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Original Research Article

Clomiphene citrate versus letrozole with gonadotropins in intrauterine insemination cycle

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ABSTRACT

Background: This study aimed to evaluate and compare the efficacy of clomiphene citrate (CC) and letrozole, both alone and in combination with gonadotropins, for ovulation induction in infertile women.
Methods: A total of 200 participants were divided into four groups: CC alone, letrozole alone, CC plus gonadotropins, and letrozole plus gonadotropins. Ovulation was monitored via transvaginal ultrasonography, with human chorionic gonadotropin (HCG) administered to trigger ovulation when follicles reached ≥18 mm. Intrauterine insemination (IUI) was performed 24-36 hours post-HCG administration.
Results: The letrozole plus gonadotropins group exhibited the highest ovulation rate (86%), followed by CC plus gonadotropins (84%), letrozole alone (72%), and CC alone (70%). Endometrial thickness was significantly greater in the letrozole group (8.53±1.40 mm) compared to the CC group (7.47±0.89 mm; p=0.000), and the size of the dominant follicle was also larger with letrozole (19.20±4.87 mm) than with CC (17.54±5.44 mm; p=0.02).
Conclusions: Letrozole, particularly when combined with gonadotropins, may be more effective than CC in inducing ovulation and enhancing endometrial receptivity, thereby potentially improving pregnancy outcomes in infertile women.

Keywords: Clomiphene citrate, Gonadotropins, Infertility, Letrozole

INTRODUCTION

Infertility is typically characterized as the inability to conceive after a minimum of twelve months of unprotected intercourse.[1] Intrauterine insemination (IUI) is commonly utilized as the initial treatment choice for couples facing unexplained infertility or mild male-factor infertility across the globe because it is believed to enhance pregnancy rates, is relatively straightforward to administer, and is cost-effective.[2] IUI can be carried out during patients' natural cycles.[3] However, studies indicate that the rates of pregnancy and live births in IUI cycles were considerably greater when ovulation induction (OI) medications were used as opposed to cycles without stimulation for couples experiencing infertility.[4]

Clomiphene citrate (CC) is the most frequently prescribed medication for inducing ovulation in the treatment of subfertility linked with irregular ovulation, and it may also be utilized as part of a superovulation approach for timed intercourse or intrauterine insemination (IUI) cycles when appropriately paired with exogenous gonadotropins. For many years, clomiphene citrate (CC) has been recognized as a standard therapy for ovarian hyperstimulation in cases of unexplained infertility. [5,6] Clomiphene citrate promotes the release of FSH from the pituitary gland by obstructing estrogen's negative feedback mechanism, thereby facilitating follicle development.[7]

In IUI cycles stimulated by gonadotropins, the pregnancy success rates fall between 15-17% per cycle.[8,9] However, utilizing gonadotropins considerably raises the overall treatment expenses and heightens the chances of ovarian hyperstimulation syndrome and multiple pregnancies. When combining gonadotropins with clomiphene citrate (CC) in IUI cycles, both the required dose of

gonadotropins and the treatment costs are reduced compared to using gonadotropins alone, but this combination results in lower pregnancy rates due to the anti-estrogenic effects of CC.[10]

Letrozole (LTZ), an aromatase inhibitor, prevents the transformation of androgens into estrogens within ovarian follicles, leading to a reduction in both circulating and local estrogen levels and an increase in intraovarian androgens. The decline in estrogen concentrations prompts the hypothalamic-pituitary axis to be liberated from the negative feedback exerted by estrogen.[11] Consequently, this causes an elevation in FSH secretion, which promotes follicular development. Unlike clomiphene citrate (CC), LTZ lacks anti-estrogenic effects and has a relatively short half-life of about 45 hours. Because of these characteristics, LTZ does not adversely affect cervical mucus or endometrial thickness, contributing to its association with higher pregnancy rates. The combination of letrozole and gonadotropins can reduce the necessary dose of FSH needed for ovarian stimulation without compromising pregnancy rates compared to using FSH alone, while also minimizing the risks of multiple gestations and ovarian hyperstimulation syndrome (OHSS).[12]

Aims and objectives

To estimate the clinical effectiveness, of letrozole and clomiphene citrate compared with letrozole and clomiphene citrate with gonadotropins in patients with infertility.

METHODS

Study design and study settings

A prospective randomized clinical trial was conducted at the Infertility Clinic of the department of obstetrics and gynecology, LLRM Medical College and associated SVBP Hospital in Meerut, spanning from October 2022 to October 2023.

Study population

The study enrolled 200 women who met specific inclusion criteria: aged between 18 and 40 years, experiencing infertility for one year or more despite regular unprotected intercourse, possessing bilaterally patent fallopian tubes, having normal pelvic ultrasonography findings, and whose partners had normal semen analyses. Participants had not undergone ovulation induction treatment in the preceding six months and had no history of treatment with exogenous gonadotropins.

Exclusion criteria

Encompassed women over 40 years of age, those with immunological causes of infertility, hyperprolactinemia, poor compliance, uterine or bilateral adnexal pathologies (such as fibroids or ovarian cysts), history of genital tract surgeries, premature ovarian failure, ovarian tumors, impaired hepatic or renal function, coital errors, or lack of willingness to participate. All participants provided written informed consent and underwent comprehensive clinical, radiological, and biochemical evaluations as part of the study protocol.

Study procedure

In this randomized clinical trial involving 200 infertile women, participants were divided into two groups of 100 each. Group 1 received ovulation induction (OI) drugs alone: 50 patients were administered clomiphene citrate (50 mg twice daily, days 3-7), and 50 received letrozole (2.5 mg twice daily, days 3-7). Group 2 received OI drugs combined with gonadotropins: 50 patients were given clomiphene citrate (same dosage) plus human menopausal gonadotropin (hMG) 75 IU on days 6 and 9, while the other 50 received letrozole (same dosage) with hMG 75 IU on the same days.

All participants underwent transvaginal ultrasonography starting on day 8 to monitor follicular development, assessing follicle number, size, and endometrial thickness from day 11 onward. When a dominant follicle reached ≥18 mm, ovulation was triggered with a single intramuscular injection of human chorionic gonadotropin (hCG) at either 5,000 or 10,000 IU. Intrauterine insemination (IUI) was performed 24-36 hours post-hCG administration. Semen samples were processed using density gradient centrifugation to isolate motile sperm, and 0.2-0.5 ml of the prepared sample was introduced into the uterine cavity via a thin catheter. Pregnancy was confirmed two weeks later through a urine pregnancy test and transvaginal ultrasound detecting an intrauterine gestational sac with fetal heartbeat.

RESULTS

In our study the mean ages across all groups are relatively similar, ranging from approximately 27 to 29 years. The standard deviations suggest a comparable age variability within each group. Such uniformity in age distribution is crucial as it minimizes age-related confounding factors.

Table 1: Age wise distribution of patients.

Treatment group	Mean age (years)	Standard deviation
Clomiphene citrate alone	28.14	2.98
Letrozole alone	28.40	2.79
Clomiphene + gonadotropins	27.18	2.98
Letrozole + gonadotropins	28.78	3.13

The combination of letrozole + gonadotropins resulted in the highest proportion of participants developing a single dominant follicle (70%), which is often considered optimal for minimizing the risk of multiple pregnancies.

Table 2: Treatment used versus number of dominant follicle.

Number of dominant follicles	Clomiphene + gonadotropins (%)	Letrozole + gonadotropins (%)	Clomiphene alone (%)	Letrozole alone (%)	Total
0	8 (16)	7 (14)	14 (28)	20 (40)	49
1	13 (26)	35 (70)	15 (30)	20 (40)	83
2	19 (38)	8 (16)	26 (52)	8 (16)	61
3	10 (20)	0 (0)	10 (20)	2 (4)	22
Total	50 (100)	50 (100)	50 (100)	50 (100)	200

Pearson chi-square value: 45.721 and p value: 0.000.

Table 3: Treatment used versus incidence of pregnancy.

Outcome (incidence of pregnancy/follicle development)	Clomiphene + gonadotropins (%)	Letrozole + gonadotropins (%)	Clomiphene alone (%)	Letrozole alone (%)	Total n (%)
No growth of dominant follicle	8 (16)	7 (14)	14 (28)	15 (30)	44 (22)
Positive (assume meaning pregnancy/follicle growth)	9 (18)	14 (28)	5 (10)	8 (24)	36 (18)
Negative	33 (66)	29 (58)	31 (62)	27 (56)	120 (60)
Total	50 (100)	50 (100)	50 (100)	50 (100)	200 (100)

Chi-square test results: value =9.879, p=0.130 (not significant).

Table 4: Treatment used versus size of dominant follicle and endometrial thickness.

Parameter	Clomiphene citrate (n=100)	Letrozole (n=100)	t-value	P value
Dominant follicle size (mm)	17.54±5.45	19.20±4.87	2.33	0.02
Endometrial thickness (mm)	7.47±0.89	8.53±1.40	6.40	0.000

Clomiphene + gonadotropins showed a higher percentage of participants developing multiple dominant follicles (38% with two follicles and 20% with three), indicating a more robust ovarian response. Clomiphene alone had the highest percentage of participants with no dominant follicles (28%), suggesting lower efficacy in inducing follicular development.

The chi-square test indicates a statistically significant association between the type of treatment and the number of dominant follicles developed (p<0.001). This suggests that the treatment regimen significantly influences follicular development outcome

Among 50 cases, incidence of pregnancy was found to be only 9 (18%) in clomiphene + gonadotropins group, pregnancy rate was 14 (28%) in letrozole + gonadotropins group, 5 (10%) in clomiphene alone and 8 (24%) in letrozole alone.

Dominant follicle size

Letrozole resulted in a significantly larger mean dominant follicle size compared to clomiphene citrate (p=0.02). endometrial thickness: letrozole also led to a significantly thicker endometrial lining than clomiphene citrate (p<0.001).

Among the combinations, letrozole + gonadotropins achieved the highest ovulation rate at 86%, slightly surpassing clomiphene + gonadotropins at 84%. In monotherapy, letrozole alone had a marginally higher ovulation rate (72%) compared to clomiphene alone (70%).

Table 5: Ovulation rate.

Treatment group	Ovulation rate (%)
Clomiphene + gonadotropins	84
Letrozole + gonadotropins	86
Clomiphene alone	70
Letrozole alone	72

DISCUSSION

In our study reported ovulation rates were 86% for letrozole + gonadotropins, 84% for clomiphene + gonadotropins, 72% for letrozole alone, and 70% for clomiphene alone. Results reported by Ilangovan et al found that ovulation was achieved in 76.0% of participants in the letrozole group compared to 55.2% in the CC group (p<0.001). Clinical pregnancy rates were significantly higher in the letrozole group (44.8%) compared to the CC group (28.1%) (p<0.001).[13]

In our study greater endometrial thickness with letrozole (8.53±1.40 mm) compared to clomiphene (7.47±0.89 mm). Ilangovan et al reported endometrial thickness of 8.7 mm with Letrozole and 7.5 mm with clomiphene.[13]

Among 50 cases, incidence of pregnancy was found to be only 9 (18%) in clomiphene + gonadotropins group, pregnancy rate was 14 (28%) in letrozole + gonadotropins group, 5 (10%) in clomiphene alone and 8 (24%) in letrozole alone. A study by Bansal et al found monofollicular development in 68.4% of letrozole cycles compared to 44.8% with clomiphene.[14]

Out of 36 subjects who became positive on UPT, majority were in the treatment arm of letrozole plus gonadotropins, followed by clomiphene plus gonadotropins, letrozole alone and then clomiphene alone. This is comparable to Verhust, Hughes, Cohlen, reported that exogenous gonadotropins with letrozole or CC increase pregnancy rates and live birth rates compared to natural cycle or other ovulation induction drugs.

CONCLUSION

The study's findings suggest that combination therapies, particularly letrozole with gonadotropins, offer superior outcomes in terms of follicular development, endometrial receptivity, and ovulation rates. Letrozole's favourable impact on endometrial thickness and controlled follicular response positions it as a potentially more effective and safer alternative to clomiphene, especially when combined with gonadotropins. These insights can inform clinical decisions in ovulation induction protocols, aiming to optimize fertility outcomes while minimizing risks.

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