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REVIEW

Letrozole versus clomiphene citrate in polycystic ovary syndrome: a meta-analysis of randomized controlled trials

Shifu Hu[1] · Qiong Yu[2] · Yingying Wang[1] · Mei Wang[1] · Wei Xia[1,3] · Changhong Zhu[1,3]

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Abstract

Purpose Polycystic ovary syndrome (PCOS) is a common endocrine disturbance affecting women in the reproductive age group. The present study aimed to compare the effects of letrozole (LE) and clomiphene citrate (CC) for ovulation induction in women with PCOS.

Methods The PUBMED, Web of Science, and EMBASE databases were screened systematically for randomized controlled trials (RCTs) published from database inception to July 2017.

Results Eleven RCTs involving 2255 patients were included, and data were independently extracted and analyzed using 95% risk ratios (RRs) and confidence intervals (CIs) based on a random- or fixed-effect model (as appropriate). Meta-analyses of nine RCTs comparing LE and CC ovulation induction, followed by timed intercourse, indicated that the former significantly increased the ovulation rate (RR = 1.18; 95% CI 1.03–1.36, $P = 0.01$), pregnancy rate (RR = 1.34; 95% CI 1.09–1.64, $P = 0.006$), and live birth rate (RR = 1.55; 95% CI 1.28–1.88, $P < 0.00001$). However, LE and CC did not differ significantly in terms of the multiple pregnancy and abortion rates. Furthermore, LE for ovulation induction significantly improved the pregnancy rate after IUI.

Conclusion LE is superior to CC for ovulation induction in patients with PCOS.

Keywords Letrozole · Clomiphene citrate · Polycystic ovary syndrome · Randomized controlled trials · Meta-analysis

Introduction

Polycystic ovary syndrome (PCOS) is a common multisystem endocrine disorder in women, with long-term health consequences [1]. The primary clinical features of PCOS include hyperandrogenism, menstrual abnormalities, polycystic ovaries, infertility, obesity, hypertension, dyslipidemia, insulin resistance, and type II diabetes mellitus [2, 3]. This chronic and heterogeneous endocrine disease affects 5–8% of women of reproductive age [4].

Ovulation induction regimens have been proposed for infertile women with anovulatory PCOS who wish to bear children. Clomiphene citrate (CC), an anti-estrogenic drug used clinically for more than 40 years to induce ovulation, is generally considered the first-line option for such women. However, clomiphene has drawbacks, such as a long half-life (2 weeks) [5] that results in long-lasting adverse effects on cervical mucus [6] and endometrial development [7], leading to discrepancies in ovulation and pregnancy rates [6, 8, 9]. In addition, 15–20% patients with PCOS are resistant to CC [10].

Therefore, a safe, more effective oral drug that could replace CC as a first-line treatment for anovulatory infertility is needed. Letrozole (LE), a third-generation aromatase inhibitor, has been widely to treat breast cancer [11]. This potent, reversible, highly selective, nonsteroidal aromatase inhibitor suppresses the enzyme responsible for

Shifu Hu and Qiong Yu contributed equally to this work.

✉ Wei Xia
tjxiawei@126.com

✉ Changhong Zhu
reprodcentre@163.com

[1] Family Planning Research Institute, Tongji Medical College, Huazhong University of Science and Technology, Hangkong Road 13, Wuhan 430030, Hubei, China

[2] Reproductive Medicine Center, Tongji Medical College, Tongji Hospital, Huazhong University of Science and Technology, Wuhan 430030, Hubei, China

[3] Reproductive Medicine Center, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, Hubei, China

the conversion of androgens to estrogens [12], and therefore could be used to induce ovulation in women with PCOS. By reducing the levels of estrogen in the body, LE promotes the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which support the growth of ovarian follicles [13]. The first report of LE for clinical ovulation induction was published in 2001 [14]. Several recent clinical studies have indicated the superiority of LE relative to CC in terms of pregnancy, ovulation, and live birth rates [15–18]. However, whether LE is more effective than CC with human chorionic gonadotropin injection for ovulation induction remains controversial [19].

The present study aimed to conduct a comprehensive, systematic search of literature databases and a subsequent meta-analysis to evaluate the effects of LE versus CC for ovulation induction in women with PCOS.

Materials and methods

Literature search strategy

For the meta-analysis, two independent researchers (YQ and HSF) identified studies from the electronic databases PubMed, Web of Science, and EMBASE. We searched for articles published only in English and from database inception to July 2017. The following keywords were used: "PCOS," "polycystic ovary syndrome," "anovulation," "letrozole," "aromatase inhibitors," "clomiphene citrate," "randomized controlled trial," and "RCT." We also manually screened the references listed at the end of each retrieved article for additional references.

Inclusion and exclusion criteria

Studies were deemed eligible if they met the following criteria: (1) a randomized controlled trial (RCT) design; (2) use of the Rotterdam 2003 criteria to diagnose PCOS [4, 20, 21]; (3) an intervention of LE versus CC for ovulation induction in women with PCOS; (4) timed intercourse or intrauterine insemination (IUI); (5) no history of treatment with other ovulation-induction agents; and (6) at least one of the following reported outcomes: pregnancy rate, abortion rate, live birth rate, ovulation rate, and multiple pregnancy rate. The exclusion criteria were as follows: (1) review articles, commentaries, letters, or observational studies; (2) non-clinical trials; (3) inability to extract data from the publication; and (4) lack of intervention or of any intervention other than an aromatase inhibitor or placebo.

Data extraction and quality assessment

The following outcome-related data were extracted independently by two investigators (YQ and HSF): first author, publication year, country, number of cases, and main results. The quality of all of the selected studies was evaluated independently by two investigators (WYY and WM) using the Cochrane Collaboration tool [20]. The following elements were applied: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other bias. When necessary, disagreements were resolved by discussion with a third author (XW).

Statistics and data analysis

All statistical tests were performed using the Mantel–Haenszel method with a fixed- or random-effect model according to statistical heterogeneity. A random-effect model was used when significant heterogeneity was present. Relative risks (RR) were combined in a fixed-effects model-based meta-analysis if no or moderate heterogeneity was observed across studies.

Effect sizes were analyzed by calculating the RRs with 95% confidence intervals (CIs). Heterogeneity across studies was explored using the Chi square-based Q test and I^2 statistics. Severe heterogeneity was defined as a $P < 0.05$ for the Q test and $I^2 > 50\%$. I^2 values $< 50\%$ indicated moderate heterogeneity. Funnel plots were performed to evaluate publication bias. All statistical analyses were implemented using Revman5.2 (Cochrane Collaboration).

Results

Study characteristics and quality assessment

The literature search procedures and results are shown in Fig. 1. Four hundred and five potentially relevant articles published up to July 2017 were systematically identified from various databases. After scrutinizing the titles and/or abstracts, 389 articles were excluded because they did not meet the inclusion criteria or met the exclusion criteria. Of the remaining 16 articles, 5 were excluded for the reasons described in Fig. 1. Finally, data from 11 studies including 2255 patients were including in this meta-analysis. Of the patients, 1112 and 1143 were classified into the LE and CC groups, respectively. Table 1 presents the characteristics of studies included in the meta-analysis [12, 13, 15, 19, 21–27]. Table 2 presents a summary of the review authors' judgments regarding the risk of bias across all of the RCTs.

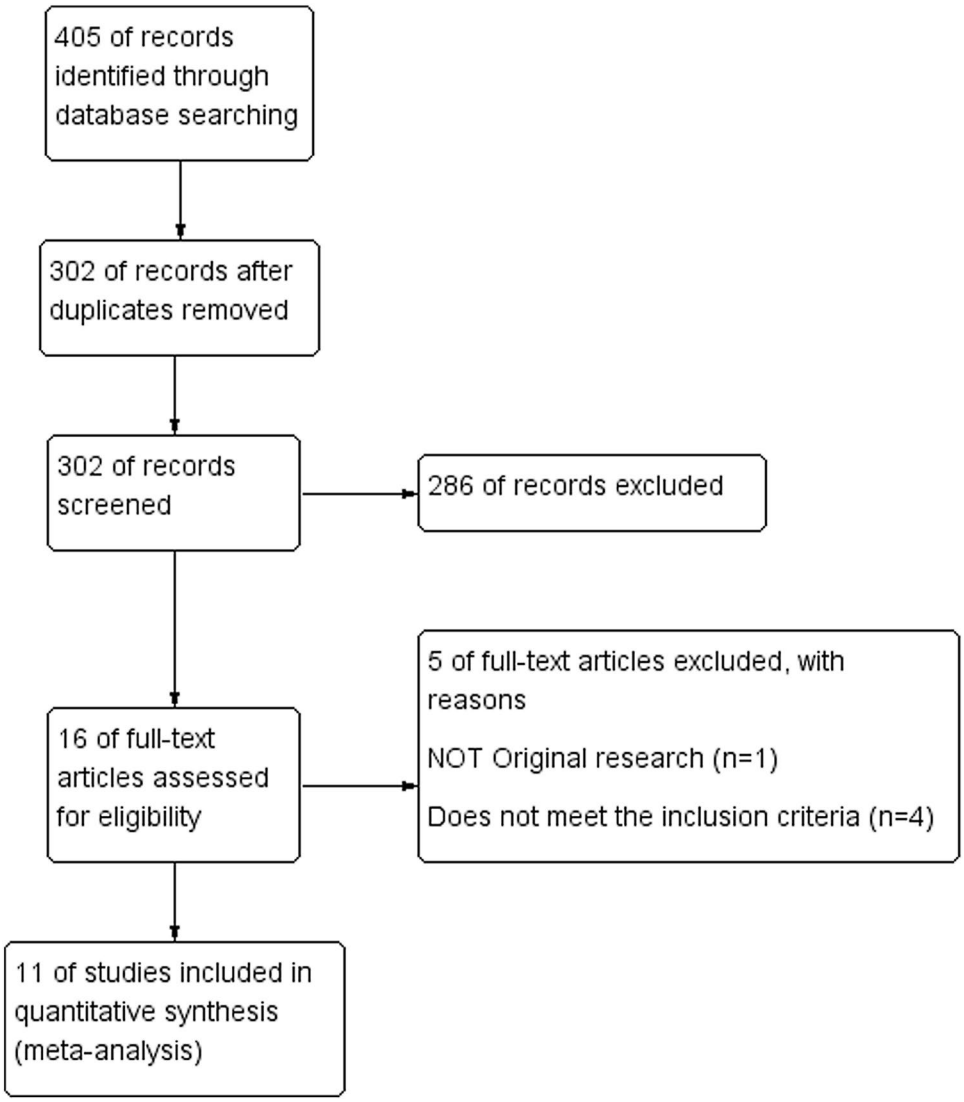

Fig. 1 Flow diagram of search strategy for the randomized controlled trials (RCT)

Ovulation rate

Ten studies evaluated the ovulation rate [12, 13, 15, 19, 21–25, 27]. A meta-analysis revealed significant heterogeneity ($I^2 = 85\%$, $P < 0.00001$), and therefore a random effect model was used. The meta-analysis indicated a statistically obvious increase in the ovulation rate in the LE group relative to the CC group (RR = 1.18; 95% CI 1.04–1.34, $P = 0.004$), as shown in Fig. 2.

A subgroup analysis was performed to determine whether ovulation induction followed by timed intercourse or intrauterine insemination (IUI) would affect the treatment outcome. Compared with the CC group, the use of LE for ovulation induction, followed by timed intercourse, significantly increased the ovulation rate (RR = 1.18; 95% CI 1.03–1.36, $P = 0.01$). Only one study reported ovulation induction followed by IUI (RR = 1.20; 95% CI 0.91–1.58, $P = 0.19$).

Pregnancy rate

As shown in Fig. 3, all of the studies [12, 13, 15, 19, 21–27] were suitable for inclusion in the meta-analysis of pregnancy rate; accordingly, 1112 and 1143 patients were included in the LE and CC groups, respectively. The meta-analysis revealed moderate heterogeneity ($I^2 = 48\%$, $P = 0.001$), and a random-effect model was used. The meta-analysis indicated that compared with the CC group, the LE group had a significantly better pregnancy rate (RR = 1.40; 95% CI 1.14–1.72, $P = 0.001$).

A subgroup analysis was again performed to determine whether ovulation induction followed by timed intercourse or intrauterine insemination (IUI) would affect the treatment outcome. Compared with the CC group, the LE group had a significantly increased pregnancy rate after ovulation induction followed by timed intercourse (RR = 1.34; 95% CI 1.09–1.64, $P = 0.006$). Two studies that evaluated

Table 1 Characteristics of the studies included in the review

Author (year)	Country	Interventions	Mode of fertilization	Patients (*n*)	Cycles (*n*)	Outcomes included in the meta-analysis
Atay (2006)	Turkey	2.5 mg LE 100 mg CC	Timed intercourse	51 55	51 55	Ovulation rate, multiple pregnancy rate, pregnancy rate
Bayar (2006)	Turkey	2.5 mg LE 100 mg CC	Timed intercourse	40 40	99 95	Ovulation rate, miscarriage rate, multiple pregnancy rate, pregnancy rate, live birth rate
Badawy (2009)	Egypt	5 mg LE 100 mg CC	Timed intercourse	218 220	540 523	Ovulation rate, miscarriage rate, multiple pregnancy rate, pregnancy rate
Dehbashi (2009)	Iran	2.5 mg LE 100 mg CC	Timed intercourse	50 50	50 50	Ovulation rate, miscarriage rate, multiple pregnancy rate, pregnancy rate, live birth rate
Zeinalzadeh (2010)	Iran	5 mg LE 100 mg CC	IUI	50 57	50 57	Ovulation rate, pregnancy rate
Kar (2012)	India	5 mg LE 100 mg CC	IUI	52 51	52 51	Ovulation rate, pregnancy rate
Ray (2012)	India	2.5 mg LE 100 mg CC	Timed intercourse	69 78	69 78	Ovulation rate, miscarriage rate, pregnancy rate, live birth rate
Roy (2012)	India	2.5–5 mg LE 50–100 mg CC	Timed intercourse	96 106	294 318	Ovulation rate, miscarriage rate, multiple pregnancy rate, pregnancy rate, live birth rate
Legro (2014)	USA	2.5–7.5 mg LE 50–150 mg CC	Timed intercourse	374 376	1,352 1,425	Ovulation rate, miscarriage rate, multiple pregnancy rate, pregnancy rate, live birth rate
Ghahiri (2016)	Iran	5 mg LE 100 mg CC	Timed intercourse	50 51	50 51	Ovulation rate, miscarriage rate, pregnancy rate
Liu (2017)	China	5 mg LE 50–150 mg CC	Timed intercourse	63 63	157 157	Ovulation rate, miscarriage rate, pregnancy rate, live birth rate

Table 2 Quality assessment of the included studies

Author (year)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Atay (2006)	No	No	No	No	Yes	No	Yes
Bayar (2006)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Badawy (2009)	Yes	No	No	No	Yes	Yes	Yes
Dehbashi (2009)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Zeinalzadeh (2010)	Yes	No	No	No	Yes	Yes	Yes
Kar (2012)	Yes	No	No	No	Yes	Yes	Yes
Roy (2012)	Yes	Yes	No	No	Yes	Yes	Yes
Ray (2012)	Yes	No	No	No	Yes	Yes	Yes
Legro (2014)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ghahiri (2016)	Yes	No	No	No	Yes	No	Yes
Liu et al. (2017)	Yes	No	No	No	Yes	Yes	Yes

ovulation induction followed by IUI yielded similar results (RR = 2.47; 95% CI 1.18–5.14, $P = 0.02$).

Live birth rate

Six studies [15, 21–24, 27] were considered suitable for the live birth rate evaluation, yielding 691 patients in the LE group and 709 in the CC group. As shown in Fig. 4, meta-analysis data indicated that the studies were not heterogeneous ($I^2 = 0\%$, $P = 0.8$), and a fixed-effect model was applied. The meta-analysis revealed a statistically significant increase in the live birth rate in the LE group relative to the CC group (RR = 1.55; 95% CI 1.28–1.88, $P < 0.00001$).

Abortion rate

Overall, 1939 patients from 8 articles [15, 19, 21–25, 27] that evaluated ovulation induction followed by timed intercourse were included in the abortion rate analysis. The heterogeneity was low ($I^2 = 0\%$, $P = 0.75$), and a fixed-effect

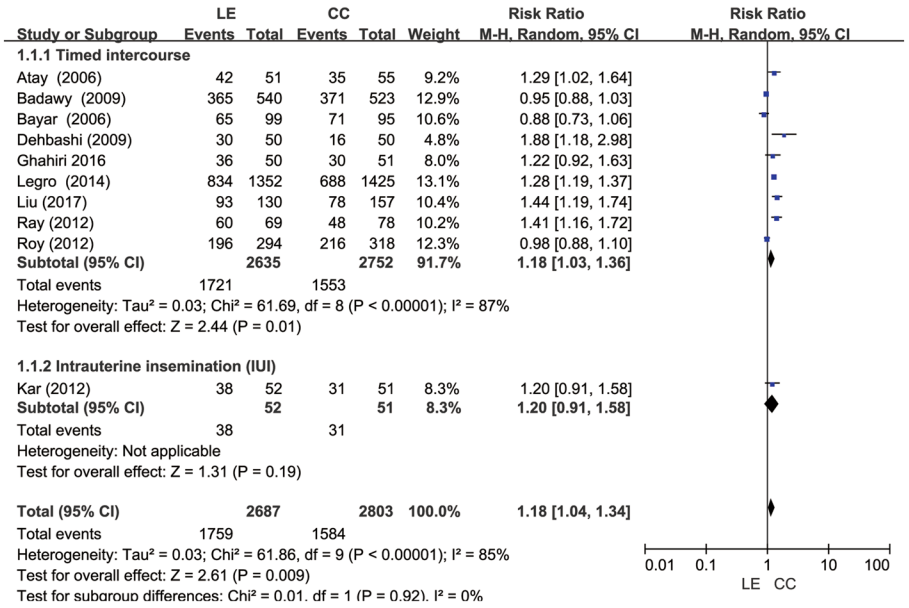

Fig. 2 Forest plot diagram showing the ovulation rate associated with comparison of letrozole (LE) with clomiphene (CC). *CI* confidence intervals

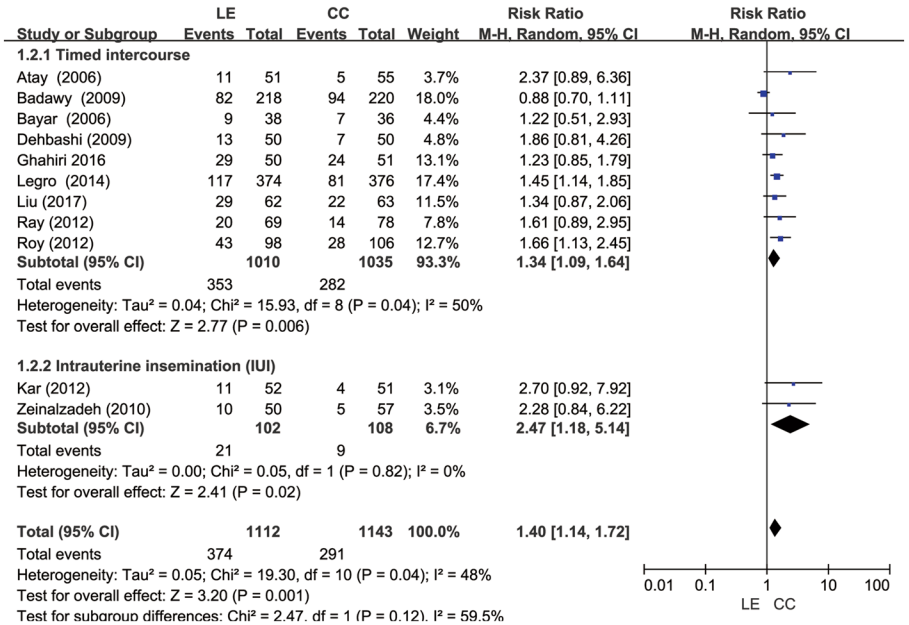

Fig. 3 Forest plot diagram showing the pregnancy rate associated with comparison of letrozole (LE) with clomiphene (CC). *CI* confidence intervals

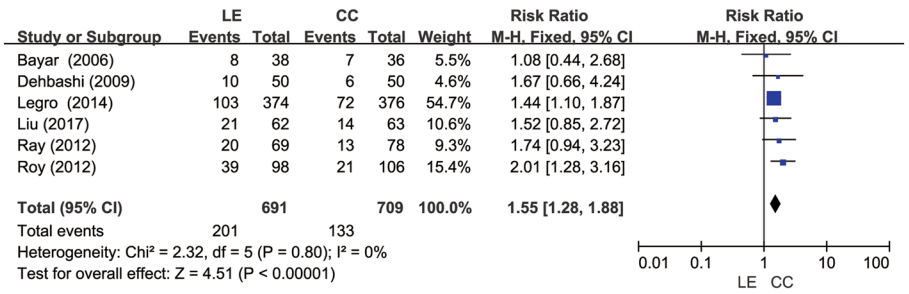

Fig. 4 Forest plot diagram showing the live birth rate associated with comparison of letrozole (LE) with clomiphene (CC). *CI* confidence intervals

model was applied. The meta-analysis indicated no significant difference in the abortion rate between the two groups (RR = 1.36; 95% CI 0.98–1.89, $P = 0.07$) (Fig. 5).

Multiple pregnancy rate

As shown in Fig. 6, 5 articles including 1598 patients reported multiple pregnancy rates [13, 15, 19, 22, 27]. There was no obvious heterogeneity across the studies ($I^2 = 0\%$, $P = 0.82$), and a fixed-effect model was applied. The meta-analysis revealed no statistically significant difference in the multiple pregnancy rate between the LE and CC groups (RR = 0.43; 95% CI 0.17–1.07, $P = 0.07$).

Publication bias

A funnel plot was conducted to qualitatively evaluate publication bias. The funnel plot for the outcome pregnancy rate shown in Fig. 7 is almost symmetrical, indicating no potential publication bias in the included studies.

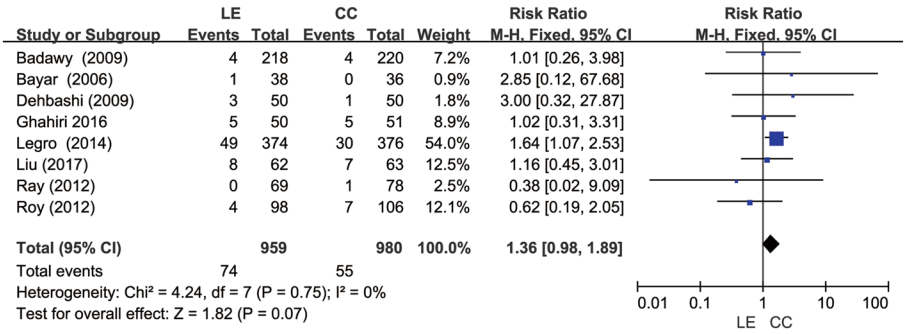

Fig. 5 Forest plot diagram showing the abortion rate associated with comparison of letrozole (LE) with clomiphene (CC). *CI* confidence intervals

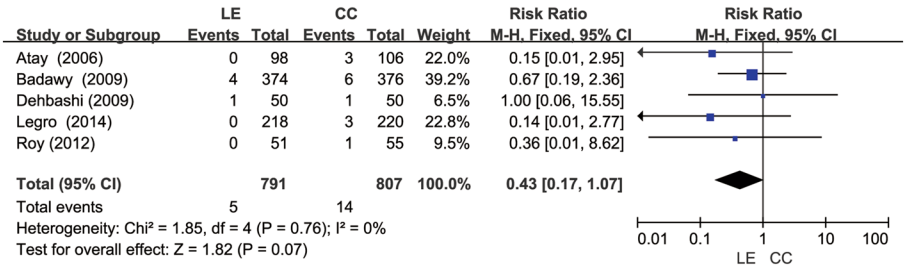

Fig. 6 Forest plot diagram showing the multiple pregnancy rate associated with comparison of letrozole (LE) with clomiphene (CC). *CI* confidence intervals

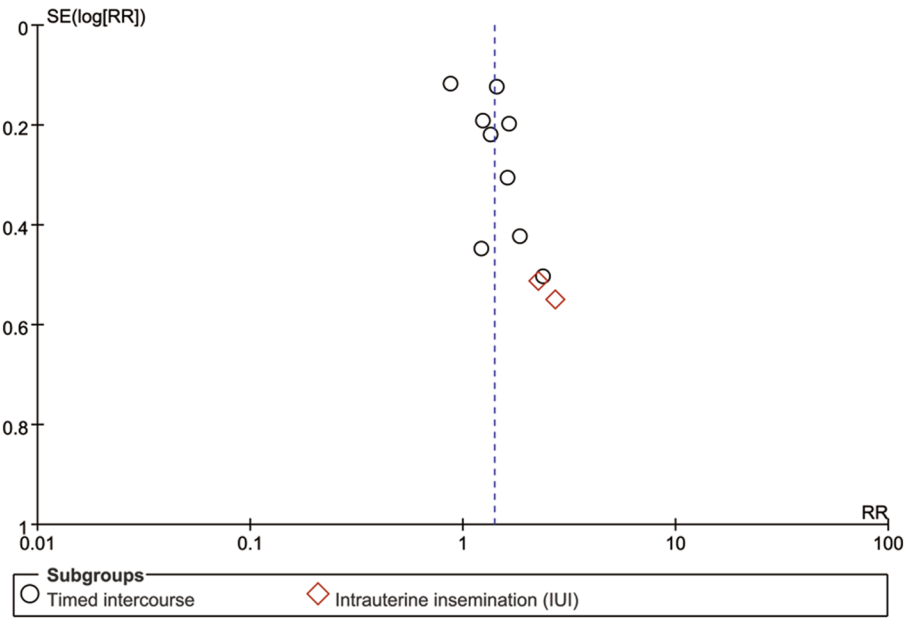

Fig. 7 Funnel plot for detecting publication bias of all 11 including studies

Discussion

Our analysis included evidence from two studies published during the 2 years since the most recent previous meta-analysis [28], and allowed a separate analysis of the effects of LE versus CC followed by timed intercourse or IUI in women with PCOS. In terms of clinical utility, our results agree some what with those of the two previous meta-analyses [28, 29], which we attribute to our inclusion of additional studies. However, our results differ from those of a meta-analysis by Franik et al. [29], which included evaluated aromatase inhibitors versus CC, with or without adjuncts (e.g., metformin, FSH), followed by intercourse in 15 studies and by IUI in 3 studies. Furthermore, the study by Franik et al. included a RCT [30] that compared LE with CC in women with CC-resistant PCOS, which reported a higher ovulation rate per patient following LE but no treatment-related difference in the pregnancy rate per patient.

In 2015, Roque et al. [28] evaluated the effect of LE versus CC for ovulation induction followed by intercourse in women with PCOS, and found that the former was superior in terms of the live birth rate and pregnancy rate. However, it remains unclear whether these effects differ when ovulation induction is followed by IUI. Our study evaluated the effect of LE versus CC (without adjuvants, i.e., other aromatase inhibitors) for ovulation induction in women with PCOS and found that the former, when followed by timed intercourse, obviously increased the ovulation, pregnancy, and live birth rates when compared with the latter. Additionally, we found that the pregnancy rate after IUI was significantly improved when using LE, compared with CC.

Although our meta-analysis demonstrated a higher pregnancy rate after IUI with LE, the meta-analysis of pregnancy rate was based on two low-quality RCTs [12, 26] with high risks of bias and no apparent statistical difference between LE and CC. Furthermore, our meta-analysis indicated that compared with CC, LE for ovulation induction, followed by timed intercourse, could have superior effects on the ovulation, pregnancy, and live birth rates. However, the RCTs included in this meta-analysis inconsistently reported the treatment cycle and CC sensitivity statuses. Five RCTs [15, 19, 21–23] were conducted for at least two consecutive ovulation cycles, whereas six RCTs [12, 13, 24–27] included patients who underwent ovulation induction for only one cycle. Furthermore, five RCTs [12, 21, 25–27] included therapy-naïve participants, whereas six RCTs failed to note the previous therapy status of the participants. Therefore, the inclusion of these documents might have led to selection bias.

Although the studies included in this meta-analysis provided evidence favoring LE, the study had some limitations. First, the literature search was limited to studies published in the English language, which might have contributed to language bias. Second, when analysis according to geographic, the ovulation rate, pregnancy rate, live birth rate, abortion rate and multiple pregnancy rate, and the RR and 95% CI did not change substantially. This may be due to most of the 11 selected RCTs were concentrated in 1 region (Asia) or country, Third, some of the included studies were of low quality and had small numbers of participants, which might have affected the reliability and validity of the conclusions. Fourth, some of the included RCTs did not illustrate the randomization, blinding, and/or allocation concealment methods and/or lacked some data, which might have led to a high risk of publication and reporting biases.

Conclusion

Despite the aforementioned limitations, the results of this meta-analysis suggest that LE is superior to CC for ovulation induction in patients with PCOS who have not previously been treated with other ovulation-induction agents. However, larger, more elegantly designed clinical trials are required to obtain further evidence.

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Author contributions SH, first author: project development, data collection, data analysis, and manuscript writing. QY, co-first author: project development, data collection, statistical analysis. YW and MW: data collection. WX, corresponding author: manuscript editing. CZ, co-corresponding author: manuscript editing.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

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