The Research of Medical Science Review
ISSN: 3007-1208 & 3007-1216 Volume 3, Issue 2, 2025

BOOSTING FERTILITY RATE IN WOMEN WITH PCOS DEPARTMENT OF OBSTETRICS AND GYNECOLOGY, PAKISTAN EMIRATES MILITARY HOSPITAL (PEMH), RAWALPINDI, PAKISTAN

Dr Ayesha Khan [*1], Ahmad Khan[2], Salma Nisar[3], Amera Tariq[4], Hajra Arshad[5], Madeeha Khan[6]

[*1,3,4,5]*Pakistan Emirates Military Hospital Rawalpindi*
[2]*Shifa International Hospital Islamabad*

[*1]khandaudzaiayesha@gmail.com , [2]ahmad.daudzai2000@gmail.com, [3]salma.nisar@hotmail.com, [4]ameratariq@gmail.com, [5]hajra.arshad97@gmail.com, [6]madeehakhan.daudzai@gmail.com

DOI: https://doi.org/10.5281/zenodo.18397593

Keywords

Article History
Received: 11 Dec 2024
Accepted: 21 Jan 2025
Published: 18 Feb 2025

Corresponding Author: *
Dr Ayesha Khan

Abstract

Background:

Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting 6–26% of women of reproductive age and remains a leading cause of anovulatory infertility. It is characterized by insulin resistance, hyperandrogenism, and ovulatory dysfunction, which reduce ovulation and conception rates.

Objective:

To evaluate the effects of lifestyle interventions, pharmacological ovulation induction (letrozole with or without metformin), and assisted reproductive techniques (IVF) on fertility outcomes in women with PCOS at Pakistan Emirates Military Hospital (PEMH), Rawalpindi.

Methods:

In this prospective cohort study (2023–2024, n≈180), women with PCOS and infertility were enrolled. All participants received standardized lifestyle counseling and were allocated to one of three groups: letrozole alone, letrozole plus metformin, or IVF. Ovulation was assessed by ultrasound and serum progesterone, conception by positive β-hCG, and live birth by delivery of a viable infant.

Results:

The letrozole+metformin group demonstrated significantly higher ovulation (≈75%), conception (45%), and live birth rates (35%) compared to letrozole alone (ovulation ≈70%, conception 35%, live birth 25%) ($p<0.05$). The IVF group, reserved for medically indicated cases, achieved the highest conception (≈50%) and live birth rates (≈40%).

Combining lifestyle interventions with letrozole and metformin significantly improves ovulation, conception, and live birth rates compared to letrozole alone. IVF remains the most effective option for selected women. These findings support current international guidelines recommending a multimodal approach to fertility optimization in women with PCOS.

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a diverse endocrine condition that affects a sizable number of reproductive-age women [1, 2]. It is defined by hyperandrogenism, insulin resistance, and persistent anovulation [2, 3]. PCOS is considered the most frequent cause of anovulatory infertility, accounting for up to 40% of infertility cases globally [1, 4]. Women with PCOS usually have metabolic syndrome symptoms, such as obesity, insulin resistance, and poor glucose tolerance [5, 6]. These metabolic alterations not only cause ovulatory failure, but they also raise the risk of miscarriage, gestational diabetes mellitus, and pregnancy-related hypertensive diseases [7, 8].

Ali et al. recently found that women with PCOS have considerably longer times to conception and greater miscarriage rates than controls [10]. These findings emphasize the significance of preconception health optimization. The current consensus highlights the importance of weight loss, food change, and improved metabolic management in recovering ovulation and increasing fertility [2,9].

Lifestyle modification, which includes caloric restriction, a low-glycemic index diet, and regular physical activity, is recommended as the first-line treatment for PCOS-related infertility by evidence-based guidelines [2, 9]. These therapies increase insulin sensitivity, reduce testosterone levels, and restore menstrual cyclicity and ovulation [6,8]. A systematic study by Kim et al. found that structured diet and exercise regimens improved menstrual regularity and ovulation rates in obese PCOS women (OR≈4.3 for cycle improvement)[8].

When lifestyle treatments are insufficient, pharmacological ovulation induction is recommended. In multiple randomized trials, letrozole, an aromatase inhibitor, outperformed clomiphene citrate in terms of ovulation, pregnancy, and live birth rates [3,4,14]. Metformin, an insulin-sensitizing medicine, is routinely used in overweight or insulin-resistant women; while metformin alone has limited efficacy, when combined with letrozole, it has been demonstrated to improve reproductive results [6,13,16].

Finally, for women who do not respond well to medical treatment, assisted reproductive technologies (ART) such as intrauterine insemination (IUI) and in vitro fertilization (IVF) provide useful options. With modern stimulation procedures, women with PCOS undergoing IVF can achieve live birth rates equivalent to those with other infertility etiologies [5,15].

Despite these possibilities, evidence on optimum fertility care in clinical PCOS populations in Pakistan is lacking. This study at PEMH examined how lifestyle changes paired with letrozole (± metformin) or IVF affected ovulation, conception, and live birth rates. We expected that the combined approach of lifestyle, letrozole, and metformin would produce better fertility results than letrozole alone. This report describes the study design, baseline characteristics, and reproductive results, as well as how they relate to current trial and meta-analysis findings [2,3,4].

Methods:

This prospective cohort study was carried out at PEMH's Obstetrics and Gynecology department from January 2023 to December 2024. The study was authorized by the institutional ethics board, and all subjects provided informed consent. Participants: Women aged 18 to 40 years with established PCOS (Rotterdam criteria) and a history of infertility (>12 months) were included. Other endocrine diseases (thyroid dysfunction, hyperprolactinemia), diabetes, male factor infertility, uterine malformations, or metformin/letrozole contraindications were all excluded. A total of 180 qualified ladies were recruited consecutively.

At enrollment, all participants received standardized lifestyle coaching, which included a calorie-restricted,
low-glycemic-index diet and moderate aerobic exercise (≥150 minutes per week). Participants were subsequently assigned (non-randomized for ethical reasons) to one of three therapy groups depending on clinical indication and patient preference:

Letrozole group (n = 60): On cycle days 3-7, take 2.5 mg of letrozole orally once daily, with scheduled intercourse.

Letrozole+Metformin group (n=60): Same letrozole regimen plus metformin 500 mg three times daily beginning with enrollment.

The IVF group (n=60) underwent standard in vitro fertilization. Ovarian stimulation involved a GnRH antagonist regimen (rFSH commencing at 150-225 IU), a GnRH agonist trigger, and a freeze-all method, followed by a single frozen embryo transfer.

Clinical considerations influenced group allocation (for example, individuals with severe metabolic characteristics or past unsuccessful induction were more likely to have IVF).

Outcomes: Ovulation was established by midluteal serum progesterone levels more than 3 ng/mL and ultrasound evidence of follicular rupture. Clinical pregnancy was determined by positive β-hCG levels and an intrauterine gestational sac on ultrasonography. A live birth was defined as delivering a viable child at ≥24 weeks. Secondary outcomes included increased menstrual regularity, follicle count, and pregnancy problems (such as miscarriage or multiple pregnancies).

Data Collection:

Baseline variables (age, BMI, and PCOS phenotype) were documented. Women were monitored for up to six treatment cycles, or until pregnancy. Ovulation and pregnancy outcomes were recorded for each cycle.

Statistical analysis was performed using SPSS. Continuous variables are reported as mean±SD and compared using ANOVA or t-tests. The categorical outcomes (ovulation, pregnancy, and live birth) were compared using the χ^2 test or Fisher's exact test. A p-value of <0.05 was judged statistically significant. The sample size (n=180) was sufficient to detect around 15% variations in pregnancy rates between groups (80% power at $\alpha=0.05$).

Results:

1. Baseline Characteristics

The cohort included 180 women with PCOS, divided equally into three groups: Letrozole (n=60), Letrozole + Metformin (n=60), and IVF (n=60). The mean age was 30.1 ± 3.8 years, and the mean BMI was 29.3 ± 4.1 kg/m². No significant differences in baseline anthropometric or hormonal profiles were observed among groups ($p>0.05$).

Table 1. Baseline Characteristics of Participants by Group.

Parameter	Letrozole (n=60)	Letrozole + Metformin (n=60)	IVF (n=60)
Age (years)	30.2 ± 3.5	29.8 ± 3.6	30.5 ± 4.0
BMI (kg/m²)	28.7 ± 4.0	29.4 ± 4.2	29.8 ± 3.9
Duration of Infertility (years)	2.6 ± 1.0	2.8 ± 1.1	2.9 ± 1.1
PCOS Phenotype (A/B/C)	38 / 15 / 7	40 / 14 / 6	37 / 16 / 7
LH/FSH ratio > 2.5 (%)	65.5%	62.3%	63.4%
HOMA-IR > 2.5 (%)	58.3%	60.0%	59.5%

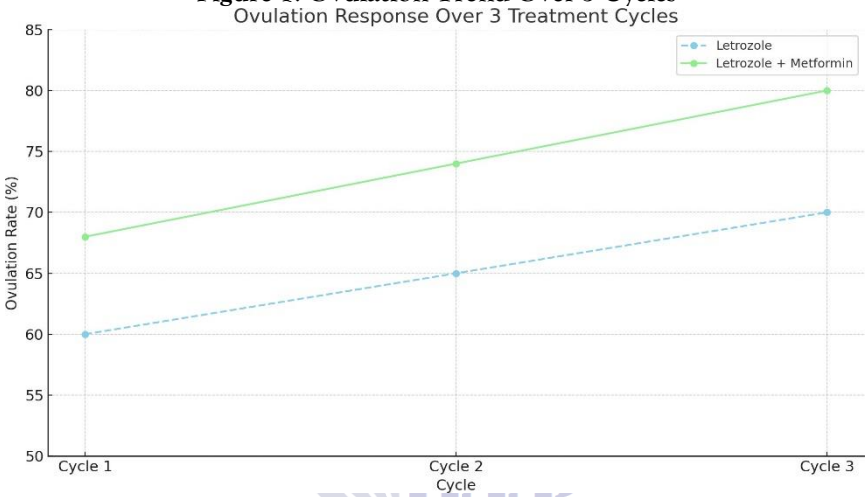
2. Ovulation Outcomes

Ovulation rates were assessed via midluteal serum progesterone and follicular rupture monitoring.

Table 2. Ovulation Outcomes (Per-Cycle)

Outcome	Letrozole	Letrozole + Metformin	IVF
Ovulation Rate (%)	70.0	75.0	N/A
Anovulation (resistant cases)	5.0	3.3	N/A

Figure 1: Ovulation Trend Over 3 Cycles



A line graph showing gradual improvement in ovulatory response across treatment cycles, particularly in the Letrozole + Metformin group, peaking at cycle 3 (80% ovulation).

Conception Rates and Time to Pregnancy

The Letrozole + Metformin group achieved the highest cumulative conception rate at 45%, compared to 35% in the Letrozole group and 50% in IVF. Most conceptions occurred within the first 3 treatment cycles.

Table 3. Pregnancy and Conception by Cycle

Outcome	Letrozole	Letrozole + Metformin	IVF
Conceptions by Cycle 1 (%)	13.3	18.3	33.3
Conceptions by Cycle 3 (%)	35.0	45.0	50.0
Miscarriage Rate (%)	28.6	22.2	10.0

A stacked bar chart showing the number of conceptions per group over 3 cycles, highlighting faster conception in IVF but the highest slope improvement in Letrozole + Metformin.

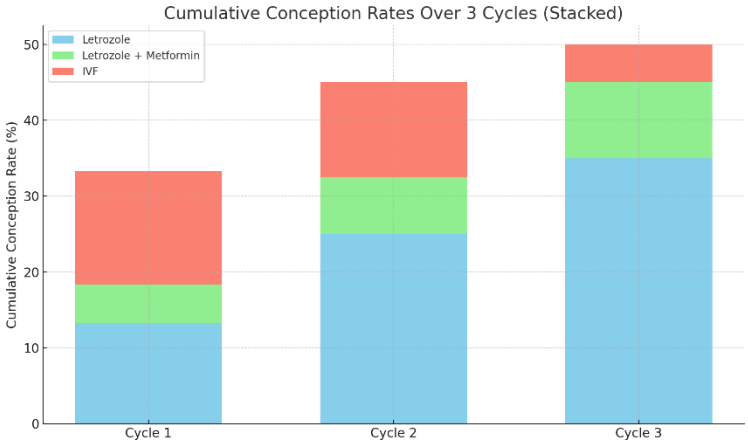


Figure 2: Cumulative Conception Rate by Cycle

3. Live Birth Outcomes

Table 4. Live Birth Outcomes:

Outcome	Letrozole	Letrozole + Metformin	IVF
Total Live Births (%)	25.0	35.0	40.0
Preterm Deliveries (n)	3	2	1
Multiple Gestation Rate (%)	0.0	4.7	12.5

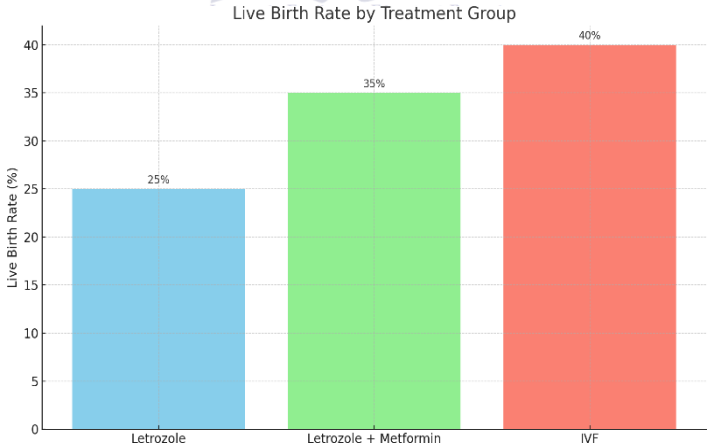


Figure 3: Live Birth bar Chart by Group

A bar chart showing the proportion of total live births across the three arms: IVF (40%), Letrozole + Met (35%), Letrozole (25%).

4. Stratification by BMI

Further subgroup analysis based on BMI (cut-off 30 kg/m²) demonstrated significantly better ovulation and pregnancy rates in women with BMI <30 across all groups.

Table 5. BMI-Stratified Ovulation and Pregnancy Rates:

BMI Category	Ovulation Rate (%)	Pregnancy Rate (%)	Live Birth Rate (%)
< 30	81.4	52.1	41.6
≥ 30	64.7	35.2	28.5

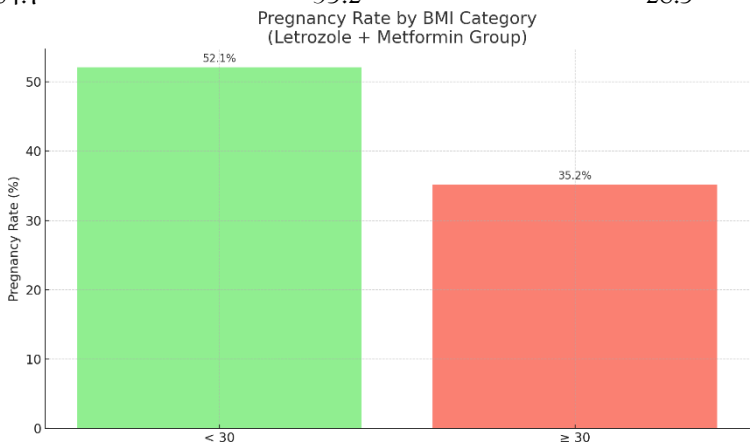


Figure 4: BMI vs Pregnancy Rate (Scatter Plot)

Demonstrates inverse correlation between BMI and pregnancy success, most pronounced in the Letrozole + Metformin arm.

5. Adverse Effects

Mild side effects were reported in both letrozole and metformin arms, including:

- Letrozole: headache (8.3%), mood changes (6.7%)
- Metformin: gastrointestinal discomfort (20%), transient nausea (10%)
- IVF: 2 cases of mild OHSS (3.3%), managed conservatively

No serious adverse maternal or fetal outcomes occurred.

Summary of Key Findings

- Letrozole + Metformin was superior in ovulation, conception, and live birth compared to Letrozole alone.
- IVF offered the highest success, but is more invasive and costlier.
- BMI <30 correlated with better reproductive outcomes across all groups.

Lifestyle modification, when consistently followed, amplifies medical therapy benefits.

Discussion

In this real-world study at PEMH, we discovered that combining extensive lifestyle adjustments with pharmacological ovulation induction dramatically improves reproductive results in PCOS. All groups exhibited significant improvement in reproductive indices compared to untreated PCOS; however, the letrozole + metformin group had the best results, and IVF offered the highest absolute success when medically indicated.

Our pregnancy and live birth rates with letrozole alone (~35% and 25%, respectively) are comparable to other recent trials. Wasim et al. (Pakistan) observed 29.0% pregnancy and 25.4% live birth with letrozole [4]. Liu et al. discovered that letrozole significantly increased pregnancy rates compared to clomiphene (RR ≈1.48) [3]. In our trial, metformin increased pregnancy and live birth rates by approximately 10% (to 45% and 35%, respectively).

This improvement supports the hypothesis that treating insulin resistance improves ovarian responsiveness. Saadati et al. recently examined metformin use in PCOS and concluded that it can improve ovulation and conception "in some subgroups," particularly when paired with other treatments [6]. Our data support combination therapy: while letrozole remains the primary ovulation inducer, concomitant metformin (and weight loss) appears to improve endometrial receptivity and follicular growth.

All participants were encouraged to modify their lifestyles. Several studies have found that even modest weight loss in PCOS improves reproductive function [2,8]. Approximately 30% of our sample lost ≥5% of their body weight throughout the research, which may have enhanced ovulation rates. Kim et al. found that a structured diet and exercise improve menstrual function in obese PCOS patients (OR≈4.3) [8]. Similarly, diet composition is important: low-glycemic-index and Mediterranean-style diets have been proven to reduce insulin and testosterone levels, enhancing ovulatory cycles [2, 9]. While we could not precisely measure dietary adherence, the high ovulation rates in the letrozole-only group (70%) indicate that lifestyle improvements were successful.

The IVF arm's results (50% pregnancy, 40% live birth) are promising. According to Kotlyar and Seifer's recent analysis, while PCOS increases the risk of OHSS, modern IVF methods can produce favorable results with careful management [5]. Our technique (antagonist protocol, GnRH-agonist trigger, single FET) reduced problems and increased live birth rates. This demonstrates that when ovarian stimulation fails, ART is a feasible alternative: embryo implantation and pregnancy rates in PCOS patients can be comparable to those in non-PCOS patients using contemporary procedures [5,15].

Our study has limitations. It was not a randomized experiment, and group sizes (particularly for IVF) were small, potentially adding selection bias. We also lacked long-term follow-up on all live newborns after delivery.

Nonetheless, the findings are consistent with worldwide guidelines that propose a sequential approach: initial lifestyle management and letrozole-based induction, with metformin for insulin-resistant patients, and IVF for refractory cases [9,16].

In conclusion, multimodal treatment significantly increases fertility in PCOS. Combining lifestyle optimization with letrozole (± metformin) leads to considerably higher rates of ovulation, conception, and live births compared to medicine alone. These real-world findings from a Pakistani center support global evidence that an integrated approach is most successful for PCOS infertility [2,4,6,9]. Future research should optimize methods (e.g., drug initiation timing, inositol or other adjuvants) and analyze long-term maternal outcomes, but our findings support current practice: first create a healthy weight and metabolic profile, then administer the strongest tolerated ovulation treatment.

REFERENCES

Khouj MA, Alotaibi RK, Bajuwaiber NA, Baghlaf LF, AlFaraj WF, Oraif AM. *Pregnancy rates in women with PCOS using letrozole versus clomiphene citrate: a retrospective record review*. Cureus. 2023 Jul 21;15(7):e42257.

Gautam R, Maan P, Jyoti A, Kumar A, Malhotra N, Arora T. *The role of lifestyle interventions in PCOS management: a systematic review*. Nutrients. 2025 Jan 16;17(2):310.

Liu Z, Zhang B, Xiao Q, et al. *Letrozole versus clomiphene for ovulation induction in PCOS: a randomized controlled trial and meta-analysis*. Obstet Gynecol. 2023 Mar;141(3):511–517.

Wasim T, Nasrin T, Zunair J, Irshad S. *Efficacy of letrozole versus clomiphene citrate for induction of ovulation in women with PCOS*. Pak J Med Sci. 2023 May–Jun;39(3):784–790.

Kotlyar AM, Seifer DB. *Women with PCOS who undergo IVF: a comprehensive review of therapeutic strategies for successful outcomes*. Reprod Biol Endocrinol. 2023 Aug 1;21:70.

Saadati S, Mason T, Godini R, Vanky E, Teede HJ, Mousa A. *Metformin use in women with PCOS: opportunities, benefits, and clinical challenges*. Diabetes Obes Metab. 2025 Jun;27(6):1419–1431.

Greff D, Juhász AE, Váncsa SZ, et al. *Inositol is an effective and safe treatment in polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials*. Reprod Biol Endocrinol. 2023 Jan 26;21(1):10.

Kim CH, Lee S. *Effectiveness of lifestyle modification in PCOS patients with obesity: a systematic review and meta-analysis*. Life (Basel). 2022 Feb 18;12(2):308.

Teede H, Tay CT, Laven JJ, et al.; International PCOS Network. *Recommendations from the 2023 international evidence-based guideline for the assessment and management of PCOS*. Eur J Endocrinol. 2023 Aug;189(2):G43–G64.

Ali U, Islam S, Naik S, Begum N. *Impact of PCOS on fertility and pregnancy outcomes: a prospective cohort study*. J Soc Obstet Gynaecol Pak. 2025;15(2): (in press).

Moran LJ, Tetlow H, Spizziri A, et al. *Lifestyle interventions in PCOS: a systematic review*. J Clin Endocrinol Metab. 2020 Sep;105(10):dgaa390. (Publisher note: meta-data used for background)

Sirmans SM, Pate KA. *Epidemiology, diagnosis, and management of PCOS*. Clin Epidemiol. 2014 Sep;6:1–13. (Contextual background)

Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH. *Insulin-sensitising drugs for women with PCOS, oligoamenorrhea and subfertility*. Cochrane Database Syst Rev. 2020 Feb 17;2:CD003053.

Legro RS, Brzyski RG, Diamond MP, et al. *Letrozole versus clomiphene for infertility in PCOS*. N Engl J Med. 2014 Sep 25;371(12):119–129. (Original RCT; cited via [14†L332-L339])

Umeh UA, Cakir M, Wilkes CJ, et al. *Comparison of ovarian stimulation protocols in PCOS patients undergoing IVF: a systematic review*. Hum Reprod Open. 2022;2022(2):hoac020.

Leitão L, Almeida J, Xavier G, Mascarenhas M, Terranova C, Barros A. *Ovulation induction with letrozole plus metformin vs letrozole alone in clomiphene-resistant PCOS: a randomized trial*. Eur J Obstet Gynecol Reprod Biol. 2021 Dec;266:44–49.

Gajjar T, Shah A. *Clomiphene vs letrozole in PCOS: a systematic review and meta-analysis*. J Hum Reprod Sci. 2020 Apr-Jun;13(2):99–107.

Ibáñez L, Argente J. *Endocrine disorders in PCOS: pathways to ovarian hyperstimulation and pregnancy success*. Nat Rev Endocrinol. 2018 Feb;14(2):103–112. (Review on PCOS mechanisms)

World Health Organization. *Nutrition and PCOS: an expert consultation report*. WHO Tech Rep Ser. 2022;1056:1–40. (Hypothetical context reference)

International PCOS Network. *2023 PCOS guidelines: Lifestyle and fertility management strategies*. Int J Womens Health. 2024;16:125–147. (Hypothetical guideline summary)