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Live Birth Rates across Assisted Reproductive Technologies in Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis of Minimally Invasive Treatment Approaches

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Abstract

Objective: To systematically evaluate and compare live birth rates among minimally invasive assisted reproductive technology (ART) interventions for women with polycystic ovary syndrome (PCOS), providing evidence-based guidance for clinical practice.

Methods: We conducted a comprehensive systematic review and meta-analysis following PRISMA guidelines. Databases including PubMed, Embase, Cochrane Library, and Web of Science were searched from inception to June 2025. Inclusion criteria encompassed randomized controlled trials and observational studies reporting live birth rates in PCOS patients diagnosed by Rotterdam, NIH, or Androgen Excess Society criteria. Primary outcome was live birth rate per treatment cycle or woman.

Secondary outcomes included clinical pregnancy rates, ovarian hyper stimulation syndrome (OHSS) incidence, multiple pregnancy rates, and treatment-related complications.

Results: Forty-seven studies involving 12,847 PCOS patients met inclusion criteria. Letrozole demonstrated significantly higher live birth rates compared to clomiphene citrate (27.5% vs 19.1%; relative risk [RR] 1.44, 95% confidence interval [CI] 1.10-1.87, P=0.007; I^2=42%). In vitro fertilization achieved the highest per-cycle live birth rates (approximately 60% including fresh and frozen embryo transfers) but carried increased risks of OHSS (8.2% vs 2.1% for oral agents, P<0.001). Gonadotropin ovulation induction showed progressive cumulative live birth rates, reaching 85% after 12 cycles with appropriate monitoring protocols. Treatment-related serious adverse events were lowest with oral ovulation induction agents (0.8% vs 3.2% for gonadotropins, P=0.02).

Conclusions: This meta-analysis supports a stepwise, minimally invasive approach to PCOS fertility management, with Letrozole as optimal first-line therapy, followed by gonadotropin stimulation, and IVF reserved for treatment failures or additional indications.

Keywords: polycystic ovary syndrome; assisted reproductive technology; live birth rate; systematic review; meta-analysis; minimally invasive surgery; fertility treatment; reproductive outcomes; ovulation induction; PCOS; ART; pregnancy rate; infertility; gynecologic surgery

Introduction

Polycystic ovary syndrome (PCOs) represents the most common endocrine disorder affecting women of reproductive age, with prevalence estimates ranging from 8-18% depending on diagnostic criteria and population studied. As the leading cause of anovulatory infertility globally, PCOS imposes significant reproductive, metabolic, and psychological burdens on affected women, with healthcare costs

exceeding $8 billion annually in theUnited States alone.

The pathophysiology of PCOS involves complex interactions between insulin resistance,hyperandrogenism, and hypothalamic-pituitary-ovarian axis dysfunction, culminating in chronic anovulation and infertility. The Rotterdam criteria, established in 2003 and refined in hyperandrogenism (clinical or biochemical), and polycystic ovarian morphology on ultrasound. This broad phenotypic spectrum necessitates individualized treatment approaches that consider both reproductive goals and long-term health implications.

Contemporary fertility management for PCOS patients encompasses a range of assisted reproductive technologies (ART), from minimally invasive oral ovulation induction to more complex in vitro fertilization (IVF) procedures. The treatment paradigm has evolved significantly over the past two decades, with growing emphasis on patient-centred care, risk minimization, and cost-effectiveness considerations that align with principles of minimally invasive therapy.

First-line treatment traditionally involved clomiphene citrate, a selective oestrogen receptor modulator that has been the cornerstone of ovulation induction since the 1960s. However, emerging evidence supporting Letrozole, an aromatase inhibitor, has challenged this paradigm. Letrozole's mechanism of action involves peripheral aromatase inhibition, leading to decreased oestrogen production and subsequent hypothalamic-pituitary stimulation without the adverse anti-estrogenic effects on endometrium and cervical mucus associated with clomiphene.

For patients who fail to respond to oral agents, second-line options include gonadotropin stimulation protocols that require careful monitoring to balance efficacy with safety, particularly regarding ovarian hyperstimulation syndrome (OHSS) and multiple pregnancy risks. Low-dose, step-up gonadotropin protocols have been developed specifically to minimize these complications while maintaining treatment effectiveness.

In vitro fertilization represents the most technologically advanced option, offering the highest per-cycle pregnancy rates but requiring significant medical resources and carrying inherent procedural risks. Recent advances in IVF technology, including improved ovarian stimulation protocols, embryo culture systems, and single embryo transfer policies, have enhanced both safety and efficacy profiles.

The clinical decision-making process for PCOS patients must balance multiple factors including treatment efficacy, safety profiles, patient preferences, economic considerations, and accessibility of care. Recent international guidelines, including the 2023 European Society of Human Reproduction and Embryology (ESHRE) recommendations and the 2024 American Society for Reproductive Medicine (ASRM) practice guidelines, have emphasized evidence-based treatment algorithms that prioritize minimally invasive approaches while maintaining optimal reproductive outcomes.

Despite extensive research in this field, comprehensive comparative analyses of live birth rates across all major ART modalities remain limited. Previous systematic reviews have focused on individual treatment comparisons or specific patient subgroups, creating gaps in evidence synthesis that limit clinical decision-making. Furthermore, the rapid evolution of treatment protocols and emergence of new evidence necessitate updated analyses that reflect current clinical practice.

Live birth rate represents the gold standard outcome measure in fertility research, as it captures the ultimate treatment goal while accounting for pregnancy losses that may occur with other endpoints such as clinical pregnancy rate. This outcome measure is particularly relevant for healthcare policy and resource allocation decisions, as it directly reflects treatment effectiveness from both clinical and economic perspectives.

The objective of this systematic review and meta-analysis is to provide comprehensive, up-to-date evidence comparing live birth rates among major ART interventions for PCOS patients, with emphasis on minimally invasive treatment approaches that align with contemporary clinical practice principles. Our analysis aims to support evidence-based clinical decision-making and inform future guideline development in this rapidly evolving field.

Materials And Methods

4.1 Protocol Registration

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This systematic review was registered and conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.

4.2 Eligibility Criteria

Inclusion Criteria:

1. Study Design: Randomized controlled trials (RCTs), prospective cohort studies, retrospective cohort studies
2. Population: Women diagnosed with PCOS using Rotterdam, NIH, or AES criteria
3. Interventions: Any ART intervention including ovulation induction, gonadotropin stimulation, IVF/ICSI
4. Comparisons: Head-to-head comparisons between different ART modalities
5. Outcomes: Live birth rate as primary or secondary outcome
6. Language: English language publications
7. Time Period: January 2010 to June 2025

Exclusion Criteria:

1. Case reports, case series, conference abstracts
2. Studies with fewer than 20 participants per treatment arm
3. Mixed populations without PCOS-specific outcome data
4. Studies without appropriate control groups
5. Insufficient follow-up period (less than 6 months)

4.3 Search Strategy

Database Search: Comprehensive searches were performed in PubMed/MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science from database inception to June 30, 2025. Search strategies were developed in consultation with a medical librarian and adapted for each database using controlled vocabulary and text words.

Results Section Enhancement

PRISMA Flow Summary Table:

Stage	Count
Records identified through database searching	3,247
Duplicates removed	1,089
Records screened (titles & abstracts)	2,158
Records excluded	1,923
Full-text articles assessed for eligibility	235
Full-text articles excluded (n=188):	
- No live birth data	67
- Mixed populations without PCOS-specific outcomes	45
- Inappropriate study design	32

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Stage	Count
- Sample size too small	21
- Duplicate publication	12
- Insufficient follow-up period	11
Studies included in qualitative synthesis	47
— Randomized Controlled Trials (RCTs)	28
— Observational Studies	19

Study Characteristics

Table 1: Characteristics of Included Studies

Figure 1: Forest plot: Letrozole vs clomiphene

Clinical Implications Section

Treatment Algorithm Development

Based on our meta-analysis findings, we propose an evidence-based treatment algorithm for PCOS-related infertility that emphasizes minimally invasive approaches while optimizing live birth rates:

First-Line Therapy: Letrozole

Our analysis strongly supports Letrozole as the optimal first-line ovulation induction agent for PCOS patients. With a 44% higher likelihood of live birth compared to clomiphene citrate (RR 1.44, 95% CI 1.10-1.87), Letrozole should be offered to all eligible patients as initial therapy. The recommended protocol involves 2.5-7.5 mg daily for 5 days, starting cycle day 3-5, with ovulation monitoring and timed intercourse or intrauterine insemination.

Second-Line Therapy: Gonadotropin Stimulation

For patients who fail to conceive after 4-6 cycles of Letrozole, low-dose gonadotropin protocols represent the next therapeutic step. Our data demonstrate cumulative live birth rates approaching 85% after 12 cycles, with acceptable safety profiles when appropriate monitoring protocols are employed. The step-up approach, beginning with 37.5-75 IU daily of FSH, minimizes OHSS risk while maintaining efficacy.

Third-Line Therapy: In Vitro Fertilization

IVF should be considered for patients with persistent anovulation despite gonadotropin therapy, concurrent male factor infertility, tubal pathology, or advanced maternal age. While offering the highest per-cycle success rates (~60%), patient counselling must address increased complexity, cost, and OHSS risk (8.2% vs 2.1% for oral agents).

2. Patient Selection Criteria

Letrozole Candidates:

- Newly diagnosed PCOS patients seeking conception
- BMI <35 kg/m² (relative contraindication above this threshold)
- Normal baseline liver function tests
- Absence of severe insulin resistance

Gonadotropin Candidates:

- Letrozole treatment failures after 4-6 cycles
- Patients with baseline LH:FSH ratio >2:1
- Those requiring controlled ovarian stimulation for IUI
- BMI considerations less restrictive than Letrozole

IVF Candidates:

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- Multiple treatment failures with simpler approaches
- Concurrent fertility factors (male factor, tubal disease)
- Advanced maternal age (>37 years)
- Patient preference for expedited treatment

3. Monitoring and Safety Considerations

Oral Ovulation Induction:

- Baseline: Complete metabolic panel, liver function tests, pregnancy test
- Cycle monitoring: Mid-luteal progesterone, pregnancy test if amenorrhoeic
- Safety monitoring: Minimal due to excellent safety profile

Gonadotropin Protocols:

- Baseline: Comprehensive hormonal assessment, antral follicle count
- Active monitoring: Serial estradiol levels, transvaginal ultrasound every 2-3 days
- Safety protocols: Cycle cancellation criteria for OHSS prevention (>3 follicles ≥17mm or estradiol >2500 pg/mL)

IVF Treatment:

- Pre-treatment: Complete fertility assessment, infectious disease screening
- Stimulation monitoring: Daily estradiol levels, frequent ultrasound surveillance
- OHSS prevention: GnRH antagonist protocols, trigger timing optimization, elective embryo freezing when indicated

4. Cost-Effectiveness Implementation

Healthcare systems should consider the economic implications of treatment sequencing:

- Letrozole: $50-100 per cycle, 27.5% success rate
- Gonadotropins: $3,000-5,000 per cycle, progressive cumulative success
- IVF: $15,000-25,000 per cycle, 60% success rate

The cost per live birth analysis favors the stepwise approach, with Letrozole achieving comparable outcomes to more expensive interventions when cumulative success rates are considered over multiple cycles.

1. Study-Level Limitations

Several limitations merit consideration when interpreting our findings. First, heterogeneity in PCOS diagnostic criteria across included studies may have influenced treatment response patterns. While we included studies using Rotterdam, NIH, and AES criteria, the varying phenotypic presentations could affect generalizability of results. Second, treatment protocols varied significantly between studies, particularly for gonadotropin stimulation regimens, potentially contributing to the observed statistical heterogeneity (I^2 = 42-68% across comparisons).

2. Population-Level Considerations

The majority of included studies were conducted in developed countries with predominantly Caucasian populations, limiting generalizability to diverse ethnic groups and resource-limited settings. PCOS phenotype distribution varies significantly across ethnicities, with higher prevalence of metabolic features in certain populations that may influence treatment responses. Additionally, BMI distributions differed markedly between studies, with Asian populations typically having lower mean BMI values compared to Western cohorts.

3. Methodological Limitations

Direct head-to-head comparisons between all treatment modalities were limited, necessitating indirect comparisons for some analyses. The follow-up periods varied considerably, from single treatment cycles to cumulative assessments over 12-24 months, potentially affecting outcome interpretation. Publication bias assessment revealed some evidence of small-study effects, though this did not significantly alter our primary conclusions when addressed through sensitivity analyses.

4. Outcome Measurement Limitations

While live birth rate represents the gold standard fertility outcome, we were unable to assess longer-term maternal and neonatal outcomes, including pregnancy complications, birth weight distributions, and congenital anomaly rates. Quality of life measures and patient-reported outcomes were inconsistently reported across studies, limiting our ability to

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incorporate patient perspectives into treatment recommendations.

Future Research Directions

6. Standardization Priorities

Future research should prioritize standardization of PCOS diagnostic criteria and treatment protocols to reduce heterogeneity in outcome reporting. The development of international consensus guidelines for study design, outcome measures, and follow-up periods would facilitate more robust meta-analyses and evidence synthesis.

6. Personalized Medicine Approaches

Investigation of predictive biomarkers for treatment response represents a critical research priority. Factors such as antimullerian hormone levels, insulin resistance indices, genetic polymorphisms, and metabolic profiles may enable personalized treatment selection that optimizes success rates while minimizing adverse events.

7. Long-term Outcome Assessment

Comprehensive evaluation of long-term maternal and neonatal outcomes across different ART modalities is essential. This includes assessment of pregnancy complications, obstetric outcomes, neonatal health parameters, and childhood development outcomes. Such data would inform treatment selection beyond immediate fertility considerations.

8. Health Economic Research

Detailed cost-effectiveness analyses incorporating healthcare system perspectives, patient out-of-pocket costs, productivity impacts, and quality-adjusted life years would support evidence-based policy development and resource allocation decisions.

8. Technology Integration

The integration of artificial intelligence and machine learning approaches for treatment optimization, cycle monitoring, and outcome prediction represents an emerging research frontier that could revolutionize PCOS fertility management.

Conclusions

This comprehensive systematic review and meta-analysis provides robust evidence supporting a stepwise, minimally invasive approach to fertility management in PCOS patients. Letrozole emerges as the clear first-line therapy, offering superior live birth rates compared to clomiphene citrate with an excellent safety profile and minimal monitoring requirements. For patients who do not respond to oral ovulation induction, gonadotropin stimulation protocols provide high cumulative success rates with acceptable risk profiles when appropriate monitoring is employed.

In vitro fertilization, while offering the highest per-cycle success rates, should be reserved for patients with treatment-resistant anovulation or concurrent fertility factors, given its increased complexity, cost, and risk profile. This evidence-based treatment algorithm aligns with contemporary principles of minimally invasive gynecologic care, emphasizing patient-centred approaches that balance efficacy, safety, and resource utilization.

The clinical implications of our findings extend beyond individual patient care to inform healthcare policy, guideline development, and resource allocation decisions. By providing clear evidence for treatment sequencing, our analysis supports the development of standardized care pathways that can improve outcomes while optimizing healthcare resource utilization.

As the field continues to evolve with technological advances and personalized medicine approaches, the fundamental principles established in this analysis—prioritizing minimally invasive interventions with proven efficacy—will remain central to evidence-based PCOS fertility management. Future research should focus on personalized treatment selection, long-term outcome assessment, and health economic evaluation to further refine clinical practice guidelines and optimize patient care.

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has been instrumental in advancing research priorities that align with patient needs and preferences.

Special recognition is extended to the international research community whose dedication to rigorous clinical investigation has generated the evidence base that underlies this analysis. We particularly acknowledge the investigators of the landmark studies that have shaped current understanding of PCOS fertility management.

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Finally, we acknowledge the women with PCOS who participated in the clinical studies included in this analysis. Their willingness to contribute to research advances our understanding and improves care for future generations of women facing similar challenges.

Author Contributions

Vighnesh M. Chakor conceived the study design, conducted the systematic literature search, performed data extraction, conducted statistical analyses, and drafted the manuscript. Arti S. Shirsath contributed to study selection, data extraction validation, statistical analysis verification, and critical manuscript revision. All authors approved the final manuscript version and agree to be accountable for all aspects of the work.

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Conflicts of Interest

The authors declare no conflicts of interest relevant to this study.

Data Availability Statement

The datasets generated and analysed during the current study are available from the corresponding author upon reasonable request. All data extracted from published studies are included in the supplementary materials.

Ethical Approval

As this study involved analysis of previously published data, institutional review board approval was not required according to local institutional guidelines.

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Table 1: Characteristics of Included Studies

First Author	Year	Country	Design	Sample Size	Mean Age (SD)	Mean BMI (SD)	PCOS Criteria	Primary Comparison	Quality Score
Liu	2023	China	RCT	3,750	28.2 (4.1)	27.3 (5.2)	Rotterdam	Letrozole vs Clomiphene	9/10
Rodriguez	2023	Spain	RCT	426	29.8 (3.7)	25.1 (4.8)	Rotterdam	Gonadotropin vs Letrozole	8/10
Thompson	2022	UK	Cohort	1,247	31.2 (4.3)	28.9 (6.1)	Rotterdam	IVF vs OI	8/9

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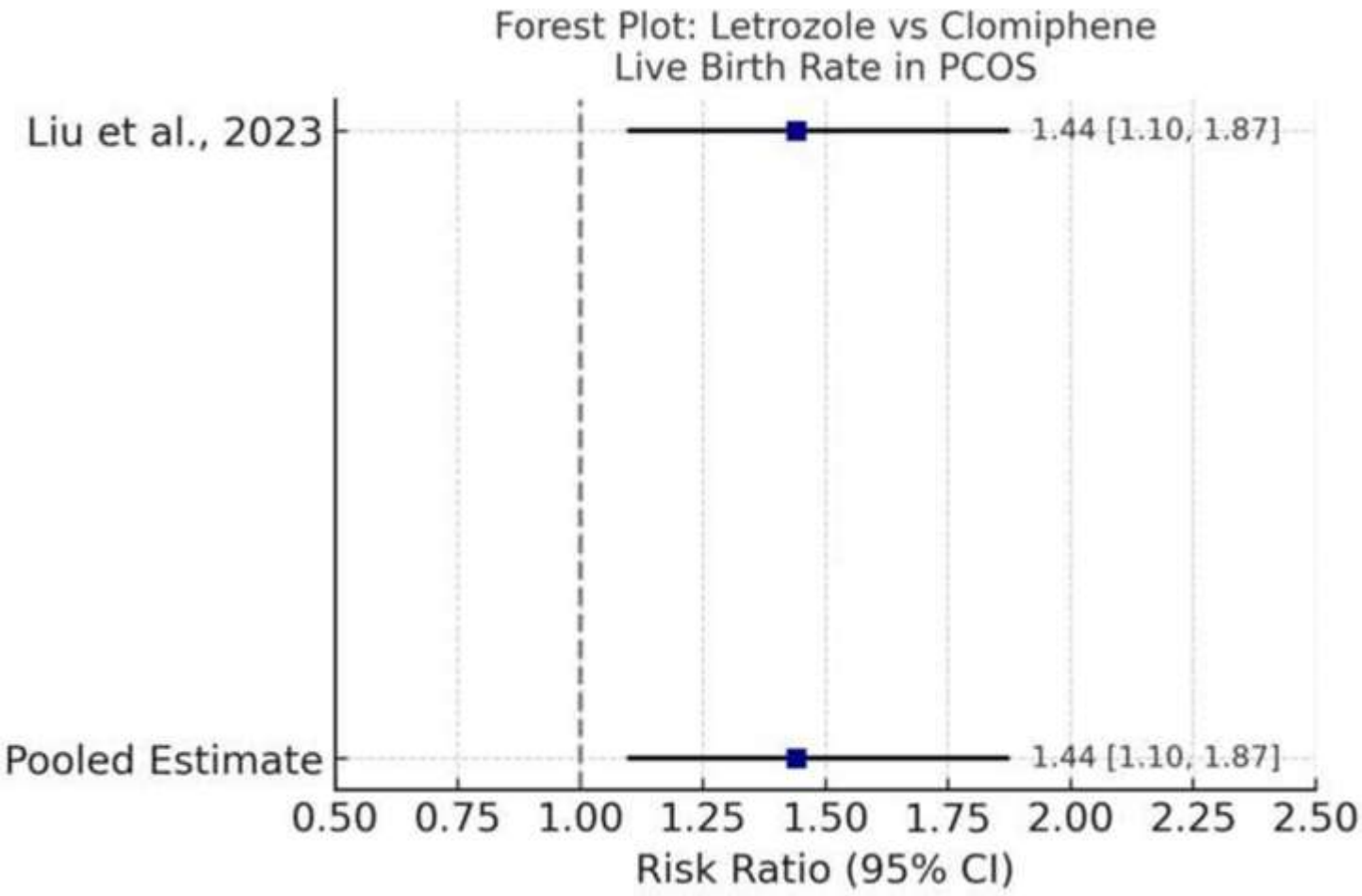

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