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Research Protocol

Obstetrics and Gynaecology Section

Efficacy of Gonadotropin with Clomiphene versus Letrozole in Women with Ovulatory Dysfunction Undergoing Intrauterine Insemination: A Research Protocol for a Randomised Controlled Trial

SANA AAFREEN[1], KAMLESH CHAUDHARI[2], EKRAMUL HAQUE[3]

ABSTRACT

Introduction: Globally, infertility poses a significant problem for young couples. In cases of mild male factor infertility, unexplained infertility, and ovulatory dysfunction, Intrauterine Insemination (IUI) is often used as a first-line treatment. Clomiphene Citrate (CC) is a selective oestrogen receptor modulator that is often used to help women ovulate. However, it can have anti-oestrogenic effects on the endometrium and cervical mucus, which could make pregnancy less likely to go well. Letrozole, a third-generation aromatase inhibitor, offers advantages such as mono-ovulation, a shorter half-life, and minimal anti-oestrogenic activity, making it a promising alternative.

Need of the study: Women with ovulatory dysfunction commonly undergo IUI, but the optimal ovulation-induction agent remains unclear. CC may impair endometrial receptivity, while letrozole offers more favourable physiological effects. Comparative evidence is needed to determine which regimen improves pregnancy outcomes in this population.

Aim: The present study aims to compare the efficacy of letrozole with Human Menopausal Gonadotropin (HMG) and CC with HMG in infertile women with ovulatory dysfunction undergoing IUI.

Materials and Methods: The current study is a Randomised Controlled Trial (RCT) that will be conducted at Acharya Vinoba Bhave Rural Hospital (AVBRH), Wardha, Maharashtra, India, from June 2024 to May 2026. A total of 142 women aged 20-38 years with ovulatory dysfunction will be enrolled and randomly assigned to two groups: Group A will receive CC 50 mg twice daily from Day 2 to 6; Group B will receive Letrozole 2.5 mg twice daily from Day 2 to 6. Both groups will receive IM HMG 75 IU from Day 6 to Day 10. Ovulation will be monitored by transvaginal ultrasonography and triggered with Human Chorionic Gonadotropin (hCG) once dominant follicles reach 18-20 mm, followed by IUI. The primary outcomes are the clinical pregnancy rate (confirmed by ultrasound) and biochemical pregnancy rate (positive β-hCG test). Secondary outcomes include endometrial thickness, number of dominant follicles, perifollicular blood flow, and incidence of Ovarian Hyperstimulation Syndrome (OHSS). Numerical data will be presented as mean±Standard Deviation (SD) or proportions. Continuous variables will be tested for normality using the Shapiro-Wilk test. Normally distributed data will be compared using the independent samples t-test; non-normally distributed data will be compared using the Mann-Whitney U test. A p-value of <0.05 will be considered statistically significant.

Keywords: Endometrium, Infertility, Pregnancy rates

INTRODUCTION

Infertility is defined as the inability to conceive after 12 months of regular, unprotected intercourse [1]. About 8-12% of reproductive-aged couples worldwide suffer from infertility [2]. Infertility not only involves the inability to conceive but also causes psychological stress, social stigma, and poor quality of life for affected couples, especially in developing countries, where parenthood is a cultural value [3]. Ovulatory dysfunction is among the most common and treatable causes of infertility [4]. The IUI is an economical, less invasive, and more widely accessible treatment compared with complex procedures such as In-Vitro Fertilisation (IVF) [5]. However, the heart of the successful treatment of IUI lies in the follicular development and endometrial receptivity, highlighting the importance of selecting appropriate ovulation-induction agents.

The CC, acting as a selective oestrogen receptor modulator, is one of the most commonly used drugs for ovulation induction [6]. However, its use is limited due to its side-effects. The anti-oestrogenic effects on the endometrium and cervical mucus may cause thinning of the endometrium, causing adverse reception and implantation conditions, ultimately leading to a reduction in pregnancy rates [7]. CC has the potential to induce multifollicular development, leading to multiple gestation and associated risks to both the mother and foetus [8].

As an alternative to CC, the third-generation aromatase inhibitor, letrozole, can be used. Letrozole reduces peripheral oestrogen synthesis, thus increasing Follicle-Stimulating Hormone (FSH) temporarily. This enhances follicular development without the prolonged anti-oestrogenic effects like with CC [9]. On the other hand, Letrozole has a better profile as it is associated with mono-ovulation, appropriate endometrial thickness, and a shorter half-life [10]. Legro RS et al., demonstrated that letrozole results in higher ovulation and live-birth rates compared with CC in women with PCOS [11]. However, comparative evidence in IUI cycles for ovulatory dysfunction specifically remains limited.

Thus, the optimal line of treatment in women undergoing IUI remains an area of research. The use of letrozole and CC is often combined with HMG to increase follicular recruitment; however, comparative data on their relative effectiveness are limited.

REVIEW OF LITERATURE

With the current lifestyle changes and habits, many women face the problems of infertility, which ultimately results in emotional

stress and social stigma. IUI is commonly used as a first-line treatment for couples presenting with unexplained infertility, mild male factor infertility, or ovulatory dysfunction. CC has long been the primary ovulation-induction agent, but has its own side-effects due to its anti-oestrogenic effects on the endometrium. Letrozole is another alternative, with more favourable physiological effects and improved endometrial receptivity [12].

A landmark RCT by Legro RS et al., demonstrated that letrozole is superior to CC for ovulation induction in women with PCOS. CC was the standard treatment for many years, but it has a low success rate. Letrozole is better tolerated and has shown improved outcomes. However, any direct evidence is lacking [11].

The study by Mitwally MF et al., found that CC is associated with lower pregnancy rates and poor implantation conditions due to its anti-oestrogenic effects on the endometrium and cervical mucus. Letrozole is better accepted and has better results, especially in women who respond inadequately to CC [13]. However, there is limited comparative evidence on the use of these agents combined with HMG in IUI cycles.

Sohrabvand F et al., demonstrated that CC-resistant Polycystic Ovary Syndrome (PCOS) patients have pregnancy success, with pregnancy rates around 16.7%, and letrozole has pregnancy rates of approximately 34.5%, along with a greater proportion of full-term pregnancies. Follicular development and ovulation rates were comparable between the two drugs, but hormonal profiles favoured letrozole [14].

Nakamura Y et al., found that CC adversely affects the endometrium and is associated with a thinner endometrium, 7.6 mm during CC cycles compared with 8.5 mm in natural cycles. This causes poor implantation and induction failure. In contrast, letrozole has been shown to improve endometrial thickness and achieve higher pregnancy rates, including 34.5% full-term pregnancies compared with 10% with clomiphene in clomiphene-resistant PCOS patients. Ovulation rates and hormonal profile are maintained with letrozole [15].

Thus, The present study aims to compare the efficacy of Letrozole plus HMG versus CC plus HMG in improving pregnancy outcomes among infertile women with ovulatory dysfunction undergoing IUI.

Study Objectives

Primary Objective:

To compare the efficacy of letrozole plus HMG vs CC plus HMG in improving pregnancy outcomes among infertile women with ovulatory dysfunction undergoing IUI.

Secondary Objective:

To compare the efficacy of letrozole plus HMG vs CC plus HMG in improving pregnancy outcomes among infertile women with ovulatory dysfunction undergoing IUI.

Hypotheses

Null hypothesis (H_0): There is no significant difference between letrozole plus HMG and CC plus HMG in improving pregnancy outcomes among infertile women with ovulatory dysfunction undergoing IUI.

Alternate hypothesis (H_1): There is a significant difference between letrozole plus HMG and CC plus HMG in improving pregnancy outcomes among infertile women with ovulatory dysfunction undergoing IUI.

MATERIALS AND METHODS

The present study is a RCT will be conducted at Acharya Vinoba Bhave Rural Hospital (AVBRH), Datta Meghe Institute of Higher Education and Research (DMIHER), Sawangi (Meghe), Wardha, Maharashtra, India. The study will be carried out from June 2024 to May 2026. Before commencement of the trial, approval has been obtained from the Institutional Ethics Committee (Ref: DMIHER(DU)/IEC/2024/326) and registered in the Indian Clinical Trial registry (CTRI No.: CTRI/2025/03/081960). Informed written consent will be obtained from all participants. Confidentiality and data protection will be ensured throughout the study.

Inclusion criteria:

- Women aged 20-38 years;
- Diagnosed with ovulatory dysfunction;
- Patent fallopian tubes;
- Mild male infertility with semen analysis showing a total sperm count >10 million/mL [16];
- Women with a previously failed cycle;
- Willing to give informed consent.

Exclusion criteria:

- PCOS;
- Thyroid dysfunction;
- Hyperprolactinaemia;
- Uterine pathology;
- Tubal blockage;
- Endometriosis;
- Contraindications to study drugs;
- BMI>30 kg / m2 [17].

PCOS is excluded because it represents a distinct pathophysiological group with markedly different ovulatory responses and pregnancy outcomes, which could confound comparative analysis between Clomiphene-HMG and Letrozole-HMG protocols [11].

Sample size calculation: Sample size was estimated using the following formula:

where:

$$N = \frac{\left[Z_{1-\alpha/2}\sqrt{2\bar{p}(1-\bar{p})}+Z_{1-\beta}\sqrt{p_1(1-p_1)+p_2(1-p_2)}\right]^2}{(p_1-p_2)^2}$$

p_1 = 12.64 % (Group A: CC + IM HMG) [18]

p_2 = 26.51 % (Group B: Letrozole + IM HMG) [18]

p = (0.1264 + 0.2651)/2 = 0.196 (average pooled proportion)

$Z_{1-\alpha}$ /2 = 1.96 (at 95% Confidence Interval (CI))

$Z_{1-\beta}$ /2 = 0.84 (at 80% power)

Thus, N =

$$\frac{\left[1.96\sqrt{2\,\mathrm{X}\,0.196(1-0.196)}+0.84\sqrt{0.1264(1-0.1264)+0.2651(1-0.2651)}\right]^2}{(0.1264-0.2651)^2}$$

$$N = \frac{(1.099 + 0.463)^2}{0.019}$$

N = 2.44 ÷ 0.0192

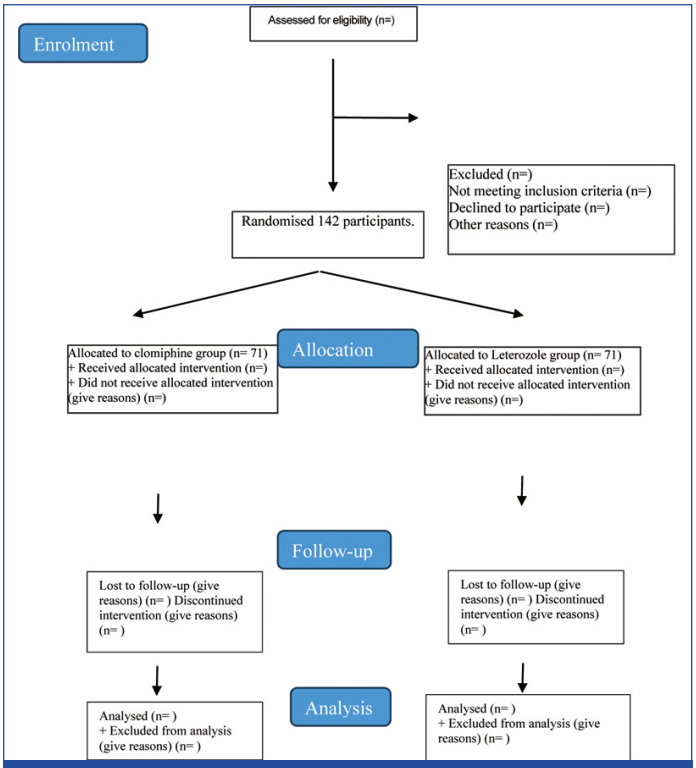
N = 127.08 ≈ 128.

The calculated sample size is 64 participants per group. 10% dropout rate will be considered; the final sample size will be 71 per group, for a total of 142 participants.

Study Procedure

Participants will be randomly allocated to two equal groups using computer-generated numbers by a senior faculty member from the department. The group allocation sequence will be concealed using sealed opaque envelopes. These envelopes will be opened only at the commencement of the intervention [Table/Fig-1].

- **Group A (Clomiphene group):** CC 50 mg twice daily from Day 2-6 + IM HMG 75 IU daily from Day 6 till Day 10 [19].



[Table/Fig-1]: CONSORT flow diagram.
CONSORT: Consolidated standards of reporting trials

- **Group B (Letrozole group):** Letrozole 2.5 mg twice daily from Day 2-6 + IM HMG 75 IU daily from Day 6 till Day 10 [20].

The maximum stimulation duration will be 10 days in both groups [21].

Follicular Monitoring: Follicular development will be assessed using transvaginal ultrasonography on Days 3, 9, and 12 of the cycle, and subsequently every three days until a dominant follicle reaches ≥16 mm.

hCG Trigger Criteria: Ovulation will be triggered with intramuscular hCG once a dominant follicle reaches 18-20 mm in diameter [22].

Timing of IUI: IUI will be performed approximately 36 hours after hCG administration.

Sperm preparation: Semen samples will be processed using density gradient centrifugation to isolate motile sperm and remove debris, dead sperm, and seminal plasma [23].

Luteal phase support: All participants will receive luteal phase support with oral progesterone, as per institutional protocol, to enhance implantation and maintain early pregnancy [24].

Cycle cancellation criteria: Cycles will be cancelled if there is poor follicular response, premature ovulation, or development of multiple mature follicles that increase the risk of OHSS or multiple gestations [25].

Study outcomes

Primary outcomes

Pregnancy rate:

- Biochemical (positive β-hCG ≥ 25 IU/L) [26]
- Clinically confirmed via ultrasonography: Follicular monitoring via transvaginal ultrasonography on Days 3, 9, 12, and then every three days until follicular size is ≥16 mm. Products of conception in a normal pregnancy should be identifiable via transvaginal ultrasound [27].

Secondary outcomes:

- Endometrial thickness will be assessed.
- Number of dominant follicles (1-2 dominant follicles) [28].
- Perifollicular blood flow (if Doppler available).
- Incidence of OHSS. Measured by the modified Golan classification of OHSS. It is categorised into three types of severity, of 5 grades, as shown below [29]:

Mild OHSS: characterised by bilateral multicystic ovarian enlargement.

Grade-1: abdominal distention and discomfort.

Grade-2: Grade 1 with nausea, vomiting and/or diarrhoea, and ovarian enlargement from 5-12 cm.

Moderate OHSS: Characterised by ascites and abdominal distension

Grade 3: Features of mild OHSS with ultrasonographic evidence of ascites

Severe OHSS: characterised by hypovolemia, haemoconcentration, thrombosis, oliguria, pleural and pericardial effusion.

Grade 4: Moderate OHSS with clinical evidence of ascites and/or hydrothorax and dyspnea.

Grade 5: Grade 4 with a change in blood volume, haemoconcentration, coagulation abnormalities, and diminished renal perfusion and function.

Outcome assessment will be conducted before the intervention (pre-intervention) and after completion of the intervention at 10 days (post-intervention).

STATISTICAL ANALYSIS

Data will be entered into Microsoft Excel and will be analysed using IBM Corp. (2022). IBM Statistical Package for the Social Sciences (SPSS) Statistics for Windows, Version 29.0. Armonk, NY: IBM Corp. Descriptive statistics will be presented as mean±SD or proportions. Continuous variables will be tested for normality using the Shapiro-Wilk test. Normally distributed data will be compared using the independent samples t-test; non-normally distributed data will be compared using the Mann-Whitney U test. A p-value of <0.05 will be considered statistically significant.

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PARTICULARS OF CONTRIBUTORS:
1. Junior Resident, Department of Obstetrics and Gynaecology, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.
2. Professor, Department of Obstetrics and Gynaecology, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.
3. Associate Professor, Department of Anaesthesia, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Sana Aafreen,
Junior Resident, Department of Obstetrics and Gynaecology, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education and Research, Sawangi Meghe, Wardha, Maharashtra, India.
E-mail: sana.afreenxl@gmail.com

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