COMPARATIVE EVALUATION OF OVULATION INDUCTION AGENTS IN POLYCYSTIC OVARY SYNDROME (PCOS)-RELATED INFERTILITY: A RANDOMIZED CLINICAL TRIAL

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Relevance

Polycystic Ovary Syndrome (PCOS) is one of the most prevalent endocrine disorders in reproductive-aged women, affecting 5–20% depending on diagnostic criteria. PCOS is a leading cause of anovulatory infertility and presents with hyperandrogenism, menstrual irregularities, and polycystic ovarian morphology.

Infertility due to anovulation remains one of the most distressing consequences of PCOS.

Various ovulation induction agents have been employed, including Clomiphene Citrate (CC), Letrozole, and gonadotropins. Clomiphene Citrate has long been considered first-line therapy; however, emerging data suggest Letrozole may offer superior outcomes in terms of ovulation, pregnancy, and live birth rates.

This study seeks to compare the efficacy and safety of Clomiphene Citrate, Letrozole, and low-dose gonadotropins in women with PCOS-related infertility through a prospective randomized clinical trial.

Aim

To evaluate and compare the ovulation, pregnancy, and live birth rates, as well as adverse effects, associated with Clomiphene Citrate, Letrozole, and gonadotropin therapy in women with PCOS-related infertility.

Materials and Methods

Study Design: A randomized, parallel-group, open-label controlled clinical trial conducted between March 2020 and May 2023 at three university-affiliated fertility clinics.

Sample Size: A total of 900 women aged 20–35 years with PCOS (diagnosed by Rotterdam criteria) and primary infertility of more than one year were included. Participants were randomized into three equal groups (n=300 each):

a. Group A: Clomiphene Citrate (50–150 mg/day, days 3–7)

b. Group B: Letrozole (2.5–7.5 mg/day, days 3–7)

c. Group C: Recombinant FSH (75 IU/day, starting from day 3)

Inclusion Criteria:

a. Confirmed PCOS by Rotterdam criteria

b. Normal uterine cavity and patent tubes

c. Normal semen analysis of male partner

Exclusion Criteria:

a. Age >35 years

b. Hyperprolactinemia, thyroid dysfunction

c. Prior ovarian surgery

Primary Outcomes:

a. Ovulation rate (confirmed by ultrasound and serum progesterone)

b. Clinical pregnancy rate (gestational sac with heartbeat)

c. Live birth rate

Secondary Outcomes:

a. Time to pregnancy

b. Incidence of ovarian hyperstimulation syndrome (OHSS)

Multiple pregnancy rate

a. Monitoring: Transvaginal ultrasound to monitor follicular development; serum estradiol and LH surge measured. Trigger given with hCG when leading follicle ≥18mm.

b. Statistical Analysis: Data analyzed with SPSS v26.0. ANOVA, Chi-square test, and Kaplan-Meier survival analysis used. Significance set at $p<0.05$.

Results

Ovulation Rate:

- Group A (CC): 62.4%
- Group B (Letrozole): 74.8%
- Group C (Gonadotropins): 86.1%

Clinical Pregnancy Rate:

1. Group A: 18.7%
2. Group B: 28.4%
3. Group C: 31.2%

Live Birth Rate:

1. Group A: 15.3%
2. Group B: 24.6%
3. Group C: 29.1%

Time to Pregnancy:

Median time shorter in Group C (3.2 months) compared to Group B (4.6 months) and Group A (5.8 months).

OHSS Incidence:

a. Group A: 0.3%
b. Group B: 0.5%
c. Group C: 5.4%

Multiple Pregnancy Rate:

a. Group A: 1.1%
b. Group B: 1.6%
c. Group C: 5.9%

Discussion

Letrozole demonstrated higher ovulation and pregnancy rates compared to Clomiphene Citrate, confirming its increasing role as the first-line agent for ovulation induction in PCOS.

Gonadotropins showed the best efficacy but were associated with higher risks of OHSS and multiple gestations.

Clomiphene, while historically dominant, had lower efficacy and longer time to conception.

Letrozole offers improved endometrial receptivity and a more physiological hormonal profile, which likely contributes to its superior outcomes.

The choice of therapy must consider efficacy, cost, availability, and patient preference.

Gonadotropins, though potent, require intensive monitoring and incur higher treatment costs. Letrozole combines superior efficacy with oral administration and fewer complications.

Conclusion

Letrozole is more effective than Clomiphene Citrate for ovulation induction in PCOS-related infertility, achieving higher ovulation, pregnancy, and live birth rates with a favorable safety profile. Gonadotropins offer the highest success but come with increased risks.

Clinical protocols should prioritize Letrozole as a first-line treatment, reserving gonadotropins for patients who fail to respond or require accelerated conception. Comprehensive counseling and individualized treatment planning are essential.

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