21.11% (n=19) of cases, with spontaneous conception occurring in 63.15% and intrauterine insemination employed in 36.84%. When 2.5 mg letrozole and 2.5 mg letrozole were combined with gonadotropins, 54.44% of cases showed one follicle, 17.78% had two follicles, and 3.33% had three follicles. 24.44% of cases resulted in a successful pregnancy. In these instances, 72.72% occurred from spontaneous conception, whereas 27.28% were obtained using intrauterine insemination (Table 3).

The average endometrial thickness was 7.04mm in instances treated with 100mg of clomiphene citrate alone, and 7.66mm in patients treated with 100mg of clomiphene citrate plus gonadotropins. In addition, the average size of the dominant follicle was 17.34mm in the former group and 18.03mm in the latter. The average endometrial thickness in patients treated with 2.5mg of letrozole and 2.5mg of letrozole plus gonadotropins was 8.58mm and 9.12mm, respectively. Similarly, the dominant follicle averaged 18.44 mm and 19.78 mm in these cases. therapy with letrozole and gonadotropins resulted in significantly larger endometrial thickness and dominant follicle size than therapy with clomiphene citrate ($p<0.05$) (Graph 2). Treatment with 2.5mg of letrozole alone or combined with gonadotropins resulted in significantly higher rates of ovulation and single follicle formation compared to 100 mg of clomiphene citrate alone or combined with gonadotropins ($p<0.05$) (Graph 4).

Sinha et al. found that endometrial thickness was considerably better in the gonadotropin-alone group compared to clomiphene (CC) in a retrospective analysis of 100 couples using ovarian stimulation and intrauterine insemination ($P < 0.05$). CC + Gonadotropin improved ovulation to 95.91 %. The pregnancy rate was 26% per couple, 18.36% for CC + Gonadotropin and 33.3% with Gonadotropin-alone, with no significant differences in indications or dominant follicle counts [10]. ElKattan EA et al. found that 5 mg Letrozole had a considerably superior endometrial response than 100 mg clomiphene (11). A single-blinded clinical study by Ganesh A et al. on 1387 PCOS women revealed ovulation rates of 79.30% and 56.95% and pregnancy rates of 23.39% and 14.35% with letrozole and Clomiphene citrate. The study also demonstrated that Letrozole induces ovulation in PCOS women with CC failure when baseline estradiol is >60 pg/ml [12]. A prospective randomised controlled study by Begum MR et al. on 64 anovulatory women with PCOS found that 62.5% of letrozole patients and 37.50% of Clomiphene citrate patients ovulated. The CC and letrozole groups had mean endometrial thicknesses of 9.03 and 10.37 mm on hCG day. Thirteen letrozole (40.63%) and six CC (18.75%) patients were pregnant. Therefore, Letrozole had superior ovulation and PR than CC in PCOS patients [13]. In a study by Sh Tehrani Nejad et al., 140 IUI patients who received letrozole or clomiphene citrate (CC)-gonadotropin showed a significantly higher endometrial thickness at hCG administration (letrozole 9.7mm vs. CC 7.8mm, $P < 0.001$). In clinical pregnancy rates, letrozole (32.8%) was substantially greater than CC (14.3%). Letrozole, an aromatase inhibitor, may be a better option to CC-gonadotropin in COH cycles with IUI for unexplained infertility [14]. Compared to clomiphene citrate, letrozole had better vascularization and thicker endometrium [15-17].

Clomiphene citrate may thin the endometrium in 15–50% of individuals and damage the cervical and endometrial mucosa. Clomiphene citrate's anti-estrogenic action and extended half-life may cause these problems [17,18]. Xia TT et al. found that letrozole with HMG resulted in higher levels of mature follicles, ovulation rate, clinical pregnancy rate, estradiol, and luteinizing hormone on the day of HCG injection, and improved endometrial receptivity ($p<0.05$) compared to clomiphene alone [19]. Chera-aree P et al. found that ovulation rates were 78% and 70% in the CC (50 mg)/letrozole (2.5 mg) and CC-alone (50 mg) groups, respectively, in a trial of 100 pregnant women ($P > 0.05$). The groups had similar mean endometrial thickness and dominant follicle counts. No major adverse events occurred in either group. CC alone and CC with letrozole do not significantly induce ovulation in infertile women with ovulatory dysfunction in one cycle [20]. Like our study, letrozole increased ovulation rate, endometrial thickness, monofollicular growth, and dominant follicle size compared to clomiphene citrate. Low participant numbers and drug comparisons hinder this research. Comparing several medication combinations requires larger investigations.

Conclusion

The combination of letrozole and gonadotropins is more effective in inducing ovulation compared to

letrozole alone, particularly in terms of producing a single mature follicle. Clomiphene plus gonadotropins is more effective than Clomiphene alone in inducing ovulation. However, the use of letrozole and gonadotropin together was shown to be effective in triggering ovulation, facilitating the formation of a suitable endometrium, obtaining an optimal size for the dominant follicle, and inducing ovulation from a single follicle. Moreover, it reduces the incidence of OHSS (ovarian hyperstimulation syndrome) and multiple pregnancies. This specific approach is the most effective treatment for superovulation in cases of unexplained infertility.

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