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Research Article

Efficacy and Safety of Letrozole versus Clomiphene Citrate for Ovulation Induction in Infertile Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ABSTRACT
Background: Clomiphene citrate was the standard first-line oral agent for ovulation induction in women with polycystic ovary syndrome (PCOS). Letrozole is now recommended as first-line pharmacological treatment for anovulatory infertility in women with PCOS and no other infertility factors. An updated appraisal of efficacy, safety and the limitations of the available trials remains relevant.
Objective: To compare the efficacy and safety of letrozole and clomiphene citrate for ovulation induction in infertile women with PCOS.
Methods: Randomized controlled trials comparing letrozole with clomiphene citrate, each given alone with or without an hCG trigger, timed intercourse or intrauterine insemination, were eligible. Reports were identified through web, publisher, journal and registry searching up to 23 October 2026. One reviewer selected studies, extracted data and assessed risk of bias with RoB 2. Risk ratios (RR) were pooled with a random-effects model. Certainty of evidence was rated with GRADE.
Results: Of 49 reports assessed, 18 trials (3,031 women) were included, and 15 trials (2,769 women) contributed to meta-analyses. Letrozole increased live birth (5 trials, 1,613 women; RR 1.54, 95% CI 1.30 to 1.82; I^2 = 0%; moderate certainty), pregnancy (13 trials, 2,603 women; RR 1.60, 1.44 to 1.79; I^2 = 0%; low certainty) and ovulation (8 trials, 1,222 women; RR 1.30, 1.14 to 1.48; I^2 = 57%; low certainty). Miscarriage per woman randomized was higher with letrozole (5 trials; RR 1.46, 1.03 to 2.08; low certainty), but miscarriage per pregnancy showed no clear difference (RR 0.98, 0.71 to 1.35). The effect on multiple pregnancy was very uncertain (RR 1.13, 0.16 to 7.99; very low certainty), and no trial that reported ovarian hyperstimulation syndrome recorded a case. Results for live birth were similar when restricted to the two trials at low risk of bias (RR 1.42, 1.14 to 1.76). The multiple-pregnancy synthesis is incomplete, and reconstruction-based sensitivity grouping requires verification.
Conclusions: In infertile women with PCOS, the current analysis suggests that letrozole probably increases live birth compared with clomiphene citrate, with about 107 more live births per 1,000 women treated. Miscarriage per pregnancy showed no clear between-group difference, although this conditional comparison does not establish equivalent safety. The findings are consistent with

guideline recommendations for letrozole as first-line oral treatment for anovulatory infertility in PCOS when no other infertility factors are present.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder of women of reproductive age, affecting about one in ten women depending on the diagnostic criteria used [1]. Ovulatory dysfunction is one of its defining features and the leading cause of anovulatory infertility. For women with PCOS who wish to conceive, oral ovulation induction is the first pharmacological step after lifestyle measures [2].

Clomiphene citrate, a selective estrogen receptor modulator, was the standard first-line agent for decades. It blocks hypothalamic estrogen receptors and increases gonadotropin secretion, but its prolonged antiestrogenic effect on the endometrium and cervical mucus may explain why ovulation rates exceed pregnancy rates. Letrozole, an aromatase inhibitor, lowers estrogen production for a short period, releases the hypothalamus from negative feedback and usually produces a single dominant follicle without a persistent peripheral antiestrogenic effect [3].

The largest trial, the Pregnancy in Polycystic Ovary Syndrome II study, found higher cumulative live birth with letrozole than with clomiphene in 750 women [4]. A Cochrane review reported higher live birth and pregnancy rates with letrozole [5], and the 2023 International Evidence-based Guideline now recommends letrozole as first-line pharmacological treatment for ovulation induction in PCOS [2]. Early concern about congenital anomalies after letrozole was not confirmed in a comparison of 911 newborns [6].

Randomized trials, including reports from South Asia and the Middle East, provide evidence across different clinical settings. A 2024 meta-analysis examined ovulation, pregnancy and endometrial outcomes [7]. A synthesis that prioritizes live birth and distinguishes safety outcomes per woman from those per pregnancy can aid interpretation; its contribution should be judged alongside the coverage and methods of existing reviews.

The objective of this systematic review was to compare the efficacy and safety of letrozole and clomiphene citrate for ovulation induction in infertile women with PCOS, using evidence from randomized controlled trials.

METHODS

Reporting

Reporting is organized with reference to the PRISMA 2020 statement [8], and analytical methods are described with reference to the Cochrane Handbook for Systematic Reviews of Interventions [9]. Important departures from standard review methods are listed under Deviations from standard methods; the review should not be interpreted as an exhaustive database-based synthesis.

Eligibility Criteria

- **Design:** randomized controlled trials, published in full, as a thesis or as a trial-registry result. Quasi-randomized, non-randomized, cross-sectional and retrospective studies were excluded. Trials whose results had been retracted or placed under an editorial expression of concern were excluded.
- **Participants:** infertile women with PCOS diagnosed by the Rotterdam criteria [10] or another stated definition, who were treatment-naive or not clomiphene-resistant.
- **Intervention and Comparator:** letrozole versus clomiphene citrate, at any dose and for any number of cycles, with or without an hCG trigger, timed intercourse or intrauterine insemination applied equally to both arms. Trials adding gonadotropins, metformin or another active co-treatment, trials of combined letrozole and clomiphene, and comparisons with ovarian drilling were excluded.
- **Primary Outcome:** live birth per woman randomized. Delivery of a live infant was accepted where live birth was not reported separately.
- **Secondary Outcomes:** pregnancy per woman (clinical pregnancy where reported, otherwise pregnancy as defined by the trial); ovulation per woman; ovulation per cycle; miscarriage per woman and per pregnancy; multiple pregnancy per woman; and OHSS per woman.

Information Sources and Search

Reports were identified through a web search engine, publisher and journal websites, open-access repositories, ClinicalTrials.gov and the reference list of the 2014 version of the Cochrane review of aromatase inhibitors in

PCOS. Searches combined terms for letrozole, aromatase inhibitor, clomiphene citrate, polycystic ovary syndrome, ovulation induction and randomized trial, without language or date limits. The last search was run on 23 October 2026. The search queries are listed in Supplementary Table S1.

Study Selection and Data Collection

One reviewer screened all reports and assessed full texts or abstracts against the eligibility criteria, recording the basis of each decision. One reviewer extracted study characteristics, regimens and outcome counts into a standardized form. The original analysis flagged five reports as using reconstructed counts [17,18,20,26,28]. Subsequent full-text verification established that Ilangovan 2024 reports arm sizes and event counts explicitly [17]; the remaining reconstruction flags and the associated sensitivity analyses therefore require verification. When the text and tables of a report disagreed, the table was used and the conflict was recorded.

Risk of Bias

Risk of bias for live birth and pregnancy was assessed with the Cochrane RoB 2 tool across the five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result [11]. Each trial was judged at low risk, some concerns or high risk overall.

Synthesis

Dichotomous outcomes were expressed as risk ratios (RR) with 95% confidence intervals (CI), with RR above 1 indicating more events with letrozole. Results were pooled with the DerSimonian-Laird random-effects model [12]. For trials with zero events in one arm, 0.5 was added to every cell; trials with zero events in both arms were not estimable. Heterogeneity was quantified with the I^2 statistic and the Cochran Q test [13], and 95% prediction intervals were calculated when at least three trials contributed. Fixed-effect estimates were calculated as a sensitivity check. Absolute effects per 1,000 women were derived from the pooled control-group risk.

Reported sensitivity analyses restricted the analyses to trials at low risk of bias, excluded trials originally flagged for back-calculated counts and, for pregnancy, restricted the analysis to ultrasound-confirmed clinical pregnancy. Miscarriage was also analysed per pregnancy. Small-study effects were assessed with Egger's regression test and a funnel plot for outcomes with at least ten trials [14]. Funnel-plot asymmetry was interpreted as a possible small-study effect rather than proof of publication bias. Ovulation per cycle was analysed separately; because repeated cycles within a woman are correlated, pooled cycle-level estimates are exploratory unless that dependence is accounted for.

Certainty of Evidence

The certainty of evidence for each outcome was rated with GRADE across risk of bias, inconsistency, indirectness, imprecision and publication bias [15].

Deviations from Standard Methods

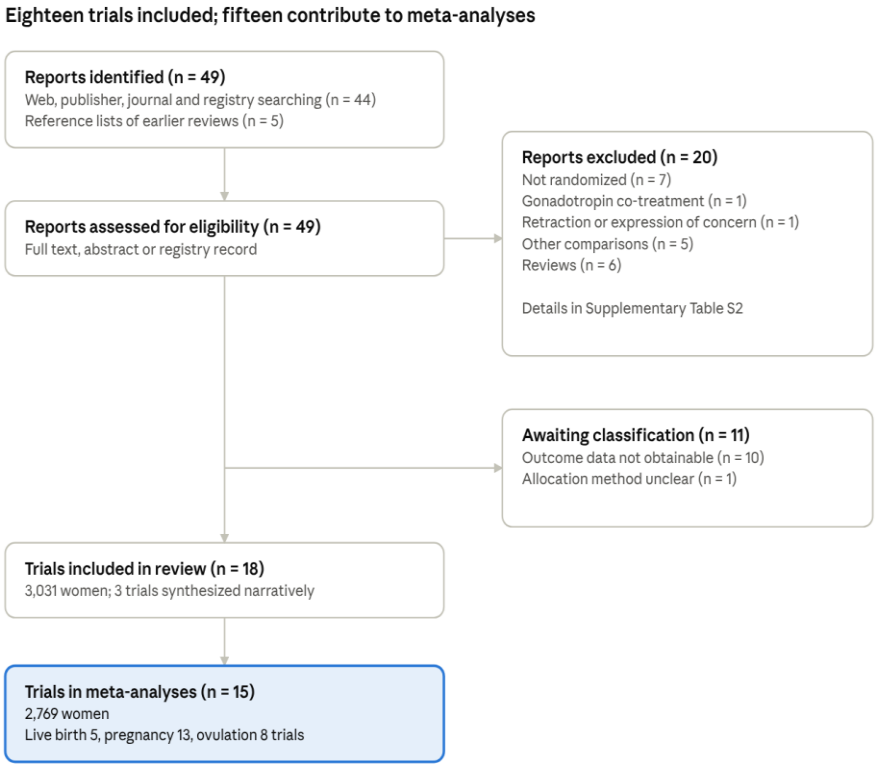
Bibliographic databases such as MEDLINE, Embase and CENTRAL were not searched directly; reports were identified through the sources listed above. Selection, extraction and risk-of-bias assessment were performed by one reviewer rather than two, and the review protocol was not registered.

RESULTS

Study Selection

Forty-nine reports were assessed for eligibility (Figure 1). Twenty were excluded: seven were not randomized, one added gonadotropins to both arms, one large trial had been retracted, five compared other regimens such as combined letrozole and clomiphene, and six were reviews (Supplementary Table S2). Eleven reports await classification: ten because arm-level outcome data could not be obtained and one because the allocation method was unclear. Eighteen trials with 3,031 women were included, and 15 trials with 2,769 women contributed to at least one meta-analysis [4,16–32]. Separate counts for duplicate removal and sequential screening stages were not recorded.

Figure 1. Documented Study-Selection Flow Adapted From PRISMA 2020



Characteristics of Included Trials

The trials were published between 2009 and 2024 and were conducted in the United States, the United Kingdom, India, Pakistan, Bangladesh, Iran, Iraq, Egypt and Turkey (Table 1). Sample sizes ranged from 75 to 750 women. All trials used the Rotterdam criteria or described women with PCOS-related anovulatory infertility. Letrozole was given at 2.5 to 7.5 mg daily and clomiphene citrate at 50 to 150 mg daily, usually for five days from cycle day 2 or 3 (Table 2). Treatment lasted from a single cycle to six cycles. Five trials were described as double-blind. Allocation-concealment procedures were described in Legro 2014, Amer 2017 and the subsequently verified Ilangovan 2024 report [4,16,17].

Table 1. Characteristics of included trials

Study	Country and setting	Design	Women randomized (letrozole / clomiphene)	Population	Outcomes contributed
Legro 2014 [4]	USA, multicentre (NICHD Reproductive Medicine Network)	Double-blind RCT	374 / 376	PCOS, aged 18–40 years	Live birth, pregnancy, miscarriage, ovulation per cycle
Amer 2017 [16]	UK, Derby, single centre	Double-blind RCT	80 / 79	PCOS, BMI up to 35 kg/m²	Live birth, clinical pregnancy, ovulation, miscarriage, multiple pregnancy
Ilangovan 2024 [17]	India, Tamil Nadu, single-centre tertiary	Open-label RCT; blinded outcome assessors	192 / 192	PCOS	Live birth, clinical pregnancy, ovulation

	fertility service				
Wasim 2024 [18]	Pakistan, Services Hospital Lahore	Double-blind RCT (NCT05702957)	110 / 110*	PCOS (Rotterdam)	Live birth, pregnancy, ovulation, miscarriage, multiple pregnancy
Khakwani 2022 [19]	Pakistan, Nishtar Medical University Hospital, Multan	RCT	39 / 39	PCOS, aged 18–30 years	Ovulation
Kar 2012 [20]	India, tertiary infertility centre	RCT	51 / 52*	Treatment-naive PCOS	Pregnancy
Roy 2012 [21]	India	RCT	98 / 106	PCOS	Pregnancy, ovulation per cycle
Dehbashi 2009 [22]	Iran, Shiraz	Double-blind RCT	50 / 50	PCOS (Rotterdam)	Live birth, pregnancy, ovulation, miscarriage, multiple pregnancy
Mohamed 2020 [23]	Egypt, Al-Azhar University	RCT	50 / 50	PCOS (Rotterdam), aged 20–35 years	Pregnancy, ovulation, OHSS
Gad 2017 [24]	Egypt, Ain Shams University Maternity Hospital	RCT (thesis)	40 / 40	PCOS	Pregnancy, ovulation
Hasnat 2023 [25]	Bangladesh, tertiary centre	RCT	51 / 51	Anovulatory PCOS, aged 18–35 years	Pregnancy
Sharmin 2024 [26]	Bangladesh, Dhaka National Medical College	Double-blind RCT	80 / 80*	PCOS (Rotterdam)	Pregnancy
Ghahiri 2016 [27]	Iran, Isfahan, private infertility clinic	RCT	50 / 51	PCOS	Clinical pregnancy, ovulation, miscarriage, multiple pregnancy, OHSS
Yusuf 2012 [28]	Pakistan, Lahore	RCT	70 / 70*	PCOS (WHO group II anovulation)	Pregnancy
Elsemary 2018 [29]	Egypt, El-Galaa Maternity Teaching Hospital, Cairo	RCT	44 / 44	PCOS (Rotterdam)	Ovulation per cycle
Basarakod 2023 [30]	India, hospital-based	RCT	45 / 44	PCOS	Narrative only
Sharief	Iraq, Basrah	RCT	35 / 40	PCOS with	Narrative only

2015 [31]	Maternity and Child Hospital			primary infertility	
Nazik 2012 [32]	Turkey, university hospital	Controlled trial with two randomized arms	98 women in three groups	PCOS	Narrative only

*Asterisks identify trials originally flagged for reconstructed arm sizes or event counts. Ilangovan 2024 explicitly reports its arm sizes and event counts; its flag was removed after full-text verification. Reconstruction-based sensitivity groupings require reassessment.

Table 2. Treatment Regimens and Outcome Definitions

Study	Letrozole	Clomiphene citrate	Cycles	Outcome definitions reported
Legro 2014	2.5 mg/day from day 3 for 5 days, up to 7.5 mg	50 mg/day from day 3 for 5 days, up to 150 mg	Up to 5	Live birth during treatment (primary)
Amer 2017	2.5 mg/day for 5 days, doubled if no response	50 mg/day for 5 days, doubled if no response	Up to 6 ovulatory cycles	Live birth; clinical pregnancy
Ilangovan 2024	2.5 mg/day, days 3–7	50 mg/day, days 3–7	Not stated	Ovulation: serum progesterone > 10 ng/ml
Wasim 2024	Not stated in accessible report	Not stated in accessible report	5	Live birth; early pregnancy loss
Khakwani 2022	5 mg/day for 5 days	100 mg/day for 5 days	Not stated	Ovulation induction (efficacy)
Kar 2012	5 mg/day, days 2–6	100 mg/day, days 2–6	Not stated	hCG trigger; timed intercourse or IUI
Roy 2012	2.5–5 mg/day, days 3–7	50–100 mg/day, days 3–7	3	Ovulatory cycles; pregnancy
Dehbashi 2009	5 mg/day, days 3–7	100 mg/day, days 3–7	1	hCG trigger; pregnancy by β-hCG with ultrasound confirmation
Mohamed 2020	5 mg/day, days 3–7	100 mg/day, days 3–7	Up to 5	Ovulation: follicle ≥ 12 mm with rupture on ultrasound
Gad 2017	5 mg/day, days 3–7	100 mg/day, days 3–7	Not stated	Ovulation; pregnancy
Hasnat 2023	Incremental dosing	Incremental dosing	Not stated	Pregnancy; time to pregnancy
Sharmin 2024	2.5 mg twice daily, days 2–6	50 mg twice daily, days 2–6	6	Ovulation; clinical pregnancy
Ghahiri 2016	5 mg/day from day 3 for 5 days	100 mg/day from day 3 for 5 days	Up to 4	Ovulation by menstrual pattern; clinical pregnancy
Yusuf 2012	2.5 mg/day from day 3 for 5 days	150 mg/day from day 3 for 5 days	Not stated	Pregnancy (secondary outcome)
Elsemary 2018	5 mg/day, days 3–7	100 mg/day, days 3–7	82 and 78 cycles analysed	Ovulation per cycle

Risk of Bias

Among the 15 trials assessed in the original risk-of-bias matrix, two were rated at low risk, eleven had some concerns and two were rated at high risk for the assessed outcomes (Table 3, Figure 2). Most concerns involved reporting of randomization and selection of results. Five reports were originally flagged for reconstructed data [17,18,20,26,28]; Ilangovan 2024 explicitly reports counts in its

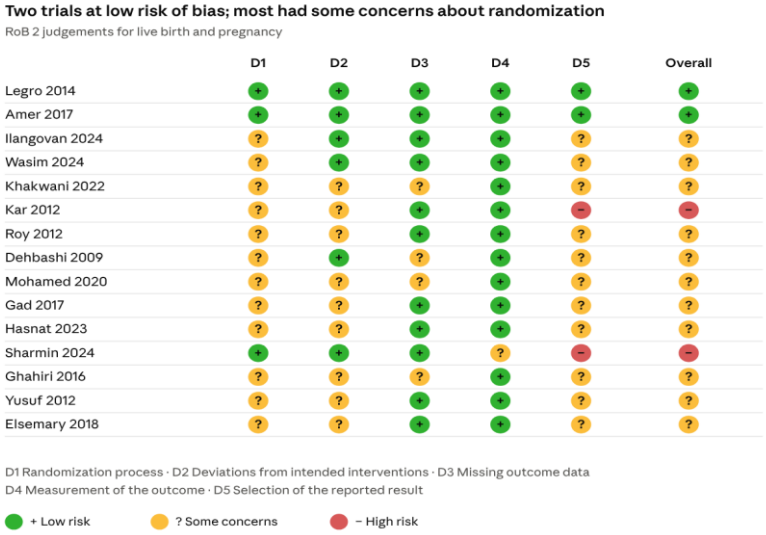
full text, so that flag is not supported by the verified report. The original risk-of-bias ratings are retained for review, but the Ilangovan assessment and reconstruction-based sensitivity analyses require reassessment. Kar 2012 and Sharmin 2024 had internally inconsistent data or figure-derived counts [20,26].

Table 3. Risk of Bias (Rob 2) For Live Birth and Pregnancy

Study	Randomization	Deviations	Missing data	Measurement	Reported result	Overall
Legro 2014	Low	Low	Low	Low	Low	Low
Amer 2017	Low	Low	Low	Low	Low	Low
Ilangovan 2024	Some concerns	Low	Low	Low	Some concerns	Some concerns
Wasim 2024	Some concerns	Low	Low	Low	Some concerns	Some concerns
Khakwani 2022	Some concerns	Some concerns	Some concerns	Low	Some concerns	Some concerns
Kar 2012	Some concerns	Some concerns	Low	Low	High	High
Roy 2012	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
Dehbashi 2009	Some concerns	Low	Some concerns	Low	Some concerns	Some concerns
Mohamed 2020	Some concerns	Some concerns	Some concerns	Low	Some concerns	Some concerns
Gad 2017	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
Hasnat 2023	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
Sharmin 2024	Low	Low	Low	Some concerns	High	High
Ghahiri 2016	Some concerns	Some concerns	Some concerns	Low	Some concerns	Some concerns
Yusuf 2012	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
Elsemary 2018	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns

The original ratings are reproduced for review. Concerns included incompletely described randomization or concealment; inconsistent denominators or percentages in Kar 2012; figure-derived counts and inconsistent tables in Sharmin 2024; retrospective registration in Wasim 2024; and unavailable protocols. Ilangovan 2024 describes computer-generated randomization, sealed opaque envelopes and blinded outcome assessment; its domain judgments require reassessment using the full RoB 2 signalling questions.

Figure 2. Risk of Bias (Rob 2) For Live Birth and Pregnancy in Trials Contributing to Meta-Analyses

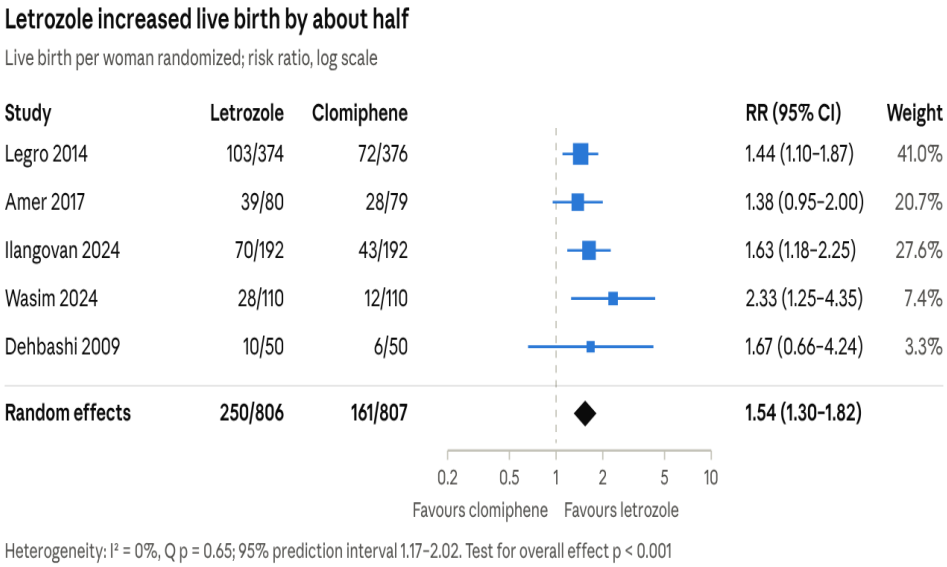


Judgements and reasons are given in Table 3.

Live Birth

Five trials with 1,613 women reported live birth. Letrozole increased live birth compared with clomiphene citrate: 250 of 806 (31.0%) versus 161 of 807 (20.0%); RR 1.54 (95% CI 1.30 to 1.82); I^2 = 0%; 95% prediction interval 1.17 to 2.02 (Figure 3). This corresponds to 107 more live births per 1,000 women (59 to 164 more). The result was similar in the two trials at low risk of bias (RR 1.42, 1.14 to 1.76) and after excluding trials with back-calculated counts (RR 1.43, 1.16 to 1.76). The certainty of evidence was moderate (Table 4).

Figure 3. Live Birth, Letrozole versus Clomiphene Citrate

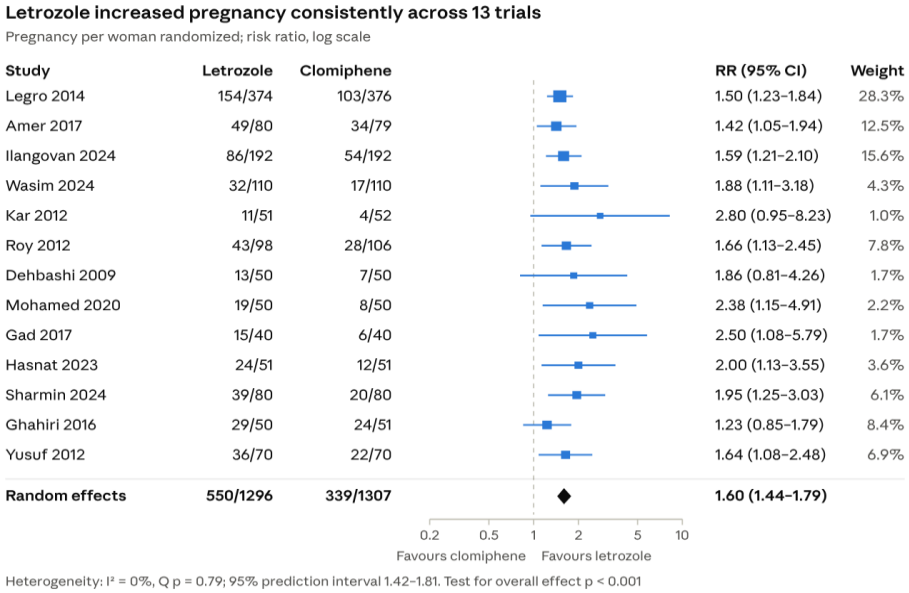


Risk ratios with 95% CIs from the reported DerSimonian–Laird random-effects model. Square size reflects trial weight. Live birth in Dehbashi 2009 is delivery of a live infant. Numerical estimates are unchanged; the Ilangovan reconstruction flag and associated sensitivity grouping require reassessment.

Pregnancy

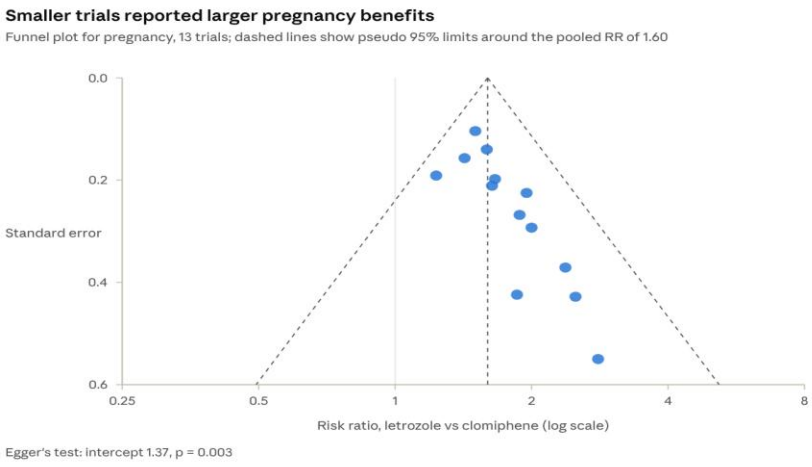
Thirteen trials with 2,603 women reported pregnancy. Letrozole increased pregnancy: 550 of 1,296 (42.4%) versus 339 of 1,307 (25.9%); RR 1.60 (1.44 to 1.79); I^2 = 0% (Figure 4). The effect was consistent in the trials at low risk of bias (RR 1.48, 1.25 to 1.75), in trials without back-calculated counts (RR 1.54, 1.35 to 1.76) and in the three trials reporting ultrasound-confirmed clinical pregnancy (RR 1.44, 1.21 to 1.73). These subgroup estimates are retained from the original analysis; the reconstruction-based grouping requires verification. Egger's test suggested small-study effects (intercept 1.37, p = 0.003): smaller trials tended to report larger benefits (Figure 5). This finding does not establish publication bias, and mathematical association between risk ratios and their standard errors may contribute to asymmetry. The reported certainty of evidence was low.

Figure 4. Pregnancy, Letrozole versus Clomiphene Citrate



Pregnancy is clinical pregnancy where reported and otherwise pregnancy as defined by the trial; Legro 2014 reports conception.

Figure 5. Funnel Plot for Pregnancy



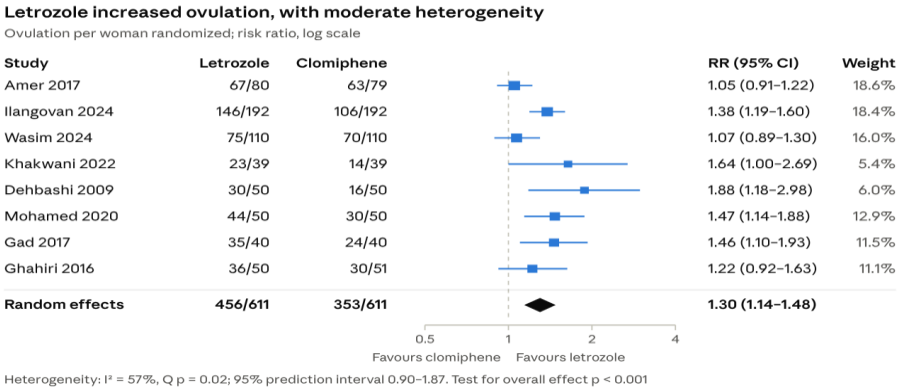
Each point represents one trial. Less precise studies appear lower in the plot; several report larger risk ratios. Asymmetry and Egger's test suggest possible small-study effects, but do not establish publication bias. Dashed lines are

pseudo 95% limits around the pooled estimate.

Ovulation

Eight trials with 1,222 women reported ovulation per woman. Letrozole increased ovulation: 456 of 611 (74.6%) versus 353 of 611 (57.8%); RR 1.30 (1.14 to 1.48), with moderate heterogeneity (I^2 = 57%, p = 0.02) and a prediction interval of 0.90 to 1.87 (Figure 6). The two largest trials in this analysis, Amer 2017 and Wasim 2024, found smaller effects than the others. Three trials reported ovulation per cycle and gave inconsistent results (RR 1.06, 0.85 to 1.32; I^2 = 91%): the PPCOS II trial favoured letrozole (RR 1.28, 1.19 to 1.37), while two smaller trials found no difference [4,21,29]. These cycle-level estimates are exploratory because a method accounting for within-woman correlation was not documented. The certainty of evidence for ovulation per woman was low.

Figure 6. Ovulation per Woman, Letrozole versus Clomiphene Citrate

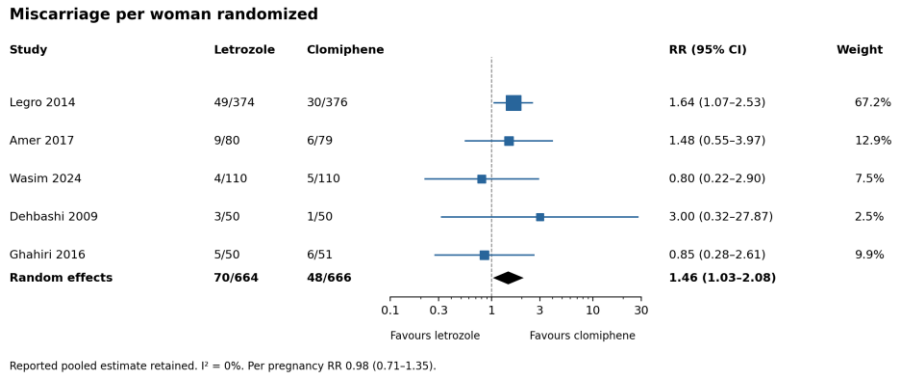


Ovulation was assessed by ultrasound, mid-luteal progesterone or menstrual pattern, which contributes to heterogeneity.

Miscarriage

Five trials with 1,330 women reported miscarriage. Per woman randomized, miscarriage was more frequent with letrozole: 70 of 664 (10.5%) versus 48 of 666 (7.2%); RR 1.46 (1.03 to 2.08); I^2 = 0% (Figure 7). Per pregnancy, there was no clear difference: 70 of 277 (25.3%) versus 48 of 185 (25.9%); RR 0.98 (0.71 to 1.35). The different results depend on the denominator and are compatible with more pregnancies occurring after letrozole. Conditioning on pregnancy, a post-randomization event, does not preserve the randomized comparison or establish equivalent miscarriage risk. The certainty of evidence was low.

Figure 7. Miscarriage per Woman Randomized, Letrozole versus Clomiphene Citrate



RR above 1 indicates more miscarriages per woman randomized with letrozole. Expressed per pregnancy, the reported pooled RR was 0.98 (0.71 to 1.35). The per-pregnancy

comparison conditions on a post-randomization event and cannot establish equivalent safety.

Multiple Pregnancy and OHSS

In the current analysis, four trials with 580 women contributed multiple-pregnancy data. Events were rare, 4 of 290 versus 3 of 290, and the effect was very uncertain (RR 1.13, 0.16 to 7.99; very low certainty). This estimate requires updating because the Ilangovan full text also reports multiple-pregnancy events not represented in the current pool [17]. The PPCOS II trial reported twin rates of 3.4% with letrozole and 7.4% with clomiphene; these data were not included in the current pooled estimate [4]. Two trials reported OHSS and recorded no cases in either arm [23,27]; absence of observed cases does not establish absence of risk. Among reported adverse effects, hot flushes were more frequent with clomiphene, and fatigue and dizziness with letrozole [4,18]. In PPCOS II, major congenital anomalies occurred in four infants after letrozole and one after clomiphene (p = 0.65) [4].

Trials Not Included in Meta-Analyses

Three included trials could not be pooled. Basarakod 2023 reported ovulation (42.5% vs 32.5%) and pregnancy (20% vs 7.5%) favouring letrozole, but its percentages did not match its arm sizes [30]. Sharief 2015 reported higher ovulation with letrozole and similar pregnancy rates without arm-level counts [31]. Nazik 2012 reported similar ovulation (70% vs 72.5%) and pregnancy (17.5% vs 20%) without per-woman denominators [32].

Table 4. Summary of Findings (GRADE)
Population: infertile women with PCOS. Intervention: letrozole. Comparison: clomiphene citrate.

Outcome	Trials (women)	Risk with clomiphene	Risk with letrozole (95% CI)	Relative effect (95% CI)	Certainty	Reasons
Live birth	5 (1,613)	200 per 1,000	307 per 1,000 (259 to 364)	RR 1.54 (1.30 to 1.82)	Moderate	Original GRADE judgment; risk of bias. Ilangovan counts are explicitly reported; reassessment required after extraction review.
Pregnancy	13 (2,603)	259 per 1,000	415 per 1,000 (372 to 463)	RR 1.60 (1.44 to 1.79)	Low	Risk of bias; small-study effects (Egger p = 0.003)
Ovulation per woman	8 (1,222)	578 per 1,000	749 per 1,000 (657 to 853)	RR 1.30 (1.14 to 1.48)	Low	Risk of bias; inconsistency (I^2 = 57%)
Miscarriage per woman	5 (1,330)	72 per 1,000	105 per 1,000 (74 to 150)	RR 1.46 (1.03 to 2.08); per pregnancy RR 0.98 (0.71 to 1.35)	Low	Risk of bias; imprecision
Multiple pregnancy	4 (580)	10 per 1,000	11 per 1,000 (1 to 82)	RR 1.13 (0.16 to 7.99)	Very low	Original judgment; risk of bias and very serious imprecision.

						Current pool omits additional reported data and requires updating.
OHSS	2 (201)	No events	No events	Not estimable	Very low	Risk of bias; very serious imprecision

DISCUSSION

Principal Findings

In the current meta-analysis of randomized trials, letrozole increased live birth by about half compared with clomiphene citrate in infertile women with PCOS. No between-study heterogeneity was detected across five trials, and the reported certainty was moderate. Pregnancy and ovulation were also higher with letrozole. Miscarriage per pregnancy showed no clear difference; interpretation is limited by conditioning on pregnancy. The current multiple-pregnancy analysis is incomplete, and OHSS events were too sparse to support firm comparative safety conclusions.

Interpretation

The benefit of letrozole was larger for pregnancy and live birth than for ovulation per cycle. This pattern fits the proposed mechanism: clomiphene citrate depletes estrogen receptors in the endometrium and cervix for a prolonged period, whereas letrozole leaves peripheral estrogen action intact once estradiol rises [3]. The PPCOS II trial showed the same gradient, with a moderate gain in ovulation per cycle and a larger gain in live birth [4]. Ovulation results varied between trials, partly because ovulation was defined differently, by ultrasound, mid-luteal progesterone or menstrual pattern.

The apparent increase in miscarriage per woman was not observed when miscarriage was expressed per pregnancy. This difference is compatible with a larger number of pregnancies after letrozole, but does not prove that pregnancy frequency fully explains the result or rule out a clinically important difference in loss risk. The per-pregnancy analysis conditions on a post-randomization event and should be interpreted cautiously.

Comparison with Other Reviews

The direction of the efficacy estimates agrees with the 2022 Cochrane review, which found higher live birth and pregnancy rates with letrozole and no clear difference in miscarriage, multiple pregnancy or OHSS [5]. A 2024 meta-analysis of 25 trials reported higher ovulation (odds ratio 1.8, 95% CI 1.21 to 2.69) and pregnancy (odds ratio 1.96, 1.37 to 2.81) with letrozole [7]. The present analysis includes trials published from 2020 to 2024, mainly from South Asia and the Middle East. The live-birth benefit persisted in the reported low-risk-of-bias sensitivity analysis, although this limited search does not establish that the review is more comprehensive than existing syntheses.

Strengths and Limitations

The review prioritized live birth and reported sensitivity analyses addressing risk of bias, reconstructed counts and outcome definitions. A retracted trial was excluded. Absolute effects are presented to aid interpretation and depend on the assumed baseline risk. These strengths do not remove the limitations arising from incomplete searching and unresolved extraction issues.

Bibliographic databases were not searched directly, so eligible trials may have been missed. One reviewer performed selection, extraction and risk-of-bias assessment. Eleven reports remain awaiting classification because outcome data or allocation details were unavailable. Several trials were initially flagged for reconstructed data; full-text verification of Ilangovan 2024 identified explicit event counts and additional safety data, requiring revision of reconstruction-based sensitivity analyses and the multiple-pregnancy synthesis. Risk-of-bias and GRADE judgments should be reconsidered after those checks. Egger's test suggested small-study effects for pregnancy, which may reflect reporting bias, methodological differences or the properties of the effect measure. Only five trials contributed live birth, and safety evidence was limited.

Implications for Practice

The direction of the findings is consistent with the 2023 international guideline recommending letrozole as first-line pharmacological ovulation induction for infertile anovulatory women with PCOS and no other infertility factors [2]. In this analysis, the model-derived absolute benefit corresponds to

approximately one additional live birth for every nine to ten women treated rather than clomiphene; the absolute benefit will vary with baseline risk. Counselling should address applicable off-label status and the uncertainty of uncommon safety outcomes. The available anomaly data do not establish equivalent safety [4,6].

Implications for Research

Future trials should be prospectively registered, report live birth as the primary outcome with full counts, use clear definitions of ovulation and clinical pregnancy and report multiple pregnancy, OHSS and congenital anomalies by arm. Trials in clomiphene-resistant women, in different BMI groups and with extended letrozole regimens would help to refine treatment choices.

CONCLUSION

In infertile women with PCOS, the current pooled analysis suggests that letrozole probably increases live birth compared with clomiphene citrate, by about 107 additional live births per 1,000 women at the assumed baseline risk, and may increase pregnancy and ovulation. Miscarriage per pregnancy showed no clear difference, but this conditional analysis does not establish equivalent safety. The multiple-pregnancy synthesis requires updating, and OHSS evidence is sparse. The direction of the efficacy findings is consistent with guideline-supported first-line letrozole use for anovulatory infertility in PCOS without other infertility factors; incomplete searching and unresolved extraction issues limit the conclusions.

Declarations

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Competing Interests: The author declares no competing interests.

Supplementary Material

Supplementary Table S1. Search Strategies

(A) Searches Run For This Review (Web Search Engine, 23 October 2026; No Language Or Date Limits)

No.	Query as entered
1	Franik 2022 Cochrane aromatase inhibitors letrozole ovulation induction PCOS live birth clomiphene included studies
2	Legro 2014 NEJM letrozole versus clomiphene infertility polycystic ovary syndrome live birth
3	randomized controlled trial letrozole versus clomiphene citrate PCOS live birth rate open access full text
4	letrozole clomiphene PCOS randomized trial 2020 2021 2022 2023 2024 ovulation rate clinical pregnancy
5	Bansal 2021 letrozole versus clomiphene citrate ovulation induction PCOS randomized live birth
6	Nazik 2012 OR Roy 2012 OR Kar 2012 letrozole clomiphene polycystic ovary syndrome randomized trial live birth
7	Begum 2009 letrozole versus clomiphene citrate ovulation induction PCOS randomized live birth
8	Sharief 2015 OR Ghomian 2015 OR Liu 2017 letrozole clomiphene PCOS randomized controlled trial live birth
9	letrozole clomiphene PCOS randomized Journal of Pakistan Medical Association OR Pakistan Journal of Medical Sciences ovulation pregnancy
10	Bayar 2006 letrozole clomiphene polycystic ovary randomized
11	Ghomian 2015 letrozole clomiphene PCOS randomized Iran OR Hajishafiha 2013 OR Zeinalzadeh 2010
12	Selim Borg 2012 letrozole clomiphene PCOS randomized OR Ray 2012 letrozole clomiphene
13	Atay 2006 letrozole clomiphene PCOS randomized ovulation pregnancy
14	letrozole versus clomiphene citrate PCOS randomized controlled trial Bangladesh OR India OR Egypt pregnancy rate live birth
15	Heliyon 2023 letrozole vs clomiphene citrate Sudanese patients infertility polycystic ovary syndrome
16	letrozole versus clomiphene randomized PCOS Iraq OR Saudi OR Nepal OR Nigeria trial ovulation pregnancy
17	Sharief Nafee 2015 letrozole clomiphene polycystic ovary syndrome
18	Liu 2017 Gynecological Endocrinology comparison of clomiphene citrate and letrozole

	prospective randomized trial
19	Zeinalzadeh 2010 Journal of Reproductive Medicine letrozole clomiphene polycystic ovary syndrome
20	Letrozole as the first-line treatment of infertile women with polycystic ovarian syndrome compared with clomiphene citrate
21	Legro 2014 PPCOS II twin pregnancy letrozole clomiphene numbers

The reference list of the 2014 Cochrane review of aromatase inhibitors in PCOS was checked for letrozole-versus-clomiphene trials.

(b) Bibliographic database strategy prepared for updating the review (MEDLINE via PubMed; not run for this version)

#1 "Letrozole"[Mesh] OR letrozole[tiab] OR "aromatase inhibitor*"[tiab] OR Femara[tiab]
#2 "Clomiphene"[Mesh] OR clomiphene[tiab] OR clomifene[tiab] OR Clomid[tiab]
#3 "Polycystic Ovary Syndrome"[Mesh] OR "polycystic ovar*"[tiab] OR PCOS[tiab] OR PCOD[tiab] OR "Stein-Leventhal"[tiab]
#4 randomized controlled trial[pt] OR randomi*[tiab] OR placebo[tiab] OR trial[ti]
#5 #1 AND #2 AND #3 AND #4

Supplementary Table S2. Excluded Reports and Reports Awaiting Classification

Report	Classification	Reason or information needed
Badawy 2009, Fertil Steril 92:849–52	Excluded	Retracted trial; excluded from synthesis.
Sakar 2020, Pak J Med Sci 36(7):1460–5	Excluded	Retrospective design
Elkhalifa 2023, Heliyon 9(7):e18107	Excluded	Cross-sectional design
Hegde 2020, Indian J Obstet Gynecol Res 7(1):12–5	Excluded	Allocation method not described; not randomized
Abdellatif 2025, Al-Azhar Int Med J	Excluded	Randomization not stated
Deif 2024, Al-Azhar Int Med J 5(9)	Excluded	Observational three-arm study
Morad 2015, Middle East Fertil Soc J 20(3):182–7	Excluded	Self-controlled cohort
Kamala 2004, J Obstet Gynecol India 54(6):579–82	Excluded	Clinician-chosen regimens; allocation not random
Ghazizadeh 2009, J Reprod Infertil 10:156	Excluded	Gonadotropins added to both arms
Liu 2015 (Cochrane extraction)	Excluded	Letrozole versus laparoscopic ovarian drilling
Combined letrozole and clomiphene versus letrozole, Fertil Steril 2019	Excluded	Other comparison
Letrozole versus combined letrozole and clomiphene, Reprod Sci 2024	Excluded	Other comparison
Clomiphene plus letrozole versus clomiphene, BMC Womens Health 2023	Excluded	Other comparison
Extended versus conventional letrozole, Hum Reprod Open 2024	Excluded	Other comparison
Franik 2022, Cochrane Database Syst Rev	Excluded	Systematic review

Franik 2018, Cochrane Database Syst Rev	Excluded	Systematic review
Vajna 2024, Pharmaceuticals 17(7):971	Excluded	Systematic review
Wiyono 2023, Science Midwifery 11(3):629–34	Excluded	Literature review
Letrozole and clomiphene in pregnancy outcomes in PCOS, Reprod Sci 2023	Excluded	Systematic review
Comparative outcomes of letrozole versus clomiphene citrate in PCOS, systematic review 2026	Excluded	Systematic review
Bayar 2006, Fertil Steril 86:1447–51	Awaiting classification	Arm-level outcome data not obtainable
Atay 2006, J Int Med Res 34:73–6	Awaiting classification	Arm-level outcome data not obtainable
Begum 2009, Fertil Steril 92:853–7	Awaiting classification	Arm-level outcome data not obtainable
Selim 2012, J Gynecol Surg 28(6):405–10	Awaiting classification	Arm-level outcome data not obtainable
Zeinalzadeh 2010, J Reprod Med 55:36–40	Awaiting classification	Arm-level outcome data not obtainable
Lorzadeh 2011, Iran J Obstet Gynecol Infertil 14(3):13–9	Awaiting classification	Ovulation reported ambiguously; no pregnancy counts
Elsedeek 2011, Middle East Fertil Soc J 16(2):125–30	Awaiting classification	Arm-level outcome data not obtainable
Ray 2012, Arch Gynecol Obstet 285(3):873–7	Awaiting classification	Ovulation and pregnancy not reported in the abstract; full text not obtained
Liu 2017, Gynecol Endocrinol	Awaiting classification	Full text not obtained
Kareem 2019, Qadisiyah Med J 15(2):105–21	Awaiting classification	Arm sizes and counts not reported
Abd-Allatif 2018, Egypt J Hosp Med 72(8):4995–5000	Awaiting classification	Allocation method not stated in the abstract

Supplementary Table S3. PRISMA 2020 Checklist

Item	Checklist item	Location	Status
1	Title	Title	Reported
2	Structured abstract	Abstract	Partly reported; abstract has no registration or funding statement; these are in Declarations.
3	Rationale	Introduction	Reported
4	Objectives	Introduction, final paragraph	Reported
5	Eligibility criteria	Methods, Eligibility criteria	Reported
6	Information sources	Methods, Information sources and search	Reported; databases not searched directly
7	Search strategy	Supplementary Table S1	Reported
8	Selection process	Methods, Study selection and data collection	Reported (one reviewer)
9	Data collection process	Methods, Study selection and data collection	Reported (one reviewer; authors not contacted)

10a	Outcomes	Methods, Eligibility criteria	Reported
10b	Other variables	Tables 1–2	Reported
11	Risk of bias assessment	Methods, Risk of bias	Reported (RoB 2)
12	Effect measures	Methods, Synthesis	Reported (risk ratio)
13a	Synthesis eligibility	Methods, Synthesis	Reported
13b	Data preparation	Methods, Study selection and data collection	Reported (back-calculated counts flagged)
13c	Tabulation and display	Tables 1–4; Figures 3, 4, 6 and 7	Reported
13d	Synthesis methods	Methods, Synthesis	Reported (random effects, DerSimonian-Laird)
13e	Heterogeneity	Methods, Synthesis	Reported (I^2, Q, prediction intervals)
13f	Sensitivity analyses	Methods, Synthesis	Reported
14	Reporting bias assessment	Methods, Synthesis	Reported (Egger's test, funnel plot)
15	Certainty assessment	Methods, Certainty of evidence	Reported (GRADE)
16a	Study selection results	Results; Figure 1	Partial: report disposition shown; duplicate and sequential screening counts unavailable.
16b	Excluded studies	Supplementary Table S2	Reported
17	Study characteristics	Tables 1–2	Reported
18	Risk of bias in studies	Table 3; Figure 2	Reported
19	Results of individual studies	Figures 3, 4, 6 and 7	Partial: four main forest plots show individual counts; complete safety and sensitivity extraction unavailable.
20a	Synthesis characteristics	Results	Reported
20b	Synthesis results	Results; Figures 3, 4, 6 and 7	Reported
20c	Heterogeneity results	Results	Reported
20d	Sensitivity results	Results	Reported
21	Reporting biases	Results, Pregnancy; Figure 5	Reported
22	Certainty of evidence	Table 4	Reported
23a	Interpretation	Discussion	Reported
23b	Limitations of evidence	Discussion, Strengths and limitations	Reported
23c	Limitations of review process	Discussion, Strengths and limitations	Reported
23d	Implications	Discussion	Reported
24a	Registration	Declarations	Reported: not registered
24b	Protocol	Declarations	Reported: no published protocol
24c	Amendments	Methods, Deviations from standard methods	Reported
25	Support	Declarations, Funding	Reported
26	Competing interests	Declarations	Reported
27	Data and code availability	Declarations, Data availability	Partial: counts in figures; complete analysis dataset and code not supplied.

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