

# Comparison of clomiphene and letrozole for superovulation in patients with unexplained infertility undergoing intrauterine insemination

## A systematic review and meta-analysis

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### Abstract

**Background:** With the medical advancement some studies put forward that letrozole (LE), a specific aromatase inhibitor with the function of reducing oestrogen synthesis, has recently been applied as a potentially better alternative compared with clomiphene citrate (CC), owing to that it has a superior efficacy as compared with CC in patients of unexplained infertility undergoing intrauterine insemination (IUI). However, there is no one study can clear and definite whether LE can replace the CC as first line drug.

**Objective:** Our objective is to compare the LE with CC in the induction of ovulation in patients with unexplained infertility IUI.

**Method:** Searching databases consist of all kinds of searching tools, such as Medline, The Cochrane Library, Embase, PubMed, etc. All the include studies should meet our demand of this meta-analysis:

1. studies are comparison between LE and clomiphene for superovulation in patients with unexplained infertility undergoing IUI;
2. the result includes one of outcomes at least or more;
3. maybe in some literature they does not use LE but the meaning is as same as it, we also adopt them;
4. the patients must be at least 1 side of the unobstructed fallopian tube confirmed by hysterosalpingography (HSG) or laparoscopy;
5. uterus is normal that is confirmed by laparoscopy, hysteroscopy, ultrasound, etc;
6. semen detection is normal or mildly abnormal that is based on WHO Standard (1999). In all interest outcomes below we take the full advantage of RevMan5 to assess, the main measure is risk ratio (RR) with 95%confidence.

**Result:** Based on the current meta-analysis, we rigorously consider that LE has a likelihood to improve dominant follicles (MD= -0.56,  $I^2= 100%$ ,  $P=.04$ ; MD= -0.39,  $I^2= 73%$ ,  $P=.0003$ , respectively) and reduces the miscarriage rate (RR= 0.61,  $I^2= 0%$ ,  $P=.03$ ). There is no significant differences between the 2 groups in The total rate of pregnancy, pregnancy rate per cycle, multiple pregnancy and endometrial thickness. (RR= 1.06,  $I^2= 11%$ ,  $P=.38$ ; RR= 1.09,  $I^2= 7%$ ,  $P=.32$ ; RR= 0.79,  $I^2= 0%$ ,  $P=.46$ ; respectively)

**Conclusion:** Combined with the results of current systematic review and meta-analysis through subgroup analysis and sensitivity analysis, we can be cautious: in general, compared with CC, LE is an effective treatment in the IUI cycle, has a likelihood to improve dominant follicles and reduces the miscarriage rate.

**Abbreviations:** CC = clomiphene citrate, HCG = human chorionic gonadotropin, HSG = hysterosalpingography, IUI = intrauterine insemination, LE = letrozole, MD = mean difference, NRCT = non-randomized controlled trial, RCT = randomized controlled trial, RR = risk ratio.

**Keywords:** clomiphene, intrauterine insemination, letrozole, superovulation, unexplained infertility

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The datasets generated during and/or analyzed during the current study are publicly available.

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## 1. Introduction

Infertility was defined as the failure to achieve a clinical pregnancy after 1 year of regular unprotected intercourse.<sup>[1]</sup> Intrauterine insemination (IUI) that was for treating couples with mild male factor infertility, minimal to mild endometriosis, and unexplained infertility IUI was implemented in. Compared with IUI alone, in addition, some randomized controlled trials those researchers considered that superovulation plus IUI increased pregnancy rates evidently, and there had been little controversy that ovarian hyperstimulation improved IUI outcome in couples with unexplained and mild male superiority compared with natural cycles.<sup>[2-4]</sup> However, which drug that promoted ovulation was considered as a first line treatment remained controversial.

Over several decades, clomiphene citrate (CC) had been the first line of treatment for ovulation disorders.<sup>[5,6]</sup> Nevertheless, it had fallacious results owing to its peripheral antiestrogenic effects.<sup>[7-10]</sup> Letrozole (LE), a specific aromatase inhibitor with the function of reducing oestrogen synthesis, had recently been applied as a potentially better alternative compared with CC. But

in contrast with CC, LE was not associated with any antioestrogenic effects on endometrium, which was supported by some recent studies reporting adequate endometrial thickness during LE treatment.<sup>[11-13]</sup> Besides, compared with CC, LE was rapidly eliminated due to its shorter half-life, leading to late follicular rise in circulating oestrogen thereby enhancing endometrial development with subsequent increase in the chances of pregnancy.<sup>[14-16]</sup> The rising oestrogen levels might also result in a shorter FSH window (mimicking the physiological cycle) with subsequent mono-ovulation and a lower risk of multiple pregnancy.

On the basis of the work above, some RCTs<sup>[17,18]</sup> considered that LE had a superior efficacy as compared with CC in patients with unexplained infertility undergoing IUI. Otherwise, some RCTs<sup>[19,20]</sup> and a few retrospective studies<sup>[21,22]</sup> considered there were no significant differences between the 2 groups. Hence, Aromatase inhibitors that were originally developed and approved for treatment of breast cancer were currently being applied in alternatives to CC with an increased frequency, because it mimics the clomiphene action but without its peripheral antiestrogenic

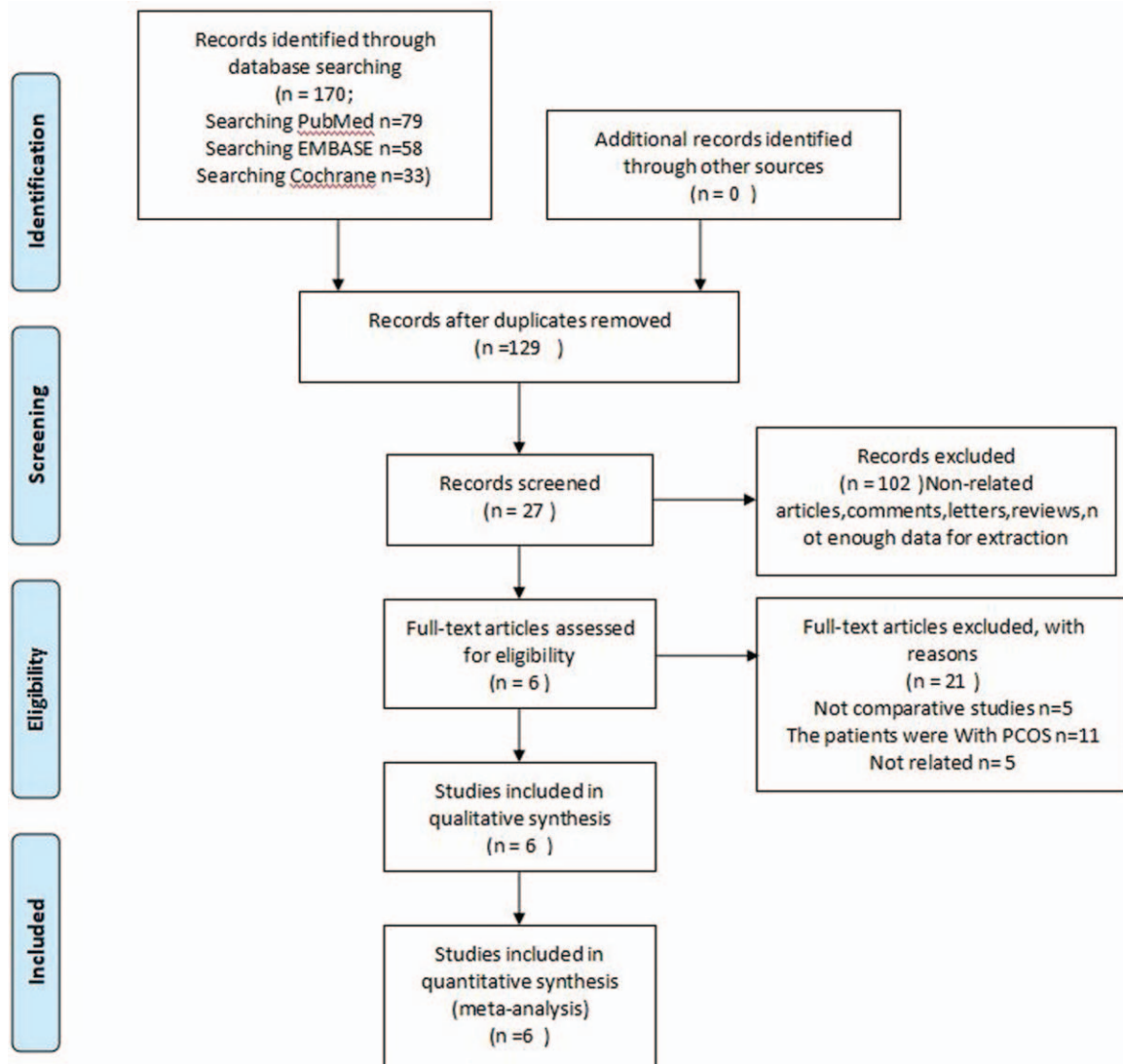


Figure 1. Flow diagram showing the selection of including studies.

**Table 1**  
**The characteristics of including studies.**

Study	Country	Design	Patents	Age (yr)	Sample size (cycles)	Treatment
Fozan 2004	Canada	RCT	Primary or secondary idiopathic infertility, at least 1 yr of infertility, no abnormalities in the fallopian tube confirmed by HSG	LE: 30.7±0.5 CC: 31.5±0.5	LE: 74(115) CC: 80(123)	LE group: 7.5mg/d, starting on the third d of menstruation, a total of 5 d + HCG+ IUI: CC group: 100mg/d, starting on the third d of menstruation, a total of 5 d +HCG+IUI
Badawy 2009	Egypt	RCT	Primary or secondary idiopathic infertility, at least 1 yr of infertility, no abnormalities in the fallopian tube confirmed by HSG	LE: 29.1±3.01 CC: 28.3±2.81	LE: 205(400) CC: 207(404)	LE group: 5.0mg/d, starting on the third d of menstruation, a total of 5 d + HCG+ IUI: CC group: 100mg/d, starting on the third d of menstruation, a total of 5 d +HCG+IUI
Fouda 2011	Egypt	RCT	Primary or secondary idiopathic infertility, at least 1 yr of infertility, no abnormalities in the fallopian tube confirmed by HSG	LE: 26.68±3.51 CC: 26.13±3.22	LE: 107(211) CC: 107(210)	LE group: 2.5mg/d, starting on the first d of menstruation, a total of 9 d + HCG + IUI: CC group: 100mg/d, starting on the third d of menstruation, a total of 5 d +HCG+IUI
Elnashar 2011	Egypt	RCT	Primary or secondary idiopathic infertility, at least 1 yr of infertility, no abnormalities in the fallopian tube confirmed by HSG	NA	LE: 205(400) CC: 208(404)	NA
Khanna 2012	India	OCS	Primary or secondary idiopathic infertility, at least 1 yr of infertility, no abnormalities in the fallopian tube confirmed by HSG	LE: 28±3.51 CC: 27.26±3.19	LE: 99(131) CC: 115(136)	LE group: 5.0mg/d, starting on the second or third d of menstruation, a spontaneous cycle + HCG+ IUI: CC group: 100mg/d, starting on the second or third d of menstruation, a total of 5 d +HCG+IUI
Akbari Sene 2018	Iran	OCS	Primary or secondary idiopathic infertility, at least 1 yr of infertility, no abnormalities in the fallopian tube confirmed by HSG	LE: 29.12±4.28 CC: 29.43±5.3	NA	NA

CC=Clomiphene Citrate, HCG=Human chorionic gonadotropin, IUI=intrauterine insemination, LE=Letrozole, NA=not available, OCS=observational cohort study, RCT=randomized controlled trial.

effect. However, there was even doubt that whether they can replace clomiphene as an ovulation inducer.

The primary outcome was the total rate of pregnancy, and the purpose of the present meta-analysis was to systematically assess the literature and identify the results of comparison studies to provide evidence for the effectiveness of LE compared with CC region for the induction of ovulation in patients with unexplained infertility IUI.

**2. Materials and methods**

Ethical approval or patient consent was not required since the present study was a review of previously published literature.

**2.1. Searching strategy**

We got the followed way to search all the literature. We used medical subject headings (MeSH) and keywords, such as IUI (Title/Abstract),

CC (Title/Abstract), LE (Title/Abstract), LE “(Mesh). In addition, we used similar words about LE such as aromatase inhibitor that belonged to the same meaning with different description type. By this way we searched from the PubMed, EMBASE, and Cochrane library to confirm the related articles. The words were contacted by AND or OR. What is more we searched the relevant literature to assess whether was available to this study. (Fig. 1).

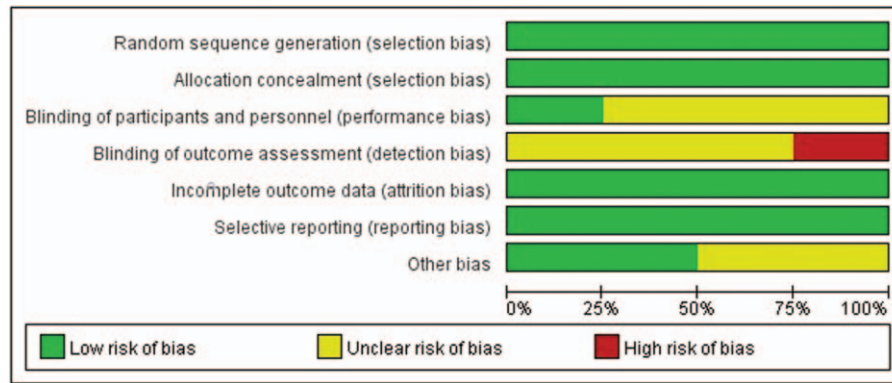
**2.2. Study selection**

Two people (Fei Qin and Yanqiong Zhou) screen the searching studies again and again, if they have divergences additional person (Wenwu Gui) reassesses the study. All the eligible studies should meet the following limitations:

1. studies are comparison between LE and clomiphene for superovulation in patients with unexplained infertility undergoing IUI;

**Table 2**  
**Assessable quality of including studies.**

Author	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Comparability between the two cohorts	Assessment of outcome	Length of follow-up
Akbarisene 2018	Representative	Same patient base	Operating record	No restriction/matching	Independent assessment	not mention
Case-control Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Comparability between the two cohorts	Assessment of outcome	Definition of Controls and cases
Khanna 2012	Potential selection bias	Hospital control	Operating record	One to one matching	Operating record	Operating record



**Figure 2.** Risk bias of graph. Each risk of bias item presented as percentages across all of the included trials, which indicated the proportion of different level risk of bias for each item.

2. the result included 1 of outcomes at least or more;
3. maybe in some literature they do not use LE but the meaning is the same as it, we also adopt them;
4. the patients must be at least one side of the unobstructed fallopian tube confirmed by hysterosalpingography (HSG) or laparoscopy;
5. uterus is normal that is confirmed by laparoscopy, hysteroscopy, ultrasound, etc;
6. semen detection is normal or mildly abnormal that is based on WHO Standard (1999).

**2.3. Data extraction**

Data extraction which is based on a standardized collection is reviewed on 2 authors (Lu Huan and Fei Qin) and crosschecks. If the study compared the LE with clomiphene for patients with polycystic ovary syndrome (PCOS) or anovulation, we should exclude. Besides, if the patients had undergone related surgery, we did not include, either. The following data is our collection: the 6 trials characteristics which mainly contain the year of publication, the authors, the design of research, the number of patients in each control, study country, intervention, the interest outcomes (Dichotomous outcomes: total pregnancy rate, cycle pregnancy rate, miscarriage rate, multiple pregnancy; Continuous outcomes: dominant follicle, endometrial thickness). (Table 1).

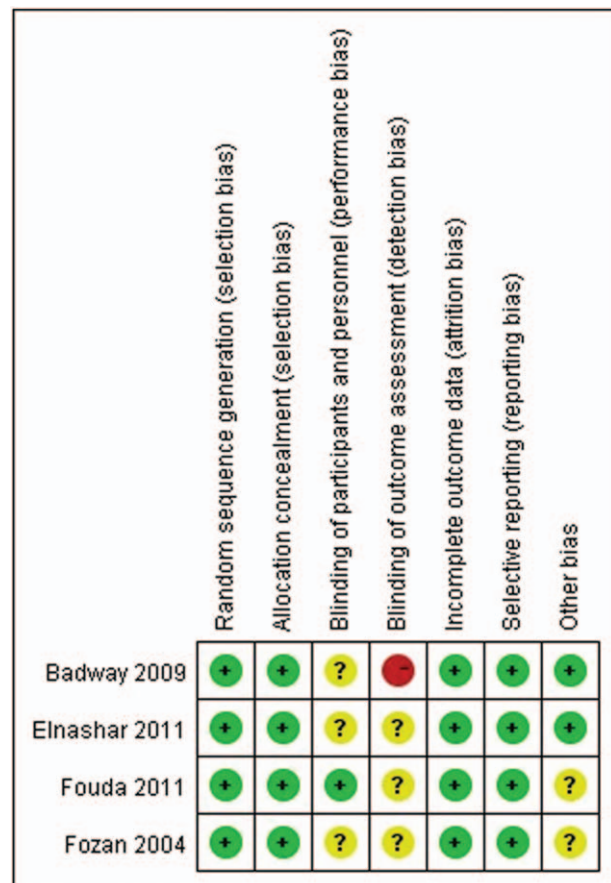
**2.4. Evaluation of quality**

The current meta-analysis includes 4 RCTs<sup>[17-20]</sup> and 2 non-randomized controlled trials (NRCTs)<sup>[21,22]</sup> their evaluation of quality are judged by 2 methods, RCT is according to the Cochrane Handbook, NRCT is on the basis of the Newcastle–Ottawa Scale. In the Cochrane Handbook we use low, high or unclear to assess the quality in 7 fields which are consist of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other sources of bias. In the NRCT we grade quality in 3 superior fields which include the selection of a research group, group’s comparability, metrical results or exposure. (Table 2, Figs. 2 and 3).

**2.5. Data synthesis and statistical analysis**

We utilized the Review Manager 5 soft-ware to complete data synthesis. In the outcomes of interest dominant follicle,

endometrial thickness are continuous variable which were described as mean difference (MD) with 95% confidence interval, the others belong to dichotomous variables which is described as risk ratios (RRs) with 95% confidence interval. To test heterogeneity 2 researchers (Yanqiong Zhou and Lu Huan) independently affiliate data into RevMan, when the value I<sup>2</sup> is beyond 50%, it means a high heterogeneity.<sup>[23]</sup> What is more, we



**Figure 3.** Risk bias of summary. Judgments about each risk of bias item for each included trials. Green indicates low risk of bias. Yellow indicates unclear risk of bias. Red indicates high risk of bias.

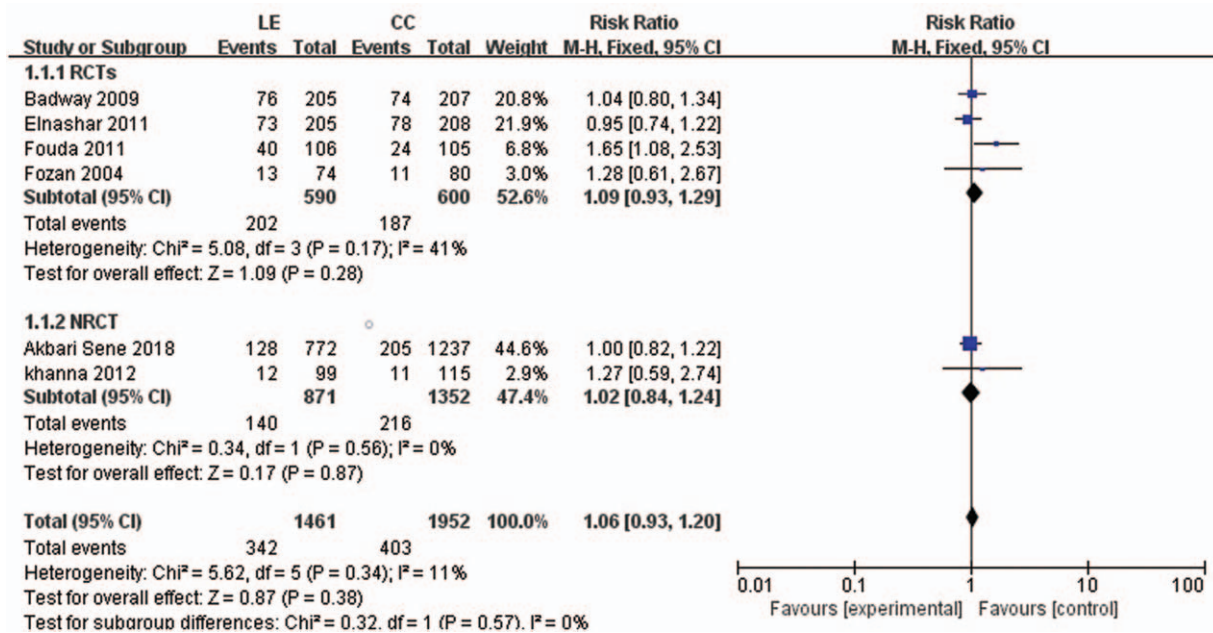


Figure 4. Forest plots of the total rate of pregnancy in infertility patients with LE versus those with CC administration.

exclude the including literature in sequence to check stability of the results. That we take the literature into subgroup is built on the design of the study. Owing to the number of including studies is lower than 10, there is no funnel plot.

2.6. Outcomes of interest

In the current meta-analysis, we include all the relevant literature and contain almost 3413 participants. The primary outcome is the total rate of pregnancy, secondary outcomes are pregnancy rate per cycle, total number of dominant follicles, miscarriage rate, multiple pregnancy, and endometrial thickness. Moreover, if there are two NRCTs at least in a pool, there will be a subgroup, where we compare the result based on RCTs and NRCTs.

2.7. Primary results

2.7.1. The total rate of pregnancy. Six studies that contain 3413 participants all reported the total rate of pregnancy. Study Akbarisene<sup>[21]</sup> and Khanna<sup>[22]</sup> belong to NRCTs, therefore, we set a subgroup to further analyze. The result suggested that there was no significant difference between the 2 groups (RR= 1.06,

I<sup>2</sup>= 11%, P= .38). After removing every study, the result does not change at all, indicating the steady of result is fine. Four RCTs and 2 NRCTs in this pool suggest there was no significant difference (RR= 1.09, I<sup>2</sup>= 41%, P= .28, RR= 1.02, I<sup>2</sup>= 0%, P= .56, respectively). (Fig. 4).

2.8. Secondary results

2.8.1. Pregnancy rate per cycle. Considering only one NRCT was included, there was no subgroup in this pool. Five studies were included and there was no significant difference (RR= 1.09, I<sup>2</sup>= 7%, P= .32). Four RCTs in this pool suggested there were no worthwhile differences (RR= 1.09, I<sup>2</sup>= 30%, P= .34). The sensitive test presented there was no significant difference and the result was stable. (Fig. 5).

2.8.2. Total number of dominant follicles. Six studies were included in this pool and there was a subgroup, owing to 2 NRCTs were included. The result suggested that there was no significant difference between the 2 groups (MD= -0.49, I<sup>2</sup>= 100%, P= .06). After removing every study the result did not change at all, indicating the steady of the result was fine. Of

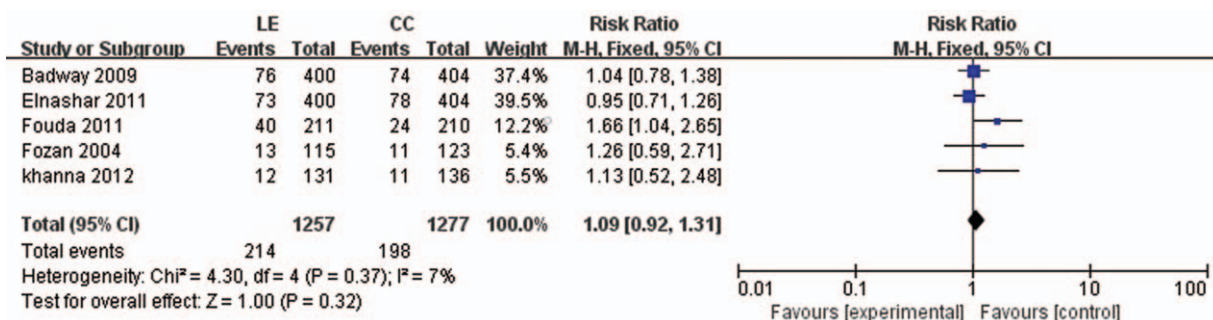


Figure 5. Forest plots of pregnancy rate per cycle suggested there was no significant difference between the LE group and CC group.

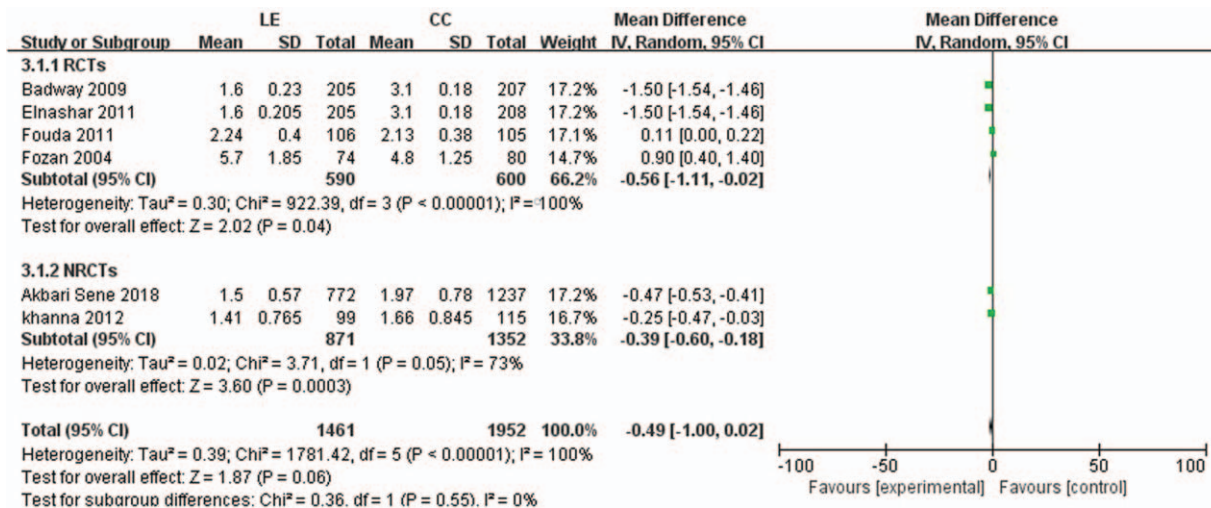


Figure 6. Patients receiving LE were more likely to Total number of dominant follicles than those with CC administration.

interest, 4 RCTs and 2 NRCTs in this pool suggested there was a slight difference with higher heterogeneity. (MD= -0.56, I<sup>2</sup>= 100%, P= .04; MD= -0.39, I<sup>2</sup>= 73%, P= .0003, respectively). (Fig. 6).

**2.8.3. Multiple pregnancy.** Considering only 1 NRCT was included, there was no subgroup in this pool. Five studies were included and there were no significant differences (RR= 0.79, I<sup>2</sup>= 0%, P= .46). Four RCTs in this pool suggested there was no significant difference (RR= 0.43, I<sup>2</sup>= 0%, P= .12). The sensitive test presented there was no significant difference and the result was stable. (Fig. 7).

**2.8.4. Miscarriage rate.** Four studies were listed without subgroup. The result suggested that LE reduced the miscarriage rate in some extent. (RR= 0.61, I<sup>2</sup>= 0%, P= .03) 3 RCTs in this pool suggested there was no significant differences (RR= 0.64, I<sup>2</sup>= 27%, P= .22) with ascending heterogeneity. After eliminating the Fozan<sup>[18]</sup> or Akbari Sene<sup>[21]</sup> the result is according with the RCTs. However, that raised the heterogeneity. By changing the model the test of the result was also stable. (Fig. 8).

**2.8.5. Endometrial thickness.** In this pool there were 5 studies. The result suggested there were no significant differences between the 2 groups with a high heterogeneity (MD= 0.01, I<sup>2</sup>= 100%,

P= .98). Three RCTs in this pool suggest there was not any significant difference with the emergence of heterogeneity, either. (MD= -0.03, I<sup>2</sup>= 100%, P= 0.95). The sensitive test presented there were no significant differences and the result was stable. (Fig. 9).

### 3. Discussion

Aromatase is a cytochrome P-450 hemoprotein-containing enzyme complex that catalyzes the conversion of androstenedione and testosterone into oestrogens.<sup>[24,25]</sup> It was postulated that blocking estrogen production by inhibiting aromatization in the ovary would release the hypothalamic/pituitary axis from estrogenic negative feedback. As a consequence, follicle-stimulating hormone (FSH) secretion increases, stimulating the development of ovarian follicles. Preliminary studies reported that aromatase inhibitors were helpful for inducing ovulation and in superovulation. Since no estrogen receptor down regulation occurs, no adverse effects on estrogen target tissues would be expected.

As presented in the current meta-analysis, we found, although, there was no significant difference in total rate of pregnancy, pregnancy rate per cycle and the number of dominant follicles, there was a tendency that LE had a little function to improve the

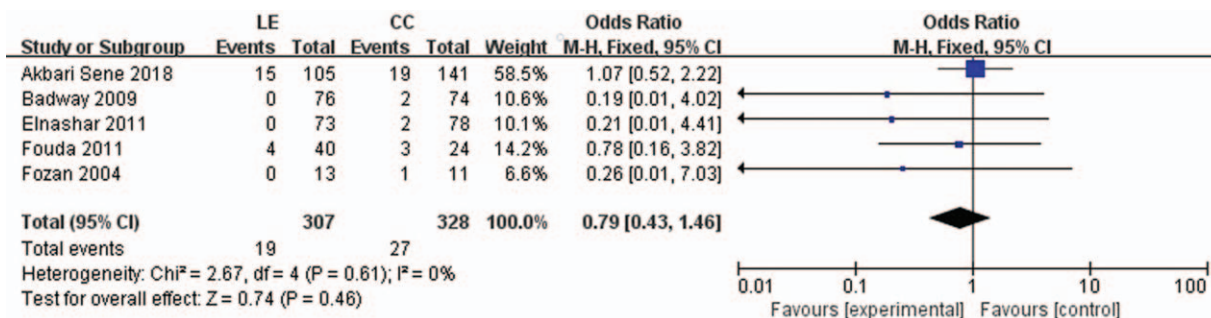


Figure 7. Forest plots of multiple pregnancy in infertility patients with LE vs those with CC administration and there was no significant difference between the 2 groups.

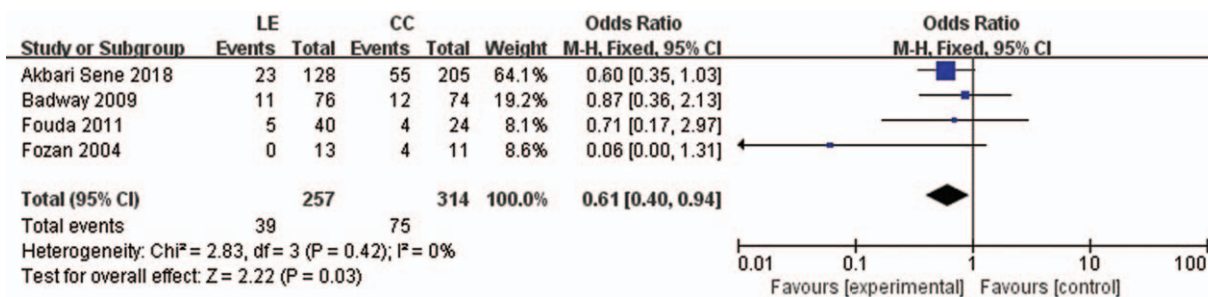


Figure 8. The result of this Forest plots showed that LE could reduce the miscarriage rate.

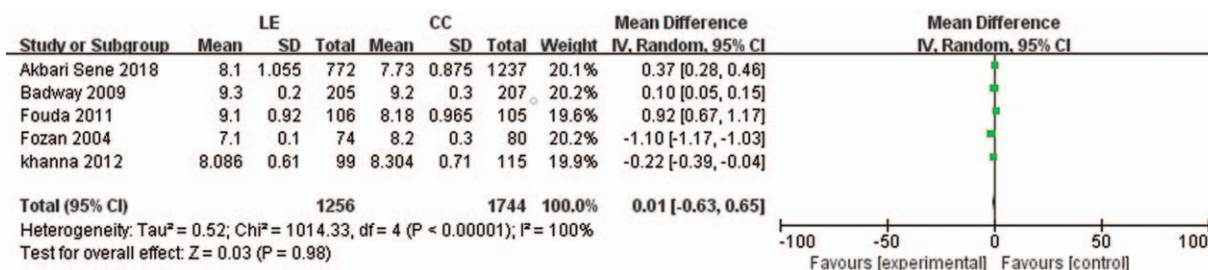


Figure 9. There was no difference in endometrial thickness for the infertility patients.

number of dominant follicles owing to the result of subgroup. This was in agreement with the previous report<sup>[26]</sup> that LE improves ovarian response to FSH in poor responder women. In some preceding study, no difference was found in the pregnancy rate between the FSH group and the LE/FSH group (20.9% vs 21.6%).<sup>[27]</sup> The higher number of mature follicles in the LE group did not result in a higher pregnancy rate. Perhaps, this was related to inadequate quality of endometrium in the LE group.

Compared with CC, LE is associated with a thicker endometrium.<sup>[11]</sup> It suggests that LE has minimal effect on the endometrium. Perhaps, due to its rapid and reversible action on the endometrium allowing the endometrium to respond well to increasing endometrium in the late follicular phase. Such findings could be attributed to the mechanism of action of LE. As an aromatase inhibitor, it works by luring the conversion of androstenedione and endometrium in the ovary. The decrease in circulating E increases gonadotropin secretion.<sup>[28]</sup> What is more, the use of CC is associated with endometrial thinning in 15% to 50% of patients.<sup>[29]</sup> This could be due to prolonged E receptor depletion in the endometrium.<sup>[30]</sup> Compared with CC, LE is involved in a thicker endometrium.<sup>[11]</sup> It suggests that LE has minimal effect on the endometrium. However, in our present study we found there was no difference between CC group and LE group with a high heterogeneity, the reason for the heterogeneity was not only related to the choice of dose, but the mechanism of action of LE. A larger study is required to clarify this matter.

Though, in the pool of total rate of pregnancy and pregnancy rate per cycle, there was no difference, compared with CC it was worth noting that LE had a lower miscarriage rate. Perhaps, this was due to the different mechanism of action between LE and CC. In previous study, the researchers reported that the addition of LE

(5 mg daily for 5 days) to gonadotropin was associated with a thinner endometrium than gonadotropin alone.<sup>[27]</sup> In the present study, the endometrial thickness was the same in the LE group and in the CC group. Moreover, the drugs used in each of the subgroups included in the meta-analysis were the same, but the specific drug usage was different. In this study, different doses of LE were used including 2.5 mg/d or 5 mg/d or 7.5 mg/d, and the effect of different doses of LE was still currently controversial. A retrospective study by Portella showed that there was no statistical difference in the endometrial thickness and pregnancy rate between the 2.5 mg/d LE and the 5.0 mg/d LE when it is time to inject human chorionic gonadotropin;<sup>[31]</sup> a randomized controlled trial by Badawy A in 2007 showed that there was no significant difference in the pregnancy rate and abortion rate between the doses of LE 2.5 mg/d, 5 mg/d and 7.5 mg/d;<sup>[32]</sup> nevertheless, a randomized controlled trial of Fadhli showed: the pregnancy rate of 5 mg/d for 5 days is higher than 2.5 mg/d.<sup>[33]</sup> These might affect the reliability and applicability of current meta-analysis, but there was no heterogeneity that showed the different doses of LE did not make a great influence on this result.

There are also some limitations in our study as following. Firstly, the quality of the original research methodology incorporated has their own limitations; Secondly, few studies based on patients with same characteristics and there is no one completely uniform medication regimen; Besides, the sample size is small; Ultimately, inadequate follow-up time leads to imperfect indicators.

#### 4. Conclusion

Combined with the results of current systematic review and meta-analysis through subgroup analysis and sensitivity analysis, we

can be cautious: in general, compared with CC LE is an effective treatment in the IUI cycle, has a likelihood to improve dominant follicles and reduces the miscarriage rate.

### Author contributions

All authors' contributions are equal.

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