

Tamoxifen Provides Comparable Reproductive Outcomes and Improved Endometrial Development Compared with Clomiphene Citrate: Findings from a Three-Arm Randomized Trial in Women with Polycystic Ovary Syndrome.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting women of reproductive age, with an estimated prevalence of 8–13%, depending on the diagnostic criteria used. It is characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology, and is responsible for approximately 70–80% of cases of anovulatory infertility. Beyond reproductive dysfunction, PCOS is associated with obesity, insulin resistance, type 2 diabetes mellitus, metabolic syndrome, and adverse psychological outcomes, making it a chronic multisystem disorder requiring individualized management.^{1,2}

Ovulation induction remains the cornerstone of infertility treatment in women with anovulatory PCOS after exclusion of other causes of infertility. The principal objectives are to achieve monofollicular ovulation, maximize the likelihood of pregnancy, and minimize complications such as multiple pregnancy and ovarian hyperstimulation syndrome (OHSS). Lifestyle modification, particularly weight reduction in overweight and obese women, is recommended as the initial intervention because even modest weight loss may restore spontaneous ovulation and improve reproductive outcomes.²

The **2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome** recommends letrozole as the preferred first-line pharmacological agent for ovulation induction in infertile anovulatory women with PCOS because of its superior ovulation, clinical pregnancy, and live birth rates compared with clomiphene citrate.³ Nevertheless, the guideline emphasizes that treatment should be

individualized according to patient characteristics, drug availability, affordability, clinician expertise, local regulatory approval, and patient preference. Consequently, clomiphene citrate, tamoxifen, and gonadotropins continue to be used in selected clinical situations, particularly in low- and middle-income countries where access to letrozole may be limited. For several decades, clomiphene citrate (CC) served as the standard first-line oral ovulation induction agent. As a selective estrogen receptor modulator (SERM), CC competitively blocks hypothalamic estrogen receptors, increasing pituitary gonadotropin secretion and stimulating follicular development. Although ovulation rates of approximately 70–85% have been reported, pregnancy rates are relatively lower because of its anti-estrogenic effects on the endometrium and cervical mucus, which may adversely affect implantation. Furthermore, 15–25% of women with PCOS exhibit clomiphene resistance, necessitating alternative therapeutic options.⁴

Tamoxifen, another SERM, has a similar hypothalamic mechanism of action but differs by exerting partial estrogen agonist activity on the endometrium. This pharmacological property may preserve endometrial proliferation and receptivity while maintaining effective ovulation induction. Randomized and prospective comparative studies have demonstrated that tamoxifen achieves ovulation and pregnancy rates comparable to clomiphene citrate, with significantly greater endometrial thickness, suggesting a more favorable endometrial environment for implantation.^{5,6} Despite these potential advantages, tamoxifen has received relatively little attention following the widespread adoption of aromatase inhibitors, and contemporary comparative evidence remains limited. Injectable gonadotropins remain an effective second-line treatment for women who fail oral ovulation induction or require controlled ovarian stimulation.

However, they require intensive ultrasound monitoring, are associated with substantially higher treatment costs, and carry an increased risk of multiple pregnancy and OHSS. Current guidelines therefore recommend individualized low-dose step-up protocols to promote monofollicular development while minimizing treatment-related complications.⁷ Although letrozole is the recommended first-line agent for ovulation induction in women with PCOS, clomiphene citrate, tamoxifen, and gonadotropins continue to be widely used because of differences in availability, affordability, contraindications, and local practice. Consequently, comparative evaluation of these therapies remains clinically relevant, particularly in resource-limited settings. Moreover, few contemporary randomized studies have examined the role of tamoxifen in the post-letrazole era.

The present randomized comparative study was therefore undertaken to compare clomiphene citrate, tamoxifen, and gonadotropins for ovulation induction in women with PCOS, with particular emphasis on whether tamoxifen provides comparable reproductive outcomes while offering superior endometrial development.

MATERIALS AND METHODS

Study Design and Participants

This prospective, randomized, comparative study was conducted in the Department of Obstetrics and Gynaecology at a tertiary care teaching hospital between December 2016 till November 2017. The study protocol was approved by the Institutional Ethics Committee , and written informed consent was obtained from all participants before enrollment. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Women presenting with primary or secondary infertility due to chronic anovulation were screened for eligibility. Ninety infertile women diagnosed with polycystic ovary syndrome (PCOS) according to the Rotterdam 2003 criteria were enrolled. PCOS was diagnosed when at least two of the following three features were present after exclusion of other etiologies: (i) oligo- or anovulation, (ii) clinical and/or biochemical hyperandrogenism, and (iii) polycystic ovarian morphology on ultrasonography.

Inclusion Criteria

Eligible participants were women aged 20–35 years with primary or secondary infertility, at least one patent fallopian tube confirmed by hysterosalpingography or laparoscopy, and a normal semen analysis of the male partner according to the World Health Organization (WHO) criteria applicable during the study period.

Exclusion Criteria

Women with tubal factor infertility, severe male factor infertility, endometriosis, hyperprolactinemia, thyroid dysfunction, congenital uterine anomalies, premature ovarian insufficiency, previous ovarian surgery, or contraindications to ovulation induction agents were excluded.

Randomization and Treatment Allocation

A total of 90 eligible women were randomly allocated in a 1:1:1 ratio using a computer-generated randomization sequence into three treatment groups (30 participants each):

- **Group A:** Clomiphene citrate
- **Group B:** Tamoxifen
- **Group C:** Gonadotropins

Treatment allocation was completed before initiation of therapy.

Ovulation Induction Protocol

Women in **Group A** received clomiphene citrate 50 mg orally once daily from Day 2 to Day 6 of the menstrual cycle. In women who failed to ovulate, the dose was increased by 50 mg in subsequent cycles to a maximum of 150 mg/day.

Women in **Group B** received tamoxifen 10 mg orally once daily from Day 2 for five consecutive days. In the absence of ovulation, the dose was increased by 10 mg in subsequent cycles to a maximum of 40 mg/day.

Women in **Group C** received recombinant follicle-stimulating hormone (rFSH) or human menopausal gonadotropin (hMG) using a low-dose step-up protocol. Gonadotropin doses were individualized according to ovarian response assessed by serial transvaginal ultrasonography.

When at least one dominant follicle reached a mean diameter of ≥ 18 mm, ovulation was triggered with 10,000 IU human chorionic gonadotropin (hCG), and timed intercourse was advised 24–36 hours later.

Follicular Monitoring

Serial transvaginal ultrasonography was commenced on Day 9 of each treatment cycle and repeated every 2–3 days until ovulation or completion of the cycle. The following parameters were recorded:

- Number of developing follicles
- Diameter of the leading follicle

- Endometrial thickness (maximum double-layer thickness measured in the midsagittal plane)
- Evidence of ovulation

Participants underwent up to six treatment cycles or until conception, whichever occurred first.

Outcome Measures

The **primary outcomes** were ovulation rate and clinical pregnancy rate. Clinical pregnancy was defined as the presence of an intrauterine gestational sac with fetal cardiac activity confirmed by transvaginal ultrasonography.

Secondary outcomes included endometrial thickness on the day of hCG administration, number of mature follicles, incidence of multiple pregnancy, ovarian hyperstimulation syndrome (OHSS), and treatment-related adverse events.

Statistical Analysis

Data were analyzed using **SPSS version 16.0** (SPSS Inc., Chicago, IL, USA) and **Epi Info version 3.5.1** (Centers for Disease Control and Prevention, Atlanta, GA, USA). Continuous variables were expressed as mean $\pm$ standard deviation (SD), while categorical variables were presented as frequencies and percentages.

Baseline characteristics and treatment outcomes were compared among the three groups using one-way analysis of variance (ANOVA) for continuous variables and the Chi-square test or Fisher's exact test for categorical variables, as appropriate. A two-sided *p* value <0.05 was considered statistically significant.

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134 RESULTS

135 A total of 90 infertile women with polycystic ovary syndrome (PCOS) were enrolled and
 136 randomized equally into three treatment groups: clomiphene citrate (n=30), tamoxifen
 137 (n=30), and gonadotropins (n=30). All participants completed the study, and there were no
 138 protocol deviations, treatment discontinuations, or losses to follow-up.

139 Baseline Characteristics

Variable	Clomiphene (A)(n=30)	Tamoxifen (B)(n=30)	Gonadotropins (C)(n=30)
Mean age (years)	27	24	26
Mean BMI (kg/m ²)	24.74	24.78	25.14
Duration of infertility(months)	25.57	26.03	26.6

140 **Table 1:** Baseline Characteristics of Study Participants

141 Baseline demographic and clinical characteristics were comparable among the three groups
 142 (Table 1). There were no statistically significant differences in mean age, body mass index
 143 (BMI), or duration of infertility (all $p>0.05$), indicating successful randomization and
 144 comparable baseline characteristics prior to treatment.

145 Treatment Outcomes

Outcome	Clomiphene(A)	Tamoxifen(B)	Gonadotropins
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			(C)
Ovulation (%)	70.0	73.3	80.0
Clinical Pregnancy rate (%)	33.3	33.3	36.7
Monofollicular development (%)	70	66.7	66.3
Endometrial thickness (mm)	7.76	8.42	8.27

Table 2: Treatment outcomes

Treatment outcomes are summarized in Table 2. Ovulation was achieved in 70.0% of women receiving clomiphene citrate, 73.3% receiving tamoxifen, and 80.0% receiving gonadotropins. Although the gonadotropin group demonstrated the highest ovulation rate, the difference among the three groups was not statistically significant ($p=0.664$). Likewise, clinical pregnancy rates were comparable, occurring in 33.3%, 33.3%, and 36.7% of women in the clomiphene citrate, tamoxifen, and gonadotropin groups, respectively ($p=0.952$). Overall, 31 clinical pregnancies were achieved during the study, with no significant difference in pregnancy outcomes among the treatment groups.

Monofollicular development was observed in approximately two-thirds of treatment cycles across all three groups (70.0%, 66.7%, and 66.3%, respectively), indicating a similar pattern of ovarian response regardless of the ovulation induction agent used.

A significant difference was observed in endometrial development. Women treated with tamoxifen achieved the greatest mean endometrial thickness (8.42 ± 1.21 mm), which was significantly higher than that achieved with clomiphene citrate (7.76 ± 1.14 mm; $p=0.020$). Endometrial thickness in the gonadotropin group (8.27 mm) was comparable to that observed with tamoxifen. Thus, while ovulation and pregnancy outcomes were similar, tamoxifen was associated with significantly better endometrial development than clomiphene citrate, suggesting preservation of endometrial receptivity without compromising treatment efficacy.

Safety Outcomes

Adverse event	Clomiphene	Tamoxifen	Gonadotropins
Mild OHSS	0	0	XX
Severe OHSS	0	0	0
Multiple gestation rate	3.3	0	3.3
Significant adverse events	Nil	Nil	Nil

Table 3: Safety outcomes

All treatment regimens were generally well tolerated (Table 3). No cases of severe ovarian hyperstimulation syndrome (OHSS) occurred during the study. Clomiphene resistance was observed in 23.3% of women treated with clomiphene citrate. One triplet pregnancy occurred in the clomiphene citrate group, while one twin pregnancy was observed in the gonadotropin group. No multiple pregnancies occurred in the tamoxifen group. No serious treatment-related adverse events were reported in any of the three treatment groups.

Overall, the three treatment modalities demonstrated comparable reproductive efficacy with respect to ovulation and clinical pregnancy rates. However, tamoxifen consistently produced a more favorable endometrial response than clomiphene citrate while maintaining similar reproductive outcomes, supporting its potential role as an effective alternative oral ovulation induction agent in women with PCOS.

DISCUSSION

The present randomized three-arm study demonstrated that tamoxifen achieved ovulation and clinical pregnancy rates comparable to those of clomiphene citrate and gonadotropins in women with polycystic ovary syndrome (PCOS). The principal finding, however, was that tamoxifen resulted in significantly greater endometrial thickness than clomiphene citrate while maintaining similar reproductive outcomes. These findings suggest that tamoxifen may preserve endometrial receptivity without compromising ovulation or pregnancy rates and support its continued role as an alternative oral ovulation induction agent in selected women with PCOS.

Current international guidelines recommend letrozole as the preferred first-line pharmacological treatment for ovulation induction in anovulatory women with PCOS because of its superior ovulation, clinical pregnancy, and live birth rates compared with clomiphene citrate. Nevertheless, the guideline also emphasizes individualized treatment based on patient characteristics, drug availability, affordability, contraindications, and local regulatory approvals. Consequently, clomiphene citrate, tamoxifen, and gonadotropins continue to be used in many parts of the world, particularly in low- and middle-income countries where access to letrozole may be limited or where alternative agents are required.²

The comparable ovulation and pregnancy rates observed in the present study are consistent with earlier comparative studies demonstrating similar reproductive efficacy between tamoxifen and clomiphene citrate. A meta-analysis by Steiner et al. reported no significant differences in ovulation or pregnancy rates between the two selective estrogen receptor modulators, although the available evidence was limited by small sample sizes and methodological heterogeneity.⁸

Likewise, Hassan et al. reported equivalent ovulation and conception rates with tamoxifen and clomiphene citrate while observing superior endometrial thickness in women receiving tamoxifen.⁹

Seyedoshohadaei and colleagues similarly found comparable reproductive outcomes between tamoxifen and clomiphene citrate in women with anovulatory infertility.¹⁰

Although these studies predate the widespread adoption of letrozole, together with the present findings they suggest that tamoxifen remains a clinically effective oral ovulation induction agent.

The significantly greater endometrial thickness observed with tamoxifen represents the most clinically relevant finding of the present study. Clomiphene citrate has a prolonged half-life and persistent anti-estrogenic effects on the endometrium and cervical mucus owing to prolonged estrogen receptor depletion. Although ovulation is successfully achieved in most women, impaired endometrial development may reduce implantation potential and contribute to the well-recognized discrepancy between ovulation and pregnancy rates observed with clomiphene citrate.¹¹

In contrast, tamoxifen acts as a selective estrogen receptor modulator with partial estrogen agonistic activity on endometrial tissue while maintaining hypothalamic estrogen antagonism

sufficient to induce ovulation. This pharmacological profile probably explains the significantly greater endometrial thickness observed in the present study and may offer an important therapeutic advantage in women who develop a thin endometrium during clomiphene treatment.

Although gonadotropins produced numerically higher ovulation rates, reproductive outcomes were not significantly different from those achieved with either oral agent. Gonadotropin therapy remains an effective second-line treatment but requires intensive ultrasound monitoring, greater treatment costs, and carries an increased risk of multiple pregnancy and ovarian hyperstimulation syndrome (OHSS).²

No cases of severe OHSS occurred in the present study, reflecting the use of individualized low-dose stimulation protocols and careful monitoring. These findings support current guideline recommendations that reserve gonadotropins for women who fail oral ovulation induction or require second-line therapy.

An important strength of the present study is its contemporary relevance. Since the adoption of letrozole as first-line therapy, relatively few randomized studies have re-examined the role of tamoxifen in women with PCOS. Consequently, evidence regarding tamoxifen in the current treatment era remains limited. The present study therefore provides additional data supporting tamoxifen as a safe, effective, and inexpensive alternative when letrozole is unavailable, contraindicated, poorly tolerated, or unsuccessful. This is particularly relevant in resource-constrained healthcare settings, where treatment decisions frequently depend on affordability and drug availability rather than efficacy alone. Recent Indian recommendations on infertility management similarly emphasize individualized treatment and appropriate selection of ovulation induction agents according to patient characteristics, local resources, and clinical expertise.¹²

The strengths of this study include its prospective randomized design, equal allocation to three treatment arms, standardized follicular monitoring, and evaluation of both reproductive and endometrial outcomes. Nevertheless, several limitations should be acknowledged. The study was conducted at a single center with a relatively modest sample size, which may have limited the power to detect small differences in pregnancy outcomes. Live birth, the most clinically meaningful reproductive outcome, was not evaluated. Furthermore, letrozole was not included because the study was performed before its widespread adoption as first-line therapy. Future adequately powered multicenter randomized controlled trials directly comparing tamoxifen with letrozole are warranted to define more clearly the role of tamoxifen within contemporary ovulation induction strategies.

In conclusion, tamoxifen achieved reproductive outcomes comparable to clomiphene citrate while producing significantly better endometrial development. Although letrozole remains the preferred first-line treatment according to current international guidelines, tamoxifen continues to represent a safe, effective, and economical oral alternative for selected women with PCOS, particularly in resource-limited settings and in those with suboptimal endometrial response to clomiphene citrate.

References:

1. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod.* 2004;19(1):41-47. doi:10.1093/humrep/deh098

2. Teede HJ, Tay CT, Laven J, et al. Recommendations from the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome†. *Hum Reprod.* 2023;38(9):1655-1679. doi:10.1093/humrep/dead156
3. Legro RS, Brzyski RG, Diamond MP, et al. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. *N Engl J Med.* 2014;371(2):119-129. doi:10.1056/NEJMoa1313517
4. Brown J, Farquhar C, Beck J, Boothroyd C, Hughes E. Clomiphene and anti-oestrogens for ovulation induction in PCOS. *Cochrane Database Syst Rev.* 2009;(4):CD002249. doi:10.1002/14651858.CD002249.pub4
5. Sharma S, Choudhary M, Swarankar V, Vaishnav V. Comparison of Tamoxifen and Clomiphene Citrate for Ovulation Induction in Women with Polycystic Ovarian Syndrome: A Prospective Study. *J ReprodInfertil.* 2021;22(4):274-281. doi:10.18502/jri.v22i4.7653
6. Boostanfar R, Jain JK, Mishell DR, Paulson RJ. A prospective randomized trial comparing clomiphene citrate with tamoxifen citrate for ovulation induction. *Fertil Steril.* 2001;75(5):1024-1026. doi:10.1016/s0015-0282(01)01749-6
7. Balen AH, Morley LC, Misso M, et al. The management of anovulatory infertility in women with polycystic ovary syndrome: an analysis of the evidence to support the development of global WHO guidance. *Hum Reprod Update.* 2016;22(6):687-708. doi:10.1093/humupd/dmw025
8. Steiner AZ, Terplan M, Paulson RJ. Comparison of tamoxifen and clomiphene citrate for ovulation induction: a meta-analysis. *Hum Reprod.* 2005;20(6):1511-1515. doi:10.1093/humrep/deh840

- 286 9. Hassan ZB. Comparison between tamoxifen and clomiphene citrate for induction of
287 ovulation and successful conception in polycystic ovarian syndrome. *International Journal*
288 *of Reproduction, Contraception, Obstetrics and Gynecology*. 2015;4(5):1349-1352.
289 doi:10.18203/2320-1770.ijrcog20150709
- 290 10. Seyedoshohadaei F, Zandvakily F, Shahgeibi S. Comparison of the effectiveness of
291 clomiphene citrate, tamoxifen and letrozole in ovulation induction in infertility due to
292 isolated unovulation. *Iran J Reprod Med*. 2012;10(6):531-536.
- 293 11. Legro RS, Brzyski RG, Diamond MP, et al. Letrozole versus clomiphene for infertility
294 in the polycystic ovary syndrome. *N Engl J Med*. 2014;371(2):119-129.
295 doi:10.1056/NEJMoa1313517
- 296 12. Malhotra J, Devi MG, Patil M. Best Practice Recommendations for Infertility
297 Management. *J Hum Reprod Sci*. 2024;17(Suppl 1):S1-S240.
298 doi:10.4103/jhrs.JHRS_ISAR_IFS