

Letrozole in GnRH Antagonist IVF for PCOS: A Propensity Score-Matched Study

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ABSTRACT

To evaluate the association of letrozole co-treatment with laboratory and clinical outcomes in women with polycystic ovary syndrome (PCOS) undergoing gonadotropin-releasing hormone (GnRH) antagonist in vitro fertilization (IVF), with live birth as the primary endpoint.

This retrospective single-center cohort study included 1,157 eligible cycles (424 letrozole, 733 standard antagonist) treated between January 2015 and December 2023. Letrozole 5 mg/day was administered on cycle days 2–6. The primary outcome was live birth per cycle with embryo transfer, analyzed with multiple-adjusted modified Poisson regression. Sensitivity analyses included inverse probability of treatment weighting, propensity score matching (n=834), and per-retrieval analysis (n=1,271).

Letrozole was associated with lower peak estradiol (1,187 vs 2,971 pg/mL; $p<0.001$) and gonadotropin use (1,351 vs 1,497 IU; $p<0.001$), and higher oocyte (14.4 vs 13.2; $p<0.001$), mature oocyte (11.2 vs 10.2; $p<0.001$), and good-quality blastocyst yields (2.0 vs 1.7; $p<0.001$). Clinical pregnancy (60.4% vs 63.0%; $p=0.57$) and moderate-to-severe OHSS (5.2% vs 5.9%; $p=0.34$) did not differ. Live birth was similar (46.9% vs 47.3%; adjusted risk ratio 1.02; 95% CI 0.90–1.15; $p=0.80$) and remained consistent across all sensitivity analyses.

Letrozole co-treatment improved laboratory outcomes and reduced gonadotropin use but did not improve live birth in antagonist IVF for PCOS. These findings do not support routine co-treatment when higher live birth is the goal; selective use may be considered when reducing peak estradiol or gonadotropin requirements is a secondary clinical objective.

Keywords: Polycystic ovary syndrome, In vitro fertilization, Letrozole, GnRH antagonist protocol, Live birth rate

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women of reproductive age and is frequently encountered in IVF practice (1). During IVF, women with PCOS often show abundant follicular response yet remain at increased risk of ovarian hyperstimulation syndrome (OHSS). Contemporary guidance therefore favors GnRH antagonist protocols because they permit flexible triggering and integrate well with modern OHSS-prevention strategies, including GnRH agonist triggering and freeze-all policies when indicated (2,3). Interventions that lower estradiol exposure or gonadotropin requirements without compromising reproductive outcomes are therefore clinically relevant in this population. Identifying adjuncts that improve laboratory yield without compromising or ideally enhancing live birth would therefore have direct clinical value in this hyper-responder population.

Letrozole, a third-generation aromatase inhibitor, suppresses estrogen synthesis and may reduce gonadotropin consumption during ovarian stimulation (4,5). Although it has an established role in ovulation induction in women with PCOS (2), its routine use as co-treatment during IVF remains less well supported. Available IVF evidence is heterogeneous and has focused largely on poor responders rather than women with PCOS (6). A recent PCOS-specific retrospective study in antagonist IVF/ICSI did not show improved pregnancy outcomes with letrozole co-treatment (7).

Whether favorable laboratory changes with letrozole translate into improved live birth in PCOS remains uncertain. We evaluated the association between letrozole co-treatment and stimulation characteristics, embryology outcomes, and live birth in women with PCOS undergoing antagonist IVF. We tested the robustness of the primary finding through multiple sensitivity analyses.

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Received: 18.05.2026, Accepted: 31.08.2026

Materials and Methods

Study Design and Setting: This retrospective cohort study analyzed cycles from women with PCOS who underwent IVF with GnRH antagonist protocols at a single tertiary IVF center between January 2015 and December 2023. The study was approved by the local institutional ethics committee (full approval reference and date are provided on the title page). It was conducted in accordance with the Declaration of Helsinki and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (8). Because the analysis used retrospective, de-identified data, the requirement for individual informed consent was waived.

Participants: We retrieved data from 1,374 GnRH antagonist IVF cycles in women diagnosed with PCOS according to Rotterdam criteria, defined by ≥ 2 features among oligo-anovulation, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology (9), consistent with contemporary international guidance (2). We excluded PGT-A cycles ($n=103$) because embryo selection may vary depending on PGT-A use. A further 114 non-PGT-A cycles without an embryo transfer were excluded from the main analysis (freeze-all without any subsequent transfer in follow-up, $n=84$; cancellation before oocyte retrieval, $n=4$; others, $n=26$), although we included them in a per-retrieval sensitivity analysis. Thus, the primary analysis included 1,157 cycles. One cycle per patient was included, verified by a unique patient identifier. Other clinical exclusion criteria applied before dataset retrieval included: male factors, including male factor infertility; tubal factors requiring surgery; stage III or IV endometriosis; diminished ovarian reserve, defined as AMH <1.0 ng/mL or AFC <5 ; and use of concomitant medications other than ovarian stimulation medications.

Treatment Protocols: Patients in the letrozole group received 5 mg of letrozole orally once daily from cycle day 2 through cycle day 6. Letrozole co-treatment was selected at the treating physician's discretion rather than assigned by a fixed allocation protocol. It was generally considered when a high ovarian response or OHSS risk was anticipated, based on ovarian reserve markers (AMH and AFC), prior stimulation characteristics when available, and/or the clinical objective of limiting peak estradiol exposure or reducing gonadotropin requirements. This dose was selected based on prior evidence suggesting superior estradiol suppression

compared with the 2.5 mg dose, without an appreciable difference in embryo or cumulative live birth outcomes (5). Gonadotropin stimulation with recombinant follicle-stimulating hormone or human menopausal gonadotropin was initiated on cycle days 2 or 3 at 75–200 IU/day, based on age, body mass index, anti-Müllerian hormone, antral follicle count, and prior response. Gonadotropins with luteinizing hormone activity (human menopausal gonadotropin or recombinant LH) could be used at the physician's discretion, primarily in patients with LH <3 IU/L or those with prior poor fertilization. GnRH antagonist treatment with cetrorelix 0.25 mg or ganirelix 0.25 mg was initiated flexibly when the leading follicle reached 12–14 mm. Final oocyte maturation was triggered with human chorionic gonadotropin 5,000–10,000 IU, GnRH agonist 0.2 mg, or a dual trigger when at least three follicles reached 17 mm. The standard group underwent the same antagonist protocol without co-treatment with letrozole.

Laboratory Procedures and Embryo Transfer: Oocyte retrieval was performed approximately 36 hours after final maturation triggering. Standard intracytoplasmic sperm injection or conventional IVF was performed according to semen parameters. Embryos were cultured to the blastocyst stage and assessed using Gardner morphologic criteria (10); good-quality blastocysts were defined as ≥ 3 BB on day 5 or day 6. Frozen embryo transfer cycles used vitrification and warming with industry-standard protocols. Embryo transfer was guided by transabdominal ultrasonography; luteal-phase support was provided with vaginal progesterone.

Outcome Measures: The primary outcome was live birth per cycle with embryo transfer, defined as the birth of at least one live infant after ≥ 24 weeks of gestation, ascertained for the index retrieval during the available follow-up period. Secondary outcomes were peak estradiol, total gonadotropin consumption, stimulation days, endometrial thickness at trigger, oocytes retrieved, mature (MII) oocytes, 2-pronuclear (2PN) embryos, day-3 good-quality embryos, total blastocysts, good-quality blastocysts, clinical pregnancy, miscarriage, multiple gestation, and moderate-to-severe OHSS.

Statistical Analysis: Continuous variables are summarized as mean $\pm$ SD and compared with Student's *t*-test; categorical variables are summarized as n (%) and analyzed with χ^2 . The primary analysis modeled live birth as a binary outcome using multiple-adjusted modified Poisson

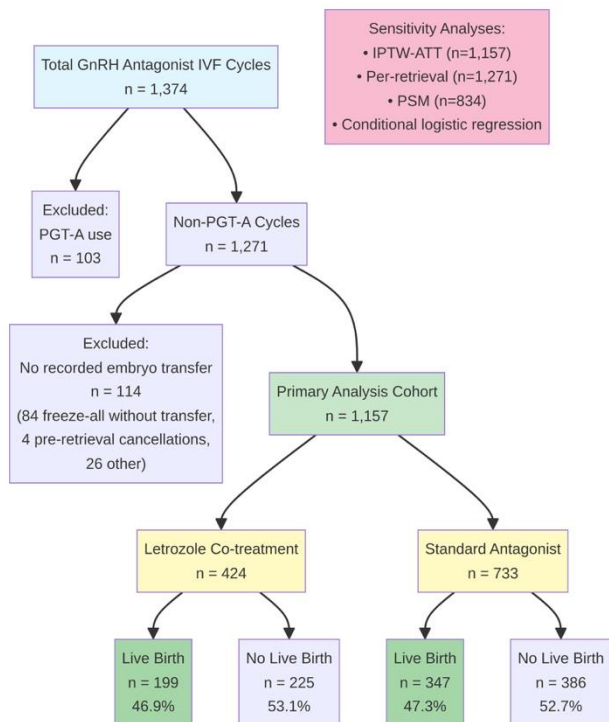


Fig. 1. Flow diagram. From 1,374 GnRH antagonist IVF cycles in women with PCOS, 103 were excluded for PGT-A use and 114 for absence of embryo transfer (84 freeze-all without subsequent transfer, 4 pre-retrieval cancellations, 26 others). The primary analysis included 1,157 cycles (424 letrozole, 733 standard). A per-retrieval sensitivity analysis included all 1,271 non-PGT-A cycles

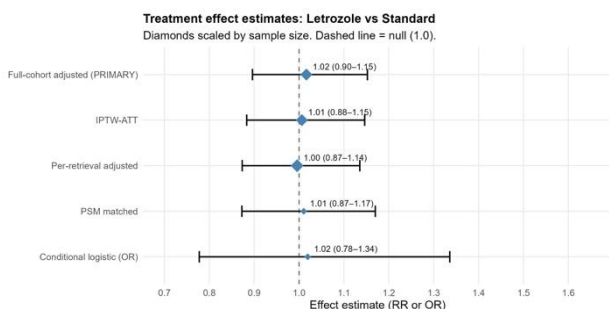


Fig. 2. Forest plot of treatment effect estimates (letrozole versus standard) for live birth across all analytic approaches. All estimates converge on the null (dashed line at 1.0). Diamonds are scaled by sample size

regression with HC0 robust variance estimation (11). Models included 16 prespecified covariates: age, body mass index, infertility duration, primary infertility, prior IVF, smoking, anti-Müllerian hormone, antral follicle count, follicle-stimulating hormone, luteinizing hormone, testosterone, HOMA-IR, hemoglobin A1c, metformin use, PCOS phenotype, and year of oocyte retrieval. Continuous covariates with plausible nonlinearity were modeled with natural cubic splines (3 df).

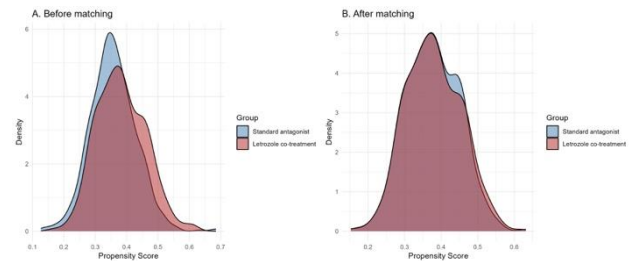


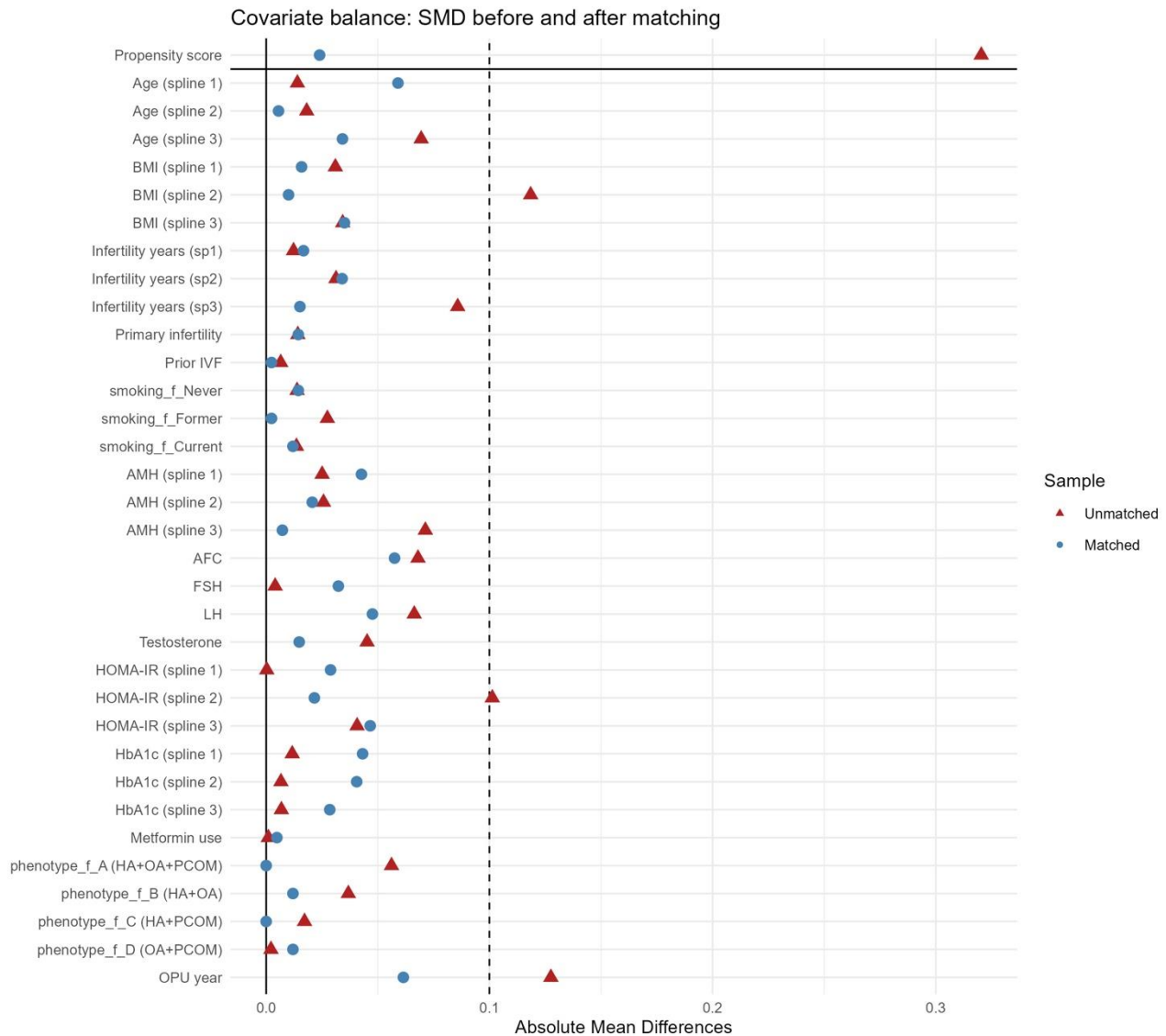
Fig. 3. Propensity score distributions before (A) and after (B) matching, demonstrating excellent overlap

Three pre-specified sensitivity analyses were performed: (i) inverse probability of treatment weighting with the average treatment effect on the treated estimand; (ii) 1:1 nearest-neighbor propensity score matching with a 0.2 SD caliper (12), yielding 417 matched pairs (n=834); and (iii) per-retrieval analysis (n=1,271) treating cycles without a transfer as non-live births. Continuous secondary outcomes were analyzed with linear regression and binary secondary outcomes with modified Poisson regression using the same covariate set. Two-sided p-values less than 0.05 were considered significant. All analyses were performed in R version 4.5.2 using MatchIt, cobalt, sandwich, lme4, clubSandwich, and WeightIt.

Results

Study Population: Of 1,374 GnRH antagonist IVF cycles, 103 were excluded for preimplantation genetic testing for aneuploidy, and 114 lacked a recorded embryo transfer, leaving 1,157 eligible cycles for the primary analysis: 424 in the letrozole group and 733 in the standard group (Figure 1). Baseline characteristics were well balanced (Table 1), with all standardized mean differences <0.10 for the core demographic, hormonal, and metabolic variables. Mean age was 29.6 versus 29.3 years, mean body mass index was 27.1 versus 27.6 kg/m², and mean anti-Müllerian hormone was 8.6 versus 8.7 ng/mL in the letrozole and standard groups, respectively. Freeze-all strategy was used in similar proportions in both groups (32.5% of letrozole vs 33.0% of standard cycles), and the distribution of PCOS phenotypes was comparable.

Stimulation and Laboratory Outcomes: Letrozole co-treatment was associated with substantially lower peak estradiol (1,187 ± 410 vs 2,971 ± 931 pg/mL; adjusted mean difference -1,763 pg/mL, 95% CI -1,840 to -1,686; p<0.001) and lower total gonadotropin consumption (1,351 ± 459 vs 1,497 ± 581 IU;



Supplementary Figure S1. Covariate balance love plot for the propensity score matching procedure, showing absolute standardized mean differences for all 16 prespecified covariates before (open circles) and after (filled circles) 1:1 nearest-neighbor matching with a 0.2 SD caliper. After matching, all standardized mean differences fell below the conventional 0.1 threshold, indicating excellent covariate balance across the 417 matched pairs

adjusted mean difference -146 IU, 95% CI -207 to -85 ; $p < 0.001$). Stimulation days and endometrial thickness at trigger were similar between groups. Letrozole was associated with higher oocyte yield (14.4 ± 5.8 vs 13.2 ± 5.8 ; $+1.5$, 95% CI 1.0 to 2.0 ; $p = 0.001$), more mature (MII) oocytes (11.2 ± 4.8 vs 10.2 ± 4.7 ; $+1.2$, 95% CI 0.8 to 1.6 ; $p = 0.001$), more 2PN embryos (8.3 ± 3.7 vs 7.7 ± 3.8 ; $+0.8$, 95% CI 0.4 to 1.1 ; $p = 0.001$), more total blastocysts (3.7 ± 2.0 vs 3.2 ± 2.0 ; $+0.6$, 95% CI 0.4 to 0.8 ; $p = 0.001$), and more good-quality blastocysts (2.0 ± 1.3 vs 1.7 ± 1.3 ; $+0.3$, 95% CI 0.2 to 0.5 ; $p = 0.001$) (Table 2).

Clinical Outcomes: Clinical pregnancy rates were 60.4% versus 63.0% (aRR, 0.97; 95% CI, 0.88–1.07; $p = 0.57$). Miscarriage was numerically lower

but not significantly different with letrozole (6.6% vs 8.7%; aRR, 0.70; 95% CI, 0.46–1.07; $p = 0.10$). Multiple gestation was numerically higher (7.3% vs 5.2%; aRR, 1.56; 95% CI, 0.98–2.50; $p = 0.06$). Moderate-to-severe OHSS occurred in 5.2% of letrozole versus 5.9% of standard cycles (aRR, 0.79; 95% CI, 0.48–1.29; $p = 0.34$). Live birth per cycle with embryo transfer was essentially identical between groups (46.9% vs 47.3%; aRR, 1.02; 95% CI, 0.90–1.15; $p = 0.80$) (Table 3).

Sensitivity Analyses: The null finding for live birth was consistent across all sensitivity analyses. Inverse probability of treatment weighting with the average treatment effect on the treated estimand yielded a risk ratio of 1.01 (95% CI, 0.88–1.15; $p = 0.93$). The per-retrieval analysis

Table 1: Baseline Characteristics of The Eligible Cohort (n=1,157)

Characteristic	Standard antagonist (n=733)	Letrozole co-treatment (n=424)	SMD	p
Age, years	29.30 ± 4.08	29.55 ± 4.18	0.06	0.31
BMI, kg/m ²	27.56 ± 5.22	27.14 ± 5.41	0.08	0.19
Infertility duration, years	4.22 ± 2.10	4.13 ± 1.98	0.04	0.49
Primary infertility, n (%)	446 (60.8)	264 (62.3)	0.03	0.68
Prior IVF, n (%)	258 (35.2)	152 (35.8)	0.01	0.87
Smoking status, n (%)			0.09	0.35
Never	572 (78.0)	325 (76.7)		
Former	94 (12.8)	66 (15.6)		
Current	67 (9.1)	33 (7.8)		
AMH, ng/mL	8.74 ± 3.71	8.56 ± 3.58	0.05	0.43
AFC	28.88 ± 9.68	28.23 ± 9.46	0.07	0.27
FSH, IU/L	5.87 ± 1.37	5.88 ± 1.46	0.00	0.95
LH, IU/L	9.45 ± 4.04	9.19 ± 3.86	0.07	0.29
Testosterone, ng/mL	0.70 ± 0.30	0.69 ± 0.28	0.04	0.48
HOMA-IR	2.86 ± 1.21	2.80 ± 1.24	0.05	0.42
HbA1c, %	5.43 ± 0.34	5.44 ± 0.34	0.02	0.77
Metformin use, n (%)	222 (30.3)	128 (30.2)	0.00	0.99
PCOS phenotype, n (%)			0.13	0.20
A (HA + OA + PCOM)	251 (34.2)	169 (39.9)		
B (HA + OA)	148 (20.2)	70 (16.5)		
C (HA + PCOM)	163 (22.2)	87 (20.5)		
D (OA + PCOM)	171 (23.3)	98 (23.1)		

Values are mean ± SD or n (%). SMD, standardized mean difference; BMI, body mass index; AMH, anti-Müllerian hormone; AFC, antral follicle count; FSH, follicle-stimulating hormone; LH, luteinizing hormone; HOMA-IR, homeostatic model assessment for insulin resistance; HbA1c, hemoglobin A1c; HA, hyperandrogenism; OA, oligo-anovulation; PCOM, polycystic ovarian morphology

(n=1,271), which classified cycles without a transfer as non-live births, returned an aRR of 1.00 (95% CI, 0.87–1.14; p=0.95). Propensity score matching produced 417 letrozole–standard pairs (n=834) with excellent covariate balance (all post-match standardized mean differences <0.05); the matched risk ratio was 1.01 (95% CI, 0.87–1.17; p=0.89) and the conditional logistic odds ratio was 1.02 (95% CI, 0.78–1.34; p=0.89) (Figure 2, Table 3, Supplementary Figure S1). Propensity score distributions showed broad overlap before matching and near-identical distributions after matching (Figure 3).

Discussion

Principal Findings: In this retrospective cohort of 1,157 eligible antagonist IVF cycles in women with PCOS, letrozole co-treatment lowered peak estradiol and gonadotropin use and increased oocyte, mature oocyte, fertilized embryo, and blastocyst yield. Despite these laboratory advantages, live birth was unchanged. The direction and magnitude of the live birth estimate remained stable across multivariable adjustment, propensity score matching, inverse probability weighting, per-retrieval analysis, and conditional logistic regression.

Interpretation: The essential clinical message from this study is that the laboratory improvements observed with letrozole did not

Table 2: Secondary outcomes in the eligible cohort (n=1,157)

Outcome	Standard antagonist (n=733)	Letrozole co-treatment (n=424)	Adjusted effect (95% CI)	p
Stimulation parameters				
Peak estradiol, pg/mL	2,971 ± 931	1,187 ± 410	-1,763 (-1,840 to -1,686)	<0.001
Total gonadotropin, IU	1,497 ± 581	1,351 ± 459	-146 (-207 to -85)	<0.001
Stimulation days	10.5 ± 1.8	10.4 ± 1.8	-0.1 (-0.3 to 0.1)	0.56
Endometrium at trigger, mm	10.2 ± 1.6	10.1 ± 1.5	-0.1 (-0.3 to 0.1)	0.29
Laboratory outcomes				
Oocytes retrieved	13.2 ± 5.8	14.4 ± 5.8	+1.5 (1.0 to 2.0)	0.001
Mature (MII) oocytes	10.2 ± 4.7	11.2 ± 4.8	+1.2 (0.8 to 1.6)	0.001
2PN embryos	7.7 ± 3.8	8.3 ± 3.7	+0.8 (0.4 to 1.1)	0.001
Day-3 good-quality embryos	3.5 ± 2.2	3.4 ± 2.1	-0.1 (-0.3 to 0.2)	0.65
Total blastocysts	3.2 ± 2.0	3.7 ± 2.0	+0.6 (0.4 to 0.8)	0.001
Good-quality blastocysts	1.7 ± 1.3	2.0 ± 1.3	+0.3 (0.2 to 0.5)	0.001
Clinical outcomes, n (%)				
Clinical pregnancy	462 (63.0)	256 (60.4)	0.97 (0.88–1.07)	0.57
Miscarriage	64 (8.7)	28 (6.6)	0.70 (0.46–1.07)	0.10
Multiple gestation	38 (5.2)	31 (7.3)	1.56 (0.98–2.50)	0.06
OHSS, moderate or severe	43 (5.9)	22 (5.2)	0.79 (0.48–1.29)	0.34

Values are mean ± SD unless otherwise indicated. Continuous outcomes are adjusted mean differences from linear regression with HC0-robust standard errors and represent the difference between letrozole and standard. Binary outcomes are adjusted risk ratios from modified Poisson regression. All models were adjusted for age, BMI, infertility duration, primary infertility, prior IVF, smoking, AMH, AFC, FSH, LH, testosterone, HOMA-IR, HbA1c, metformin use, PCOS phenotype, and year of oocyte retrieval. CI, confidence interval; 2PN, two-pronuclear (i.e., fertilized embryos with two pronuclei observed at the appropriate post-fertilization check); OHSS, ovarian hyperstimulation syndrome

translate into a higher live birth rate during the available follow-up period for the index retrieval. In women with PCOS, standard antagonist IVF already produced a mean oocyte yield above 13 and a live birth rate near 47%, suggesting that embryo quantity is unlikely to be the main limiting factor in this setting. Several explanations may account for this dissociation. First, a higher number of oocytes and embryos does not necessarily imply superior developmental competence, because conventional morphology cannot fully capture chromosomal or metabolic

fitness. Second, endocrine and metabolic abnormalities inherent to PCOS may continue to influence oocyte competence, implantation, and endometrial receptivity despite modification of the stimulation regimen; androgen excess, for example, is widely described as a contributor to impaired endometrial receptivity in PCOS (13). Third, the analysis was based on the index retrieval and did not capture cumulative live birth from subsequent frozen-embryo transfers, where the higher blastocyst yield with letrozole could plausibly translate into incremental benefits.

Table 3: Primary Outcome (live birth) Across Analytic Approaches

Analysis	n	Estimand	Estimate	95% CI	p
Full-cohort adjusted (primary)	1,157	aRR	1.02	0.90–1.15	0.80
IPTW-ATT (full cohort)	1,157	RR	1.01	0.88–1.15	0.93
Per-retrieval adjusted	1,271	aRR	1.00	0.87–1.14	0.95
PSM matched (CR2 SE)	834	RR	1.01	0.87–1.17	0.89
Conditional logistic (matched)	834	OR	1.02	0.78–1.34	0.89

Crude live birth rates: letrozole 46.9% (199/424) versus standard 47.3% (347/733). aRR, adjusted risk ratio; RR, risk ratio; OR, odds ratio; IPTW-ATT, inverse probability of treatment weighting with average treatment effect on the treated; PSM, propensity score matching; CR2 SE, bias-reduced linearization clustered standard errors

Cumulative Live Birth Considerations:

Cumulative live birth across all transfers from a single retrieval is increasingly considered the more clinically meaningful comparison than the index-transfer outcome alone (14,15). In this cohort, 32.5% of letrozole and 33.0% of standard cycles followed a freeze-all strategy, and a substantial fraction of non-live-birth cycles had remaining cryopreserved embryos. The available follow-up period for the index retrieval may therefore underestimate the potential downstream contribution of the additional blastocysts observed in the letrozole group. Randomized trials with cumulative live birth as the primary endpoint and adequate follow-up are needed to resolve this question.

Comparison with Previous Studies: Our findings are consistent with a recent PCOS-specific retrospective study in antagonist IVF/ICSI that did not show improved pregnancy outcomes with letrozole co-treatment (7). They extend prior evidence by providing the most adequately powered evaluation to date in a PCOS-specific antagonist IVF cohort, with multiple methodologically robust sensitivity analyses converging on the same null finding. Earlier studies that reported favorable laboratory effects of letrozole have similarly documented reductions in peak estradiol and gonadotropin requirements but have been heterogeneous and often underpowered for live birth (6). The 5 mg dose used here aligns with prior evidence suggesting greater estradiol suppression than 2.5 mg without compromising embryo yield (5).

Clinical Implications: These findings do not support routine adjunctive letrozole when a higher live birth rate is the primary clinical objective. Selective use may be considered when reducing peak estradiol exposure, lowering gonadotropin requirements, or mitigating OHSS risk is a

secondary clinical objective, particularly in patients with anticipated extreme ovarian response (16). A pre-treatment conversation describing the laboratory–clinical dissociation observed here would help align patient expectations with realistic outcomes.

Study Limitations: Several limitations warrant consideration. First, the retrospective single-center design limits external generalizability, and physician-directed treatment assignment introduces selection bias that statistical adjustment may not fully mitigate. This physician-directed allocation may have reflected anticipated ovarian response, perceived OHSS risk, prior treatment characteristics, or the goal of limiting estradiol exposure or gonadotropin requirements; therefore, residual treatment-selection bias remains possible despite adjustment for measured covariates. Second, follow-up was limited to the index retrieval, and cumulative live birth from subsequent frozen-embryo transfers was not captured. Third, the absence of formal randomization precludes definitive causal inference despite multiple sensitivity analyses converging on the same estimate. Fourth, residual confounding by unmeasured variables (e.g., embryo aneuploidy, endometrial transcriptomic markers, lifestyle factors) cannot be excluded. Strengths include the largest PCOS-specific antagonist IVF cohort of letrozole co-treatment to date, prespecified sensitivity analyses, and a single tertiary center with uniform protocols throughout the study period.

Letrozole co-treatment in antagonist IVF for PCOS reduced estradiol exposure and gonadotropin use and increased oocyte and blastocyst yields, but did not improve live birth rates during the observed follow-up. These findings do not support routine co-treatment with letrozole when the principal goal is a higher live

birth rate. However, selective use may warrant individualized consideration in patients for whom lowering peak estradiol, reducing gonadotropin requirements, or mitigating OHSS risk is a secondary clinical objective—particularly in those with an anticipated extreme ovarian response or elevated baseline estradiol sensitivity. Randomized trials with cumulative live births as the primary endpoint are needed to resolve the question definitively.

Use of AI and AI-Assisted Technologies:

During the preparation of this manuscript, the authors used artificial intelligence (AI)-assisted tools exclusively for language editing and minor typographical and structural improvements. The authors take full responsibility for the content of the manuscript, have critically reviewed and verified all outputs generated by these tools, and confirm that all intellectual contributions, analyses, and interpretations are their own.

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