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Effect of clomiphene citrate on endometrial thickness, ovulation, pregnancy and live birth in anovulatory women: systematic review and meta-analysis

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KEYWORDS: anovulation; clomiphene; endometrial thickness; ovulation induction; PCOS

ABSTRACT

Objectives *To compare the impact of clomiphene citrate (CC)* vs *other drug regimens on mid-cycle endometrial thickness (EMT), ovulation, pregnancy and live birth rates in women with World Health Organization (WHO) group II ovulatory disorders.*

Methods *We searched MEDLINE, EMBASE, Scopus, Web of Science, The Cochrane Central Register of Clinical Trials (CENTRAL) and the non-MEDLINE subset of PubMed from inception to December 2016 and cross-checked references of relevant articles. We included only randomized controlled trials (RCTs) comparing CC used alone* vs *other drug regimens for ovulation induction in women with WHO group II anovulation. Outcomes were mid-cycle EMT, ovulation, pregnancy and live birth rates. We pooled weighted mean differences (WMD) with 95% confidence intervals (CI) for continuous variables (EMT) and risk ratios (RR) with 95% CI for binary variables (ovulation, pregnancy and live birth rates).*

Results *We retrieved 1718 articles of which 33 RCTs (4349 women, 7210 ovulation induction cycles) were included. In 15 RCTs that compared CC with letrozole, EMT was lower in the CC group (1957 women, 3892 cycles; WMD, −1.39; 95% CI, −2.27 to −0.51;* $I^2 = 100\%$*), ovulation rates after CC and letrozole were comparable (1710 women, 3217 cycles; RR, 0.97; 95% CI, 0.90–1.04;* $I^2 = 47\%$*), while CC led to a lower pregnancy rate (1957 women, 3892 cycles; RR, 0.78; 95% CI, 0.63–0.95;* $I^2 = 43\%$*) and a lower live birth rate (RR, 0.70; 95% CI, 0.49–0.98;* $I^2 = 35\%$*). In two RCTs that compared CC with CC plus metformin, EMT, ovulation and pregnancy rates were comparable (101 women, 140 cycles; WMD, −0.23; 95% CI, −0.92 to 0.45;* $I^2 = 78\%$*; RR, 0.84; 95% CI, 0.67–1.06;* $I^2 = 0\%$*; and RR, 0.79; 95% CI, 0.33–1.87;* $I^2 = 0\%$*). In three studies that compared CC with CC plus* N*-acetyl cysteine (NAC), EMT was lower in the CC group (340 women, 300 cycles; WMD, −1.51; 95% CI, −1.98 to −1.04;* $I^2 = 45\%$*). In two studies that compared CC with CC + nitric oxide (NO) donor, EMT was lower in the CC group (120 women, 304 cycles; WMD, −1.75; 95% CI, −2.08 to −1.41;* $I^2 = 0\%$*). Compared with CC plus NO donor or NAC, CC showed statistically significant lower ovulation and pregnancy rates. Compared with tamoxifen in three studies, CC showed a tendency towards lower EMT (571 women, 844 cycles; WMD, −1.34; 95% CI, −2.70 to 0.01;* $I^2 = 96\%$*) with comparable ovulation and pregnancy rates.*

Conclusions *In women with WHO group II ovulatory disorders, ovulation induction with CC might result in lower EMT than other ovulation induction regimens. Whether the lower EMT caused the lower pregnancy and live birth rates remains to be elucidated. Letrozole seems to be beneficial for these women. However, our findings should be interpreted with caution as the quality of evidence was very low. Copyright © 2017 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Infertility is defined as failure to achieve a successful pregnancy after 12 months or more of appropriately timed unprotected intercourse or therapeutic donor

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insemination[1]. It is estimated to affect 186 million people worldwide[2]. While many treatments can help infertile couples, areas of the world with the highest rates of infertility are often those with poor access to fertility treatment due to limited resources[2].

About 25% of infertility is caused by ovulatory disorders[3]. The World Health Organization (WHO) classifies these into three groups. Group II includes women with hypothalamic–pituitary–ovarian dysfunction (predominantly polycystic ovary syndrome; PCOS)[3]. Ovulation induction is by far the most commonly used treatment for women with WHO group II anovulation and clomiphene citrate (CC) has historically been the drug most used[4]. CC is a non-steroidal triphenylethylene derivative that exhibits both estrogenic agonist and estrogenic antagonist properties. Its mechanism of action for ovulation induction is by competitive binding to estrogen receptors in the hypothalamus and pituitary reducing signaling of estrogen via its receptors. This interferes with the feedback mechanism of endogenous estrogen resulting in an increase in FSH and LH secretion to stimulate ovarian follicular production[5,6]. If ovulation cannot be achieved with increasing doses of CC, the patient is labeled as CC resistant, while women who are not pregnant after six ovulatory cycles with CC are labeled as having CC failure[3,7].

In many fertility guidelines, CC is recommended as the first-line treatment for women with group II anovulation or PCOS who wish to conceive[3,8–11]. However, other guidelines recommend both CC and letrozole as first-line treatments[12–15]. While cost differences between letrozole and CC in highly resourced countries in Europe, North-America, Australia and New Zealand are not a concern, the threefold greater cost of letrozole over CC is important in low-resourced countries such as Egypt and India.

It is hypothesized that CC resistance and failure are related to anti-estrogenic effects of CC on the endometrium, cervical mucus and uterine blood flow[16–18]. However, such an impact of CC and other ovulation induction drugs on endometrial thickness (EMT) in women with ovulatory disorders has not been assessed systematically, thus necessitating a systematic review on this topic.

METHODS

Search

Our review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines for reporting systematic reviews[19]. We searched for all published clinical trials studying the impact of CC alone *vs* other drug regimens on mid-cycle EMT in women with WHO group II ovulatory disorders. We searched the following electronic databases: MEDLINE, EMBASE, Scopus, Web of Science, The Cochrane Central Register of Clinical Trials (CENTRAL) and the non-MEDLINE subset of PubMed from inception to December 2016 (Table S1). We also searched the reference lists of relevant studies. We did not apply language restrictions. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42017057458).

Selection criteria

Two reviewers (M.G. and S.H.) independently screened titles and abstracts of the identified studies and read the full articles for final inclusion. Disagreement between the reviewers was resolved through discussion with a third reviewer (B.M.). We only included randomized controlled trials (RCTs) in the review. We included RCTs reporting on mid-cycle EMT in women with WHO group II anovulation receiving ovulation induction with CC as one of the interventions. The included comparative drug regimens could be aromatase inhibitors, gonadotropins, CC plus adjunctive treatments or any other regimen.

Study quality assessments and data extraction

We used the risk of bias assessment tool in the *Cochrane Handbook* to assess the quality of included studies[20]. Then we used GRADEPRO software to generate a summary of findings table[21]. This table evaluated the overall quality of the body of evidence for EMT, ovulation, pregnancy and live birth rates in the main comparison of the study between CC and letrozole. We used the GRADE criteria (study limitations (i.e. risk of bias), consistency of effect, imprecision, indirectness and publication bias)[21].

We extracted data on the following domains: study design, trial setting, inclusion criteria, age, body mass index, duration of infertility, sample size, number of ovulation induction cycles, details of interventions and outcomes as means and standard deviations (SD) of mid-cycle EMT in mm and number of events, cycles and patients for ovulation, pregnancy and live birth. If data were missing, we contacted authors by email for additional information.

Outcomes

The outcomes of our review were mid-cycle EMT per cycle and per woman, ovulation rate per cycle detected by ultrasound scan or mid-luteal progesterone, clinical pregnancy rate per woman defined as ultrasonographic visualization of one or more gestational sacs (positive pregnancy test was included if it was the only type reported in the included studies) and live birth rate per woman randomized defined as delivery of a live baby after 24 weeks of gestation.

Statistical analysis

We performed meta-analyses by using a random effects model. We pooled weighted mean differences (WMD) with 95% confidence intervals (CI) for continuous variables (EMT) and risk ratios (RR) with 95% CI for binary variables (ovulation, pregnancy and live birth rates). In cases of high heterogeneity ($I^2 \geq 50\%$), we

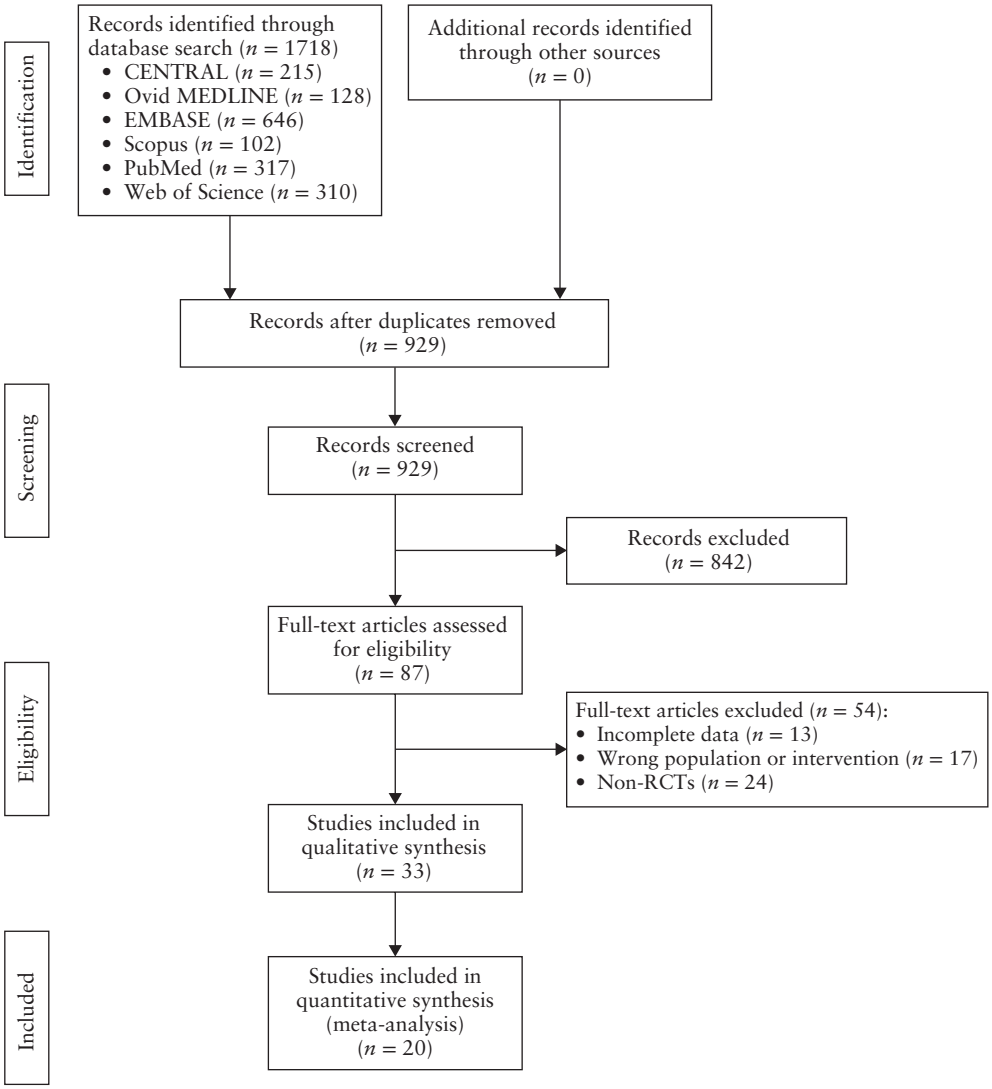

Figure 1 Flowchart of studies included in systematic review and meta-analysis. RCT, randomized controlled trial.

performed sensitivity analyses by including studies with low risk of bias. For statistical analysis, we used Review Manager 5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). In order to study the impact of publication bias, a funnel plot was produced if there were more than 10 trials included in a comparison.

RESULTS

Characteristics of included studies

Our electronic search revealed 1718 articles of which we selected 87 after screening of titles and abstracts. After full-text evaluation, we excluded 54 studies due to incomplete data ($n = 13$), wrong population or intervention ($n = 17$), or non-RCTs ($n = 24$) (Figure 1 and Tables S1 and S2). There were 33 RCTs comprising a total of 4349 women with WHO group II anovulation, undergoing 7210 treatment cycles. Of the 33 included studies, participants were women with PCOS (without CC resistance) in 25 studies[22–46], women with CC-resistant PCOS in five studies[47–51], women with WHO group II anovulation (with or without PCOS) in two studies[52,53] and women with WHO group II anovulation (without PCOS) in one study[54]. The characteristics of these 33 included studies are listed in Table 1. The average quality of the studies was low. Risk of bias for included studies is presented in a summary table (Figure S1).

We included 15 RCTs comparing CC with letrozole (1957 women, 3892 cycles)[23–25,27–29,33,38–41,44,46,51,54], two RCTs comparing CC with anastrozole (329 women, 329 cycles)[52,53], two RCTs comparing CC with CC plus metformin (101 women, 140 cycles)[35,42], three RCTs comparing CC with tamoxifen (571 women, 844 cycles)[26,38,54], three RCTs comparing CC with CC plus *N*-acetyl cysteine (NAC; 340 women, 300 cycles)[35,43,49] and two RCTs comparing CC with CC plus isosorbide mononitrate (ISMN) as nitric oxide (NO) donor (120 women, 304 cycles)[30,36].

Endometrial thickness was reported in all included RCTs. Live birth rate was reported in seven RCTs[27,29,34,40–42,54]. Pregnancy rate was reported in all

Table 1 Characteristics of studies included in systematic review

Study	*Population*	n*	*Intervention*	*Comparison*	*Outcomes*
Abu Hashim (2012)[22]	PCOS	113	153 cycles of CC 100 mg/day on day 3–7	159 cycles of CC + uFSH 150 IU on day 9	EMT, OR, PR
Atay (2006)[23]	PCOS	106	55 cycles of CC 100 mg/day for 5 days on day 3–7	51 cycles of letrozole 2.5 mg/day for 5 days on day 3–7	EMT, OR, PR
Aygen (2007)[24]	PCOS	15	24 cycles of CC 100 mg/day for 5 days on day 3–7	23 cycles of letrozole 2.5 mg/day for 5 days on day 3–7 and 20 cycles of 2.5 mg/day letrozole + 850 mg metformin thrice daily (on day 3–7)	EMT, OR, PR
Badawy (2009)[25]	PCOS	438	523 cycles of CC 100 mg/day for 5 days on day 3–7	540 cycles of letrozole 5 mg/day for 5 days on day 3–7	EMT, OR, PR
Badawy (2011)[26]	PCOS	371	187 cycles of CC 100 mg/day on day 3–7	184 cycles of tamoxifen 40 mg/day on day 3–7	EMT, OR, PR
Bayar (2006)[27]	PCOS	74	95 cycles of CC 100 mg/day for 5 days on day 3–7	99 cycles of letrozole 2.5 mg/day for 5 days on day 3–7	EMT, OR, PR, LBR
Chen (2016)[28]	PCOS	156	200 cycles of CC 50–100 mg/day for 5 days on day 3–7	215 cycles of letrozole 2.5–5 mg/day for 5 days on day 3–7 and 179 cycles of letrozole 2.5–5 mg/day on day 3–7 plus hMG 75 IU every other day	EMT, OR, PR
de Paula Guedes Neto (2011)[31]	PCOS	68	37 cycles of 100 mg/day on day 3–7	31 cycles of raloxifene 100 mg/day on day 3–7	EMT, OR
Dehbashi (2009)[29]	PCOS	100	50 cycles of CC 100 mg/day for 5 days on day 3–7	50 cycles of letrozole 5 mg/day for 5 days on day 3–7	EMT, OR, PR, LBR
El-Berry (2010)[30]	PCOS	30	40 cycles of CC 100 mg/day on day 5–9	37 cycles of CC + ISMN (NO donor) 20 mg vaginally/day on day 5 until ovulation	EMT, OR, PR
Elnashar (2006)[47]	PCOS resistant to CC	80	40 cycles of CC 100 mg/day on day 3–7	40 cycles of CC + DEX 2 mg/day on day 3–12	EMT, OR, PR
Hendawy (2011)[51]	PCOS resistant to CC	54	26 cycles of CC 100 mg/day for 5 days on day 3–7	28 cycles of letrozole 2.5 mg/day for 5 days on day 3–7	EMT, OR, PR
Ismail (2014)[48]	PCOS resistant to CC	170	85 cycles of CC 150 mg/day on day 3–7	85 cycles of CC + L-carnitine 3 g/day on day 3 until pregnancy	EMT, OR, PR
Kamel (2013)[32]	PCOS	97	49 cycles of CC 100 mg/day on day 2–6	48 cycles of phytoestrogens 40 mg/day on day 2–12	EMT, PR
Kar (2012)[33]	PCOS	103	51 cycles of CC 100 mg/day for 5 days on day 2–6	52 cycles of letrozole 5 mg/day for 5 days on day 2–6	EMT, OR, PR
Keikha (2010)[49]	PCOS resistant to CC	93	40 cycles of CC 100 mg/day on day 3–7	53 cycles of CC + NAC 1200 mg/day on day 3–7	EMT, OR
Lima (2016)[34]	PCOS	96	52 cycles of CC 100 mg/day on day 3–7	44 cycles of rFSH 50 IU on day 4	EMT, PR, LBR
Maged (2015)[35]	PCOS	120	16 cycles of CC 100 mg/day on day 3–7	24 cycles of CC + NAC 1200 mg/day on day 3–7 and 18 cycles of CC + metformin 1500 mg/day continuously	EMT, OR, PR
Mahran (2016)[36]	PCOS	90	81 cycles of CC 100 mg/day on day 5–9	74 cycles of CC + ISMN (NO donor) 10 mg/day on day 2–15 72 cycles of CC + ISMN (NO donor) 20 mg/day on day 2–15	EMT, OR, PR
Moini (2015)[37]	PCOS	95	50 cycles of CC 100 mg/day on day 3–7	45 cycles of CC + EE 0.05 mg/day on day 8–12	EMT, PR
Moussa (2016)[38]	PCOS	150	50 cycles of CC 100 mg/day for 5 days on day 3–7	50 cycles of letrozole 5 mg/day for 5 days on day 3–7 50 cycles of tamoxifen 40 mg/day on day 3–7	EMT, OR, PR
Nahid (2012)[39]	PCOS	100	50 cycles of CC 100 mg/day for 5 days on day 3–7	50 cycles of letrozole 2.5 mg/day for 5 days on day 3–7	EMT, OR, PR

Continued over.

Table 1 *Continued.*

Study	*Population*	n*	*Intervention*	*Comparison*	*Outcomes*
Ray (2012)[40]	PCOS	147	156 cycles of CC 100 mg/day for 5 days on day 3–7	132 cycles of letrozole 2.5 mg/day for 5 days on day 3–7	EMT, PR, LBR
Refaeey (2014)[50]	PCOS resistant to CC	101	71 cycles of CC 150 mg/day on day 3–7	82 cycle of CC + CoQ10 180 mg/day on day 2 until ovulation	EMT, OR, PR
Roy (2012)[41]	PCOS	204	318 cycles of CC 50–100 mg/day for 5 days on day 3–7	294 cycles of letrozole 2.5–5 mg/day for 5 days on day 3–7	EMT, OR, PR, LBR
Sahin (2004)[42]	PCOS	21	55 cycles of CC 100 mg/day on day 3–7	51 cycles of CC + metformin 1700 mg/day for 3 months	EMT, OR, PR, LBR
Salehpour (2012)[43]	PCOS	167	85 cycles of CC 100 mg/day on day 3–7	82 cycles of CC + NAC 1200 mg/day on day 3–7	EMT, OR, PR
Selim (2012)[44]	PCOS	201	99 cycles of CC 100 mg/day for 5 days on day 3–7	102 cycles of letrozole 5 mg/day for 5 days on day 3–7	EMT, OR, PR
Seyedoshohadaei (2012)[54]	Non-PCOS anovulatory women	150	199 cycles of CC 50–100 mg/day for 5–7 days starting on day 3	194 cycles of letrozole 2.5–7.5 mg/day for 5–7 days starting on day 3 and 174 cycles of tamoxifen 10–30 mg/day for 5–7 days on day 3 to 7 or 9	EMT, PR, LBR
Shahin (2014)[45]	PCOS	194	192 cycles of CC 150 mg/day on day 3–7	204 cycles of CC + phytoestrogens 120 mg/day on day 1 until pregnancy	EMT, PR
Sheikh-El-Arab Elsedeek (2011)[46]	PCOS	116	57 cycles of CC 100 mg/day for 5 days on day 3–7	59 cycles of letrozole 5 mg/day for 5 days on day 3–7	EMT, OR, PR
Tredway (2011)[52]	Ovulation dysfunction	271	77 cycles of CC 50 mg/day on day 3–7	79 cycles of anastrozole 1 mg/day on day 3–7 and 76 cycles of anastrozole 5 mg/day on day 3–7 and 39 cycles of anastrozole 10 mg/day on day 3–7	EMT, OR, PR
Yang (2006)[53]	Anovulatory women	58	14 cycles of CC 100 mg/day on day 3–7	14 cycles of anastrozole 1 mg/day on day 3–7 and 15 cycles of anastrozole 2 mg/day on day 3–7 and 15 cycles of anastrozole 4 mg/day on day 3–7	EMT, OR, PR

*Number of participants. CC, clomiphene citrate; CoQ10, coenzyme Q10; DEX, dexamethasone; EE, ethinyl estradiol; EMT, endometrial thickness; hMG, human menopausal gonadotropin; ISMN, isosorbide mononitrate; LBR, live birth rate; NAC, *N*-acetyl cysteine; NO, nitric oxide; OR, ovulation rate; PCOS, polycystic ovary syndrome; PR, pregnancy rate; rFSH, recombinant follicle stimulating hormone; uFSH, urinary follicle stimulating hormone.

RCTs except two[31,49]; it was reported as clinical pregnancy rate except in four studies[25,27,30,36] in which it was reported as a positive pregnancy test. Ovulation rate per cycle was reported in all RCTs except for four[32,34,37,45].

Results of meta-analyses

Results of meta-analyses are summarized in Table S3.

CC vs *letrozole*

Pooled analysis of five studies showed a lower live birth rate in the CC group (RR, 0.70; 95% CI, 0.49–0.98; $I^2 = 35\%$)[27,29,40,41,54] (Figure 2). Pooled analysis of 15 studies showed EMT to be lower (WMD, −1.39; 95% CI, −2.27 to −0.51; $I^2 = 100\%$) with a lower pregnancy rate (RR, 0.78; 95% CI, 0.63–0.95; $I^2 = 43\%$) in the CC group than in the letrozole group (Figures 2 and 3)[23–25,27–29,33,38–41,44,46,51,54]. Ovulation rates were comparable between the groups (13 trials, RR, 0.97; 95% CI, 0.90–1.04; $I^2 = 47\%$; Figure 4)[23–25,27–29,33,38,39,41,44,46,51]. Data of EMT per woman were available in eight studies; pooled analysis showed EMT to be lower in the CC group (WMD, −2.10; 95% CI, −3.22 to −0.98; $I^2 = 96\%$)[23,29,33,38,39,44,46,51].

CC vs *anastrozole*

Two studies compared CC with anastrozole in different doses[52,53]. Pooled analysis of these two studies showed no evidence of significant difference in EMT (WMD, −0.12; 95% CI, −2.17 to 1.94; $I^2 = 89\%$) and no statistical difference in pregnancy rate (RR, 2.44; 95% CI, 0.90–6.66; $I^2 = 0\%$) between the CC group and the 1 mg anastrozole group, with a higher ovulation rate (RR, 1.98; 95% CI, 1.43–2.76; $I^2 = 0\%$) in the CC group than the 1 mg anastrozole group.

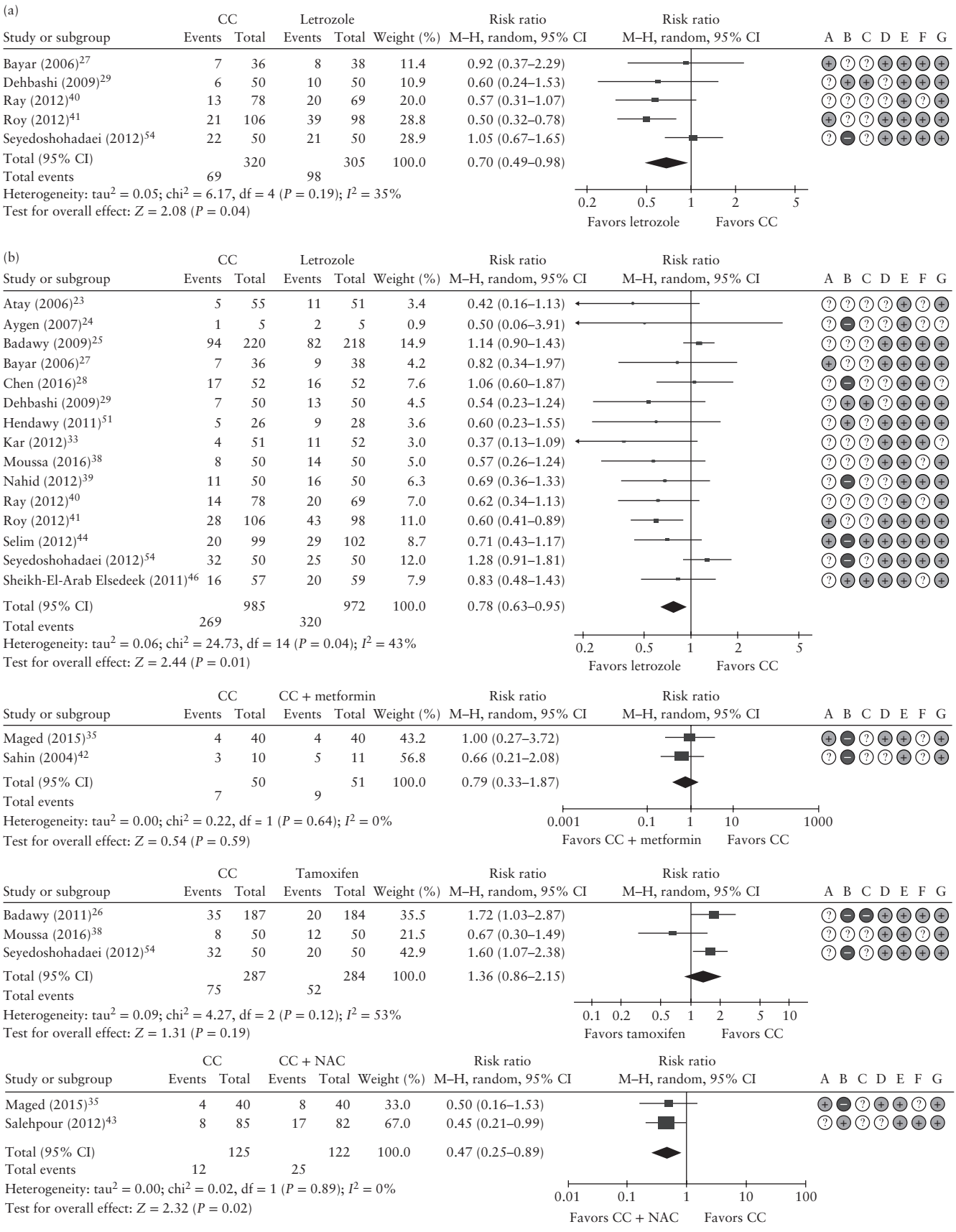

Figure 2 *Continued over*. Forest plots for comparison of: (a) live birth rate between clomiphene citrate (CC) and letrozole groups; (b) pregnancy rate between CC and letrozole, CC + metformin, tamoxifen, CC + *N*-acetyl cysteine (NAC) and CC + nitric oxide (NO) donor groups. Only first author of each study is given. M–H, Mantel–Haenszel. Risk of bias: low (+), high (−) or unclear (?); A, allocation concealment (selection bias); B, blinding of participants and personnel (performance bias); C, blinding of outcome assessment (detection bias); D, random sequence generation (selection bias); E, incomplete outcome data (attrition bias); F, selective reporting (reporting bias); G, other bias.

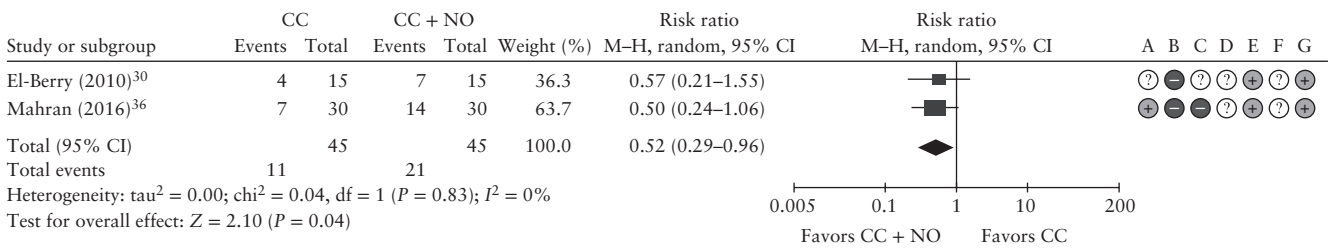

Figure 2 (*Continued*) Forest plots for comparison of: (a) live birth rate between clomiphene citrate (CC) and letrozole groups; (b) pregnancy rate between CC and letrozole, CC + metformin, tamoxifen, CC + *N*-acetyl cysteine (NAC) and CC + nitric oxide (NO) donor groups. Only first author of each study is given. M–H, Mantel–Haenszel. Risk of bias: low (+), high (−) or unclear (?); A, allocation concealment (selection bias); B, blinding of participants and personnel (performance bias); C, blinding of outcome assessment (detection bias); D, random sequence generation (selection bias); E, incomplete outcome data (attrition bias); F, selective reporting (reporting bias); G, other bias.

CC vs *CC plus metformin*

Comparison of CC with CC plus metformin showed EMT, ovulation and pregnancy rates to be similar (two trials, WMD, −0.23; 95% CI, −0.92 to 0.45; $I^2 = 78\%$; RR, 0.84; 95% CI, 0.67–1.06; $I^2 = 0\%$; and RR, 0.79; 95% CI, 0.33–1.87; $I^2 = 0\%$; Figures 2–4). One study reported no statistical difference in live birth rate between the groups (RR, 0.82; 95% CI, 0.24–2.82)[42].

CC vs *tamoxifen*

Pooled analysis of three studies showed no statistical difference in EMT (WMD, −1.34; 95% CI, −2.70 to 0.01; $I^2 = 96\%$) and a comparable pregnancy rate (RR, 1.36; 95% CI, 0.86–2.15; $I^2 = 53\%$) between the groups (Figures 2 and 3). Pooled analysis of two studies that reported on ovulation rate showed this to be comparable between the groups (RR, 1.12; 95% CI, 0.88–1.43; $I^2 = 55\%$; Figure 4)[26,38].

CC vs *CC plus NAC*

Pooled analysis of three studies showed EMT to be lower in the CC group (WMD, −1.51; 95% CI, −1.98 to −1.04; $I^2 = 45\%$) and a lower ovulation rate (RR, 0.58; 95% CI, 0.44–0.76; $I^2 = 0\%$; Figures 3 and 4). Pooled analysis of the two studies showed a statistically significant lower pregnancy rate in the CC group (RR, 0.47; 95% CI, 0.25–0.89; $I^2 = 0\%$; Figure 2)[35,43].

CC vs *CC plus coenzyme Q10*

One study that compared CC with CC plus coenzyme Q10[50] showed EMT to be lower in the CC group (WMD, −1.79; 95% CI, −2.16 to −1.42), and lower ovulation (RR, 0.24; 95% CI, 0.13–0.41) and pregnancy (RR, 0.16; 95% CI, 0.05–0.51) rates in the CC group.

CC vs *CC plus dexamethasone*

One study that compared CC with CC plus dexamethasone[47] showed EMT to be lower in the CC group (WMD, −1.79; 95% CI, −2.31 to −1.27), and lower ovulation (RR, 0.20; 95% CI, 0.09–0.43) and pregnancy (RR, 0.13; 95% CI, 0.03–0.51) rates in the CC group.

CC vs *CC plus ethinyl estradiol*

One study that compared CC with CC plus ethinyl estradiol[37] showed EMT to be lower in the CC group (WMD, −0.80; 95% CI, −1.56 to −0.04), with a lower clinical pregnancy rate in the CC group (RR, 0.35; 95% CI, 0.13–0.89), while there was no statistical difference in ongoing pregnancy rate between the groups (RR, 0.41; 95% CI, 0.15–1.09).

CC vs *CC plus ISMN as NO donor*

Pooled analysis of two studies showed EMT to be lower in the CC group than the 20 mg NO donor group (WMD, −1.75; 95% CI, −2.08 to −1.41; $I^2 = 0\%$), with lower ovulation (RR, 0.59; 95% CI, 0.44–0.78; $I^2 = 0\%$) and pregnancy (RR, 0.52; 95% CI, 0.29–0.96; $I^2 = 0\%$) rates in the CC group than the 20 mg NO donor group (Figures 2–4).

CC vs *letrozole plus metformin*

One study that compared CC with letrozole plus metformin[24] showed EMT to be lower in the CC group (WMD, −2.80; 95% CI, −3.39 to −2.20) but a comparable ovulation rate (RR, 0.90; 95% CI, 0.56–1.43) without statistical difference in pregnancy rate (RR, 0.50; 95% CI, 0.06–3.91) between the groups.

CC vs *letrozole plus human menopausal gonadotropin*

One study that compared CC with letrozole plus human menopausal gonadotropins[28] showed EMT to be lower in the CC group (WMD, −3.20; 95% CI, −3.38 to −3.01), with a comparable ovulation rate (RR, 0.93; 95% CI, 0.80–1.09) and lower pregnancy rate (RR, 0.59; 95% CI, 0.37–0.93) in the CC group.

CC vs *raloxifene*

One study that compared CC with raloxifene[31] showed EMT (WMD, −0.60; 95% CI, −1.81 to 0.61) not to differ between the groups without statistical difference in ovulation rate (RR, 1.49; 95% CI, 0.77–2.89) between the groups.

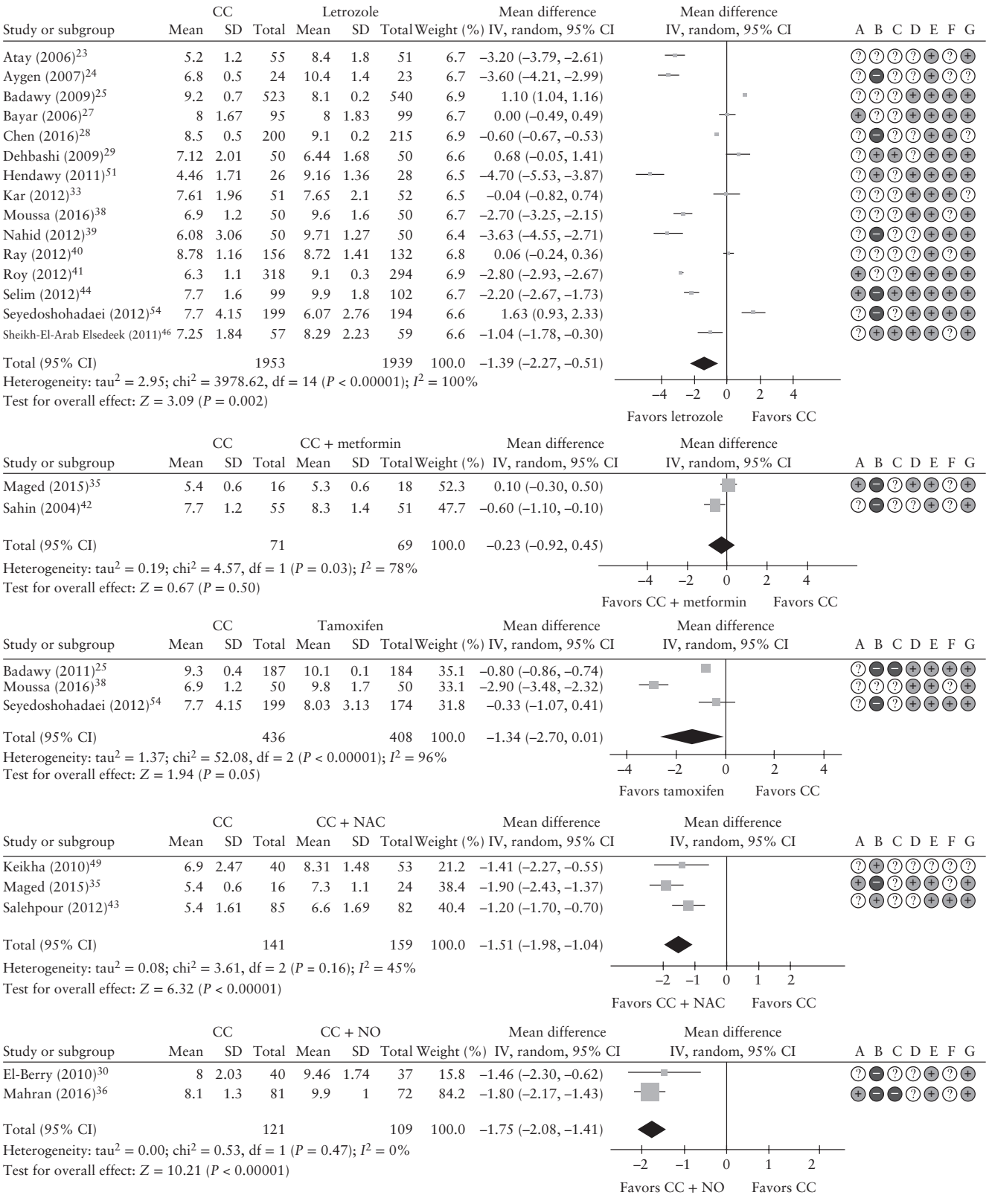

Figure 3 Forest plots for comparison of endometrial thickness between clomiphene citrate (CC) and letrozole, CC + metformin, tamoxifen, CC + *N*-acetyl cysteine (NAC) and CC + nitric oxide (NO) donor groups. Only first author of each study is given. IV, inverse variance. Risk of bias: low (+), high (−) or unclear (?); A, allocation concealment (selection bias); B, blinding of participants and personnel (performance bias); C, blinding of outcome assessment (detection bias); D, random sequence generation (selection bias); E, incomplete outcome data (attrition bias); F, selective reporting (reporting bias); G, other bias.

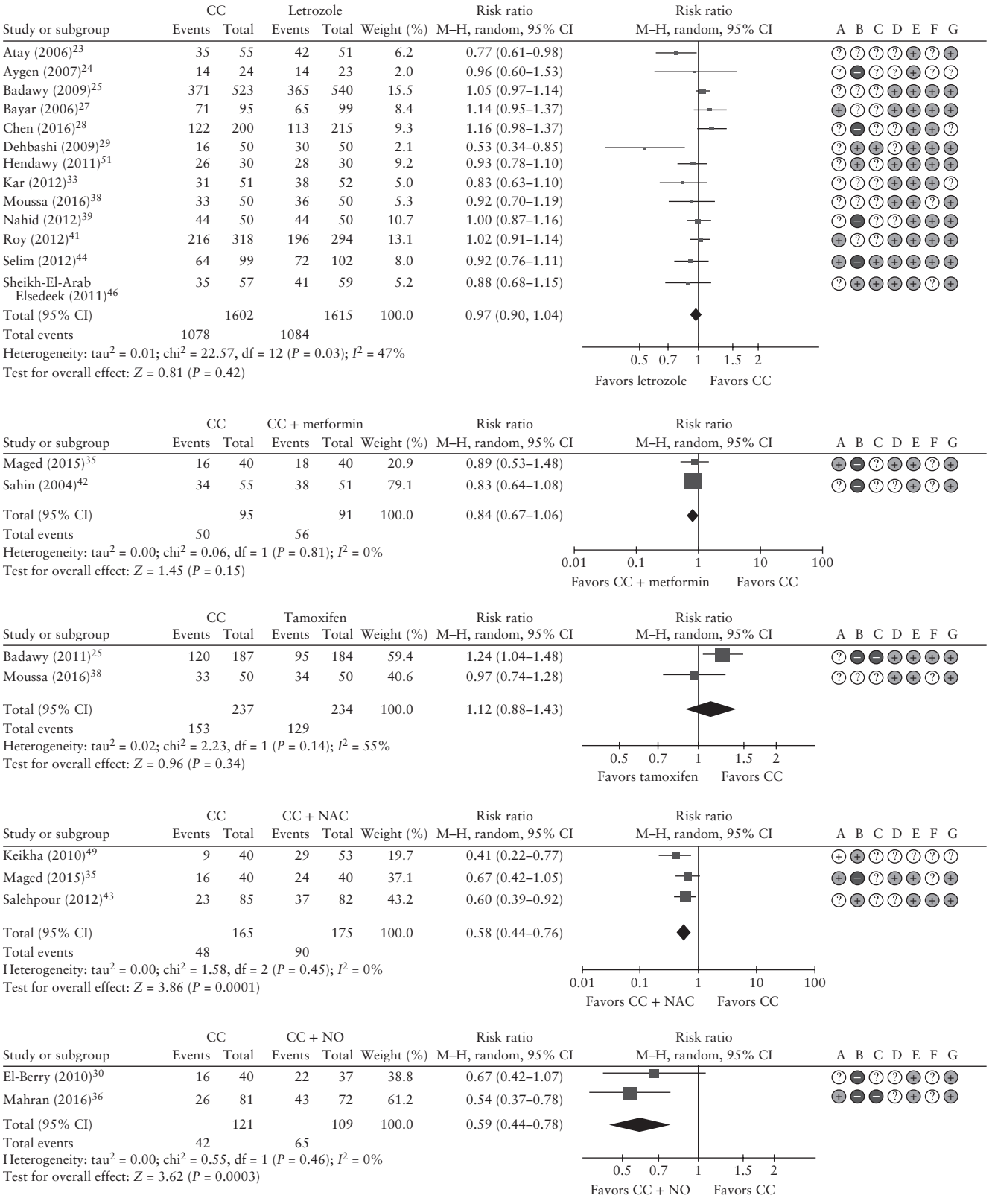

Figure 4 Forest plots for comparison of ovulation rate between clomiphene citrate (CC) and letrozole, CC + metformin, tamoxifen, CC + *N*-acetyl cysteine (NAC) and CC + nitric oxide (NO) donor groups. M–H, Mantel–Haenszel. Risk of bias: low (+), high (−) or unclear (?); A, allocation concealment (selection bias); B, blinding of participants and personnel (performance bias); C, blinding of outcome assessment (detection bias); D, random sequence generation (selection bias); E, incomplete outcome data (attrition bias); F, selective reporting (reporting bias); G, other bias.

CC vs *CC plus urinary follicle stimulating hormone*

One study that compared CC with CC plus urinary follicle stimulating hormone[22] showed EMT to be slightly lower in the CC group (WMD, −0.20; 95% CI, −0.32 to −0.08), while ovulation (RR, 0.98; 95% CI, 0.81–1.19) and pregnancy (RR, 0.90; 95% CI, 0.46–1.78) rates did not differ.

CC vs *CC plus L-carnitine*

One study that compared CC with CC plus L-carnitine[48] showed EMT to be lower in the CC group (WMD, −4.58; 95% CI, −4.77 to −4.39), with lower ovulation (RR, 0.27; 95% CI, 0.17–0.44) and pregnancy (RR, 0.02; 95% CI, 0.00–0.17) rates in the CC group.

CC vs *recombinant follicle stimulating hormone*

One study compared CC with recombinant follicle stimulating hormone[34] and showed no evidence of significant differences in EMT (WMD, −0.08; 95% CI, −0.89 to 0.73), pregnancy (RR, 0.71; 95% CI, 0.23–2.15) and live birth (RR, 0.85; 95% CI, 0.26–2.73) rates between the groups.

CC vs *phytoestrogens*

One study that compared CC with phytoestrogens[32] showed EMT to be lower in the CC group (6.9 mm in the CC group *vs* 8.3 mm in phytoestrogens group; $P < 0.0004$) without statistical difference in pregnancy rate (RR, 0.49; 95% CI, 0.05–5.23) between the groups.

CC vs *CC plus phytoestrogens*

One study that compared CC with CC plus phytoestrogens[45] showed lower EMT (WMD, −4.40; 95% CI, −4.81 to −3.99) and lower pregnancy rate in the CC group (RR, 0.46; 95% CI, 0.34–0.62).

Sensitivity analysis

In the three studies with low risk of allocation concealment bias[27,41,44], the comparison between CC and letrozole showed lower EMT in the CC group (WMD, −1.68; 95% CI, −3.27 to −0.08; $I^2 = 98\%$). However, including studies with low risk of randomization bias[25,27,33,38,41,44,46,51,54], performance bias[29,46,51] and detection bias[29,44,46] showed a similar effect estimate but without statistical significance, which could be due to low power of the studies.

In comparison between CC and tamoxifen, exclusion of one study[38] showed a lower EMT in the CC group (WMD, −0.72; 95% CI, −1.07 to −0.36; $I^2 = 35\%$) with a higher pregnancy rate in the CC group (RR, 1.56; 95% CI, 1.08–2.24; $I^2 = 0\%$; Figure S2).

In the comparison between CC and letrozole, exclusion of one study with participants with PCOS resistant to CC did not affect the effect estimate for all outcomes[51]. In the comparison between CC and CC plus NAC, exclusion of one study with participants with PCOS resistant to CC did not affect the effect estimate for all outcomes[49].

Also, we performed an additional analysis in which we included one additional large RCT[55]. This study did not report on mid-cycle EMT, but reported on ovulation, pregnancy and live birth in the main comparison between CC and letrozole. This additional analysis showed no change from our initial results (Figure S3).

Publication bias

Funnel plots were produced for EMT, ovulation and pregnancy rates in comparison between CC and letrozole. For ovulation and pregnancy outcomes there was strong asymmetry suggesting high risk of publication bias. The EMT funnel plot was almost symmetrical (Figure S4). There were not enough studies for other comparisons.

Quality of the evidence

The quality of the evidence was rated as very low for all outcomes in our main comparison between CC and letrozole (Table 2). The findings showed that in a population in which 67%, 33% and 32% achieve ovulation, pregnancy and live birth, respectively, using letrozole, about 60–70%, 21–31% and 16–32% would achieve ovulation, pregnancy and live birth, respectively, using CC. Also, EMT was 1.4 mm lower in the CC group compared with the letrozole group.

DISCUSSION

Summary of key findings

Our systematic review and meta-analysis on the effect of CC and other ovulation induction drugs in infertile women with WHO group II anovulation showed that CC resulted in lower endometrial thickness and lower pregnancy and live birth rates than letrozole for comparable ovulation rates. When compared with NO donor or NAC, CC resulted in lower endometrial thickness and lower ovulation and pregnancy rates, but the number of studies on these comparisons was limited. We found no evidence of statistically significant differences in EMT, ovulation and pregnancy rates when comparing CC with tamoxifen, raloxifene, recombinant follicle stimulating hormone and phytoestrogens.

Quality of evidence

The overall quality of evidence in the main comparison between CC and letrozole was rated as very low. Possible reasons include unclear or high risk of selection, detection and performance bias in most of the included studies and substantial heterogeneity that was not improved by sensitivity analyses. Furthermore, there was a high possibility of publication bias demonstrated by strong asymmetry in the funnel plots.

Table 2 Summary of findings on impact of clomiphene citrate (CC) *vs* letrozole on endometrial thickness, ovulation, pregnancy and live birth in women with WHO group II ovulatory disorders

	Anticipated absolute effect(95% CI)*				
Outcome	*Risk with letrozole*	*Risk with CC*	*Relative effect: RR (95% CI)*	*No. of participants/ cycles (RCTs)*	*Quality of evidence (grade)*
Endometrial thickness	Mean EMT was 6–10 mm	Mean EMT/cycle in CC group was 1.4 mm (2.3–0.5 mm) lower	—	1957/3892 (15)	⊕○○○ Very low†‡§
Ovulation	67%	65% (60–70%)	0.97 (0.90–1.04)	1710/3217 (13)	⊕○○○ Very low†¶
Pregnancy	33%	26% (21–31%)	0.78 (0.63–0.95)	1957/3892 (15)	⊕○○○ Very low†¶
Live birth	32%	23% (16–32%)	0.70 (0.49–0.98)	625/1587 (5)	⊕○○○ Very low†**

GRADE Working Group grades of evidence – high quality: we are very confident that the true effect lies close to that of the estimate of the effect; moderate quality: we are moderately confident in the effect estimate i.e. the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; low quality: our confidence in the effect estimate is limited i.e. the true effect may be substantially different from the estimate of the effect; very low quality: we have very little confidence in the effect estimate i.e. the true effect is likely to be substantially different from the estimate of the effect. *Risk in intervention group (and its 95% CI) is based on assumed risk in comparison group and relative effect of intervention (and its 95% CI). †Most studies have unclear or high risk of selection, detection and performance bias. ‡There is substantial heterogeneity that was not improved in sensitivity analyses. §Funnel plot for this outcome is almost symmetrical. ¶Funnel plot for this outcome has strong asymmetry. **Downgraded one level for imprecision (total events < 300). EMT, endometrial thickness; RCTs, randomized controlled trials; RR, risk ratio.

Strengths and limitations

Our study dealt with a topic that has not been addressed thoroughly in systematic reviews. We focused our analysis on CC, as this is, in many guidelines, still the most commonly recommended drug as first-line treatment for ovulation induction[3,8–11]. Another strength of our systematic review was that we did not use language restrictions and included trials published as abstracts in order to reduce publication bias as much as possible.

However, there were also limitations. The average quality of the included studies was low. Most studies were underpowered and the data on EMT in comparison of CC with letrozole, CC plus metformin and tamoxifen indicated considerable heterogeneity, which was not reduced after sensitivity analysis. Potential explanations for such heterogeneity are different drug protocols (dosage, duration and treatment days), publishing dates (from 2006 onwards), improvements in ultrasound equipment and measurement technique, and discrepancies in EMT values between groups and between studies. We reported EMT both per cycle and per woman, although women, not cycles, were the unit of randomization. Data for EMT per woman were available in only eight studies with one treatment cycle. The other studies reported EMT measurements in multiple treatment cycles. Despite this heterogeneity, we found an overall lower EMT in the CC group. Another limitation was that our search strategy was based on the primary outcome mid-cycle EMT, so estimates of ovulation, pregnancy and live birth were not based on all the available evidence.

Comparison with previous reviews

Most of the systematic reviews comparing ovulation induction drugs in women with WHO group II ovulatory disorders have not reported on EMT[4,7,56–62]. Ding *et al.*[63] compared CC used in the luteal phase *vs* CC used in the follicular phase and found significantly thicker EMT in the latter group after pooled analysis of four studies. Another meta-analysis reported mid-cycle EMT in five studies but pooled analysis was not performed due to the significant heterogeneity[64]. Regarding ovulation and pregnancy rates, results of recent studies showed that letrozole led to higher ovulation and pregnancy rates in women with PCOS[59,65–67]. Our study is partially in agreement with these studies; it showed greater mid-cycle EMT, comparable ovulation, and higher pregnancy and live birth rates in the letrozole group.

On the other hand, Misso *et al.*[7] found comparable ovulation rates between CC and letrozole (RR, 0.94; 95% CI, 0.82–1.07; $I^2 = 0\%$) while the pregnancy rate was higher in the letrozole group, albeit there was no evidence of significant difference (RR, 1.53; 95% CI, 0.91–2.58; $I^2 = 50\%$). Brown *et al.*[6] found no evidence of a difference between CC and tamoxifen in ovulation and pregnancy rates while finding higher rates of both when adding dexamethasone to CC compared with CC alone, and these results are also in agreement with our study results. In women with unexplained subfertility undergoing intrauterine insemination, a recent meta-analysis reported no difference in EMT between CC and letrozole (WMD, −0.84; 95% CI, −1.97 to 0.28)[68]. A large RCT showed no statistical difference in pregnancy (absolute difference, 5.9%; 95% CI, −1.0 to 12.9%) and live birth rates (absolute difference, 4.6%; 95% CI, −1.9 to 11.1%) between CC and letrozole groups[69]. This raises the question of the mechanisms by which letrozole led to better results than CC in women with PCOS and not those with unexplained infertility.

Implications

We found that anovulatory women with a thin endometrium using CC had lower pregnancy and live

birth rates compared with letrozole despite ovulation. While in highly resourced settings CC can be easily replaced by letrozole, in low-resourced settings its low price still makes CC the treatment of first choice. Also, CC is a registered drug for ovulation induction, while letrozole is not. Furthermore, the issue of risk of congenital anomalies following CC or letrozole is still a concern. A large retrospective study on 626 babies reported anomalies in 3.9%, 2.5% and 2.9% following women pregnant after CC, letrozole or natural conception, respectively[70]. It reported also higher cardiac and hypospadias anomalies following CC. Previous studies reported similar results[71,72]. We hypothesize that thin endometrium might have contributed to lower chances of pregnancy and live birth. However, we have very little confidence in the effect estimate since numbers were small in underpowered studies and the quality of evidence was very low. These findings have to be investigated in future studies, as it could result in the choice of cheaper alternatives to letrozole, thus facilitating treatment of women in low resourced settings.

Conclusion

In women with WHO group II ovulatory disorders, ovulation induction with CC might result in lower EMT than other ovulation induction regimens. Whether the lower EMT caused the lower pregnancy and live birth rates remains to be elucidated. Letrozole seems to be beneficial for these women. However, our findings should be interpreted with caution as the quality of evidence was very low.

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REFERENCES

1. Practice Committee of American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss: a committee opinion. *Fertil Steril* 2013; **99**: 63.
2. Inhorn MC, Patrizio P. Infertility around the globe: new thinking on gender, reproductive technologies and global movements in the 21st century. *Hum Reprod Update* 2015; **21**: 411–426.
3. National Institute for Health and Clinical Excellence (NICE). *Fertility: Assessment and Treatment for People with Fertility Problems*. NICE: London, 2013.
4. Misso ML, Costello MF, Garrubba M, Wong J, Hart R, Rombauts L, Melder AM, Norman RJ, Teede HJ. Metformin versus clomiphene citrate for infertility in non-obese women with polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod Update* 2013; **19**: 2–11.
5. Kerin JF, Liu JH, Phillipou G, Yen SSC. Evidence for a hypothalamic site of action of clomiphene citrate in women. *J Clin Endocrinol Metab* 1985; **61**: 265–268.
6. Brown J, Farquhar C. Clomiphene and other antioestrogens for ovulation induction in polycystic ovarian syndrome. *Cochrane Database Syst Rev* 2016; **12**: CD002249.
7. Misso ML, Wong JL, Teede HJ, Hart R, Rombauts L, Melder AM, Norman RJ, Costello MF. Aromatase inhibitors for PCOS: a systematic review and meta-analysis. *Hum Reprod Update* 2012; **18**: 301–312.
8. Moghetti P, Carmina E, De Leo V, Lanzone A, Orio F, Pasquali R, Toscano V. How to manage the reproductive issues of PCOS: a 2015 integrated endocrinological and gynecological consensus statement of the Italian Society of Endocrinology. *J Endocrinol Invest* 2015; **38**: 1025–1037.
9. Conway G, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Franks S, Gambineri A, Kelestimur F, Macut D, Micic D, Pasquali R, Pfeifer M, Pignatelli D, Pugeat M, Yildiz BO. The polycystic ovary syndrome: a position statement from the European Society of Endocrinology. *Eur J Endocrinol* 2014; **171**: P1–P29.
10. Consensus on infertility treatment related to polycystic ovary syndrome. *Hum Reprod* 2008; **23**: 462–477.
11. Vause TD, Cheung AP, Sierra S, Claman P, Graham J, Guillemin JA, Lapensee L, Stewart S, Wong BC. Ovulation induction in polycystic ovary syndrome. *J Obstet Gynaecol Can* 2010; **32**: 495–502.
12. Legro RS, Arslanian SA, Ehrmann DA, Hoeger KM, Murad MH, Pasquali R, Welt CK. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2013; **98**: 4565–4592.
13. Balen AH, Morley LC, Misso M, Franks S, Legro RS, Wijeyaratne CN, Stener-Victorin E, Fauser BC, Norman RJ, Teede H. The management of anovulatory infertility in women with polycystic ovary syndrome: an analysis of the evidence to support the development of global WHO guidance. *Hum Reprod Update* 2016; **22**: 687–708.
14. Goodman NF, Cobin RH, Futterweit W, Glueck JS, Legro RS, Carmina E. American Association of Clinical Endocrinologists, American College of Endocrinology, and Androgen Excess and PCOS Society Disease State Clinical Review: Guide to the best practices in the evaluation and treatment of polycystic ovary syndrome – Part 2. *Endocr Pract* 2015; **21**: 1415–1426.
15. Boyle J, Teede HJ. Polycystic ovary syndrome – an update. *Aust Fam Physician* 2012; **41**: 752–756.
16. Unfer V, Costabile L, Gerli S, Papaleo E, Marelli G, Di Renzo GC. Low dose of ethinyl estradiol can reverse the antiestrogenic effects of clomiphene citrate on endometrium. *Gynecol Obstet Invest* 2001; **51**: 120–123.
17. Massai MR, de Ziegler D, Lesobre V, Bergeron C, Frydman R, Bouchard P. Clomiphene citrate affects cervical mucus and endometrial morphology independently of the changes in plasma hormonal levels induced by multiple follicular recruitment. *Fertil Steril* 1993; **59**: 1179–1186.
18. Hsu C-C, Kuo H-C, Wang S-T, Huang K-E. Interference with uterine blood flow by clomiphene citrate in women with unexplained infertility. *Obstet Gynecol* 1995; **86**: 917–921.
19. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol* 2009; **62**: e1–e34.
20. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. www.handbook.cochrane.org [Accessed 1 January 2017].
21. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; **336**: 924–926.
22. Abu Hashim H, Bazeed M, Elaal IA. Minimal stimulation or clomiphene citrate as first-line therapy in women with polycystic ovary syndrome: a randomized controlled trial. *Gynecol Endocrinol* 2012; **28**: 87–90.
23. Atay V, Cam C, Muhcu M, Cam M, Karateke A. Comparison of letrozole and clomiphene citrate in women with polycystic ovaries undergoing ovarian stimulation. *J Int Med Res* 2006; **34**: 73–76.
24. Aygen EM, Güzel Z, Özgün T, Atakul T, Şahin Y. The use of letrozole for ovulation induction in infertile women with polycystic ovarian syndrome. *Erciyes Tip Dergisi* 2007; **29**: 195–200.
25. Badawy A, Abdel Aal I, Abulatta M. Clomiphene citrate or letrozole for ovulation induction in women with polycystic ovarian syndrome: a prospective randomized trial. *Fertil Steril* 2009; **92**: 849–852.
26. Badawy A, Gibreal A. Clomiphene citrate versus tamoxifen for ovulation induction in women with PCOS: a prospective randomized trial. *Eur J Obstet Gynecol Reprod Biol* 2011; **159**: 151–154.
27. Bayar Ü, Basaran M, Kiran S, Coskun A, Gezer S. Use of an aromatase inhibitor in patients with polycystic ovary syndrome: a prospective randomized trial. *Fertil Steril* 2006; **86**: 1447–1451.
28. Chen Z, Zhang M, Qiao Y, Yang J. Effects of letrozole in combination with low-dose intramuscular injection of human menopausal gonadotropin on ovulation and pregnancy of 156 patients with polycystic ovary syndrome. *Pak J Med Sci* 2016; **32**: 1434–1438.
29. Dehbashi S, Dehbashi S, Kazerooni T, Robati M, Alborzi S, Parsanezhad ME, Shadman A. Comparison of the effects of letrozole and clomiphene citrate on ovulation and pregnancy rate in patients with polycystic ovary syndrome. *Iran J Med Sci* 2009; **34**: 23–28.
30. El-Berry S, Razik MA. Nitric oxide donors increases pregnancy rate in clomiphene citrate treated polycystic ovary infertile patients. *Middle East Fertil Soc J* 2010; **15**: 106–109.
31. de Paula Guedes Neto E, Savaris RF, von Eye Corleta H, de Moraes GS, do Amaral Cristovam R, Lessey BA. Prospective, randomized comparison between raloxifene and clomiphene citrate for ovulation induction in polycystic ovary syndrome. *Fertil Steril* 2011; **96**: 769–773.
32. Kamel HH. Role of phyto-oestrogens in ovulation induction in women with polycystic ovarian syndrome. *Eur J Obstet Gynecol Reprod Biol* 2013; **168**: 60–63.
33. Kar S. Clomiphene citrate or letrozole as first-line ovulation induction drug in infertile PCOS women: A prospective randomized trial. *J Hum Reprod Sci* 2012; **5**: 262–265.
34. Lima ML, Barbosa MA, Nastri CO, Ferriani RA, Navarro PA, Hossein-Rashidi B, Khandzad B, Shahrokh-Tehraninejad E, Bagheri M, Gorginzadeh M. Recombinant FSH compared to clomiphene citrate as the first-line in ovulation induction in polycystic ovary syndrome using newly designed pens: a randomized controlled trial. *Ultrasound Obstet Gynecol* 2016; **10**: 42–48.
35. Maged AM, Elsawah H, Abdelhafez A, Bakry A, Al Mostafa W. The adjuvant effect of metformin and N-acetylcysteine to clomiphene citrate in induction of ovulation in patients with Polycystic Ovary Syndrome. *Gynecol Endocrinol* 2015; **31**: 635–638.
36. Mahran A, Abdelmeged A, Shawki H, Moheyelden A, Ahmed AM. Nitric oxide donors improve the ovulation and pregnancy rates in anovulatory women with

polycystic ovary syndrome treated with clomiphene citrate: A RCT. *Int J Reprod Biomed* 2016; **14**: 9–14.
37. Moini A, Ahmadi F, Jahangiri N, Ahmadi J, Akhoond MR. A randomized controlled trial evaluating the effect of ethinyl estradiol during clomiphene citrate cycles among women with polycystic ovary syndrome. *Int J Gynaecol Obstet* 2015; **131**: 129–132.
38. Moussa AA, Torky H, Dief O, Elwahed AA, Senna HA. The effect of clomiphene citrate versus tamoxifen versus letrozol on endometrial thickness and blood flow in ovulation induction in women with polycystic ovaries. *Acta Med Int* 2016; **3**: 88–92.
39. Nahid L, Sirous K. Comparison of the effects of letrozole and clomiphene citrate for ovulation induction in infertile women with polycystic ovary syndrome. *Minerva Ginecol* 2012; **64**: 253–258.
40. Ray PB, Ray A, Chakraborti PS. Comparison of efficacy of letrozole and clomiphene citrate in ovulation induction in Indian women with polycystic ovarian syndrome. *Arch Gynecol Obstet* 2012; **285**: 873–877.
41. Roy K, Baruah J, Singla S, Sharma J, Singh N, Jain S, Goyal M. A prospective randomized trial comparing the efficacy of Letrozole and Clomiphene citrate in induction of ovulation in polycystic ovarian syndrome. *J Hum Reprod Sci* 2012; **5**: 20–25.
42. Sahin Y, Yirmibes U, Kelestimur F, Aygen E. The effects of metformin on insulin resistance, clomiphene-induced ovulation and pregnancy rates in women with polycystic ovary syndrome. *Eur J Obstet Gynecol Reprod Biol* 2004; **113**: 214–220.
43. Salehpour S, Sene AA, Saharkhiz N, Sohrabi MR, Moghimian F. N-Acetylcysteine as an adjuvant to clomiphene citrate for successful induction of ovulation in infertile patients with polycystic ovary syndrome. *J Obstet Gynaecol Res* 2012; **38**: 1182–1186.
44. Selim MF, Borg TF. Letrozole and clomiphene citrate effect on endometrial and subendometrial vascularity in treating infertility in women with polycystic ovary syndrome. *J Gynecol Surg* 2012; **28**: 405–410.
45. Shahin AY, Mohammed SA. Adding the phytoestrogen Cimicifugae Racemosae to clomiphene induction cycles with timed intercourse in polycystic ovary syndrome improves cycle outcomes and pregnancy rates – a randomized trial. *Gynecol Endocrinol* 2014; **30**: 505–510.
46. Sheikh-El-Arab Elsedeek M, Elmaghraby HAH. Predictors and characteristics of letrozole induced ovulation in comparison with clomiphene induced ovulation in anovulatory PCOS women. *Middle East Fertil Soc J* 2011; **16**: 125–130.
47. Elnashar A, Abdelmageed E, Fayed M, Sharaf M. Clomiphene citrate and dexamethazone in treatment of clomiphene citrate-resistant polycystic ovary syndrome: a prospective placebo-controlled study. *Hum Reprod* 2006; **21**: 1805–1808.
48. Ismail AM, Hamed AH, Saso S, Thabet HH. Adding L-carnitine to clomiphene resistant PCOS women improves the quality of ovulation and the pregnancy rate. A randomized clinical trial. *Eur J Obstet Gynecol Reprod Biol* 2014; **180**: 148–152.
49. Keikha F. Combination N-acetyl cysteine and clomiphene citrate in clomiphene citrate resistant polycystic ovary syndrome. *Iran J Reprod Med* 2010; **8**: 12–13.
50. Refaeey A, Selem A, Badawy A. Combined coenzyme Q10 and clomiphene citrate for ovulation induction in clomiphene-citrate-resistant polycystic ovary syndrome. *Reprod Biomed Online* 2014; **29**: 119–124.
51. Hendawy SF, Samaha HE, Elkholy MF. Letrozole versus clomiphene citrate for induction of ovulation in patients with polycystic ovarian syndrome undergoing intrauterine insemination. *Clin Med Insights Reprod Health* 2011; **5**: 11–16.
52. Tredway D, Schertz JC, Bock D, Hemsey G, Diamond MP. Anastrozole vs. clomiphene citrate in infertile women with ovulatory dysfunction: A phase II, randomized, dose-finding study. *Fertil Steril* 2011; **95**: 1720–1724.e8.
53. Yang JS, Yoo EH, Lee JY, Hong SY, Shin JH, Park CH. A comparison of the effect of Anastrozole and Clomiphene citrate in anovulatory patients. *Korean J Obstet Gynecol* 2006; **49**: 1723–1731.
54. Seyedoshohadaei F, Zandvakily F, Shahgeibi S. Comparison of the effectiveness of clomiphene citrate, tamoxifen and letrozole in ovulation induction in infertility due to isolated unovulation. *Iran J Reprod Med* 2012; **10**: 531–536.
55. Legro RS, Brzyski RG, Diamond MP, Coutifaris C, Schlaff WD, Casson P, Christman GM, Huang H, Yan Q, Alvero R, Haisenleder DJ, Barnhart KT, Bates GW, Usadi R, Lucidi S, Baker V, Trussell JC, Krawetz SA, Snyder P, Ohl D, Santoro N, Eisenberg E, Zhang H. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. *N Engl J Med* 2014; **371**: 119–129.
56. Cantineau AEP, Cohlen BJ. Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility. *Cochrane Database Syst Rev* 2007: CD005356.
57. George K, Kamath MS, Nair R, Tharyan P. Ovulation triggers in anovulatory women undergoing ovulation induction. *Cochrane Database Syst Rev* 2014: CD006900.
58. Moll E, van der Veen F, van Wely M. The role of metformin in polycystic ovary syndrome: a systematic review. *Hum Reprod Update* 2007; **13**: 527–537.
59. Roque M, Tostes AC, Valle M, Sampaio M, Geber S. Letrozole versus clomiphene citrate in polycystic ovary syndrome: systematic review and meta-analysis. *Gynecol Endocrinol* 2015; **31**: 917–921.
60. Siebert TI, Viola MI, Steyn DW, Kruger TF. Is metformin indicated as primary ovulation induction agent in women with PCOS? A systematic review and meta-analysis. *Gynecol Obstet Invest* 2012; **73**: 304–313.
61. Wang LL, Ren W, Cheng QF, Fan XD. Therapeutic effect of metformin for clomiphene-resistant infertility patients with polycystic ovary syndrome: a systematic analysis. *Zhonghua Fu Chan Ke Za Zhi* 2012; **47**: 659–663.
62. Xiao J, Chen S, Zhang C, Chang S. The effectiveness of metformin ovulation induction treatment in patients with PCOS: a systematic review and meta-analysis. *Gynecol Endocrinol* 2012; **28**: 956–960.
63. Ding N, Chang J, Jian Q, Liang X, Liang Z, Wang F. Luteal phase clomiphene citrate for ovulation induction in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Gynecol Endocrinol* 2016; **32**: 866–871.
64. He D, Jiang F. Meta-analysis of letrozole versus clomiphene citrate in polycystic ovary syndrome. *Reprod Biomed Online* 2011; **23**: 91–96.
65. Wang R, Kim BV, van Wely M, Johnson NP, Costello MF, Zhang H, Ng EH, Legro RS, Bhattacharya S, Norman RJ, Mol BW. Treatment strategies for women with WHO group II anovulation: systematic review and network meta-analysis. *BMJ* 2017; **356**: j138.
66. Franik S, Kremer JA, Nelen WL, Farquhar C. Aromatase inhibitors for subfertile women with polycystic ovary syndrome. *Cochrane Database Syst Rev* 2014: CD010287.
67. Legro RS, Zhang H. Letrozole or clomiphene for infertility in the polycystic ovary syndrome. *N Engl J Med* 2014; **371**: 1463–1464.
68. Weiss NS, van Vliet MN, Limpens J, Hompes PGA, Lambalk CB, Mochtar MH, van der Veen F, Mol BWJ, van Wely M. Endometrial thickness in women undergoing IUI with ovarian stimulation. How thick is too thin? A systematic review and meta-analysis. *Hum Reprod* 2017; **32**: 1009–1018.
69. Diamond MP, Legro RS, Coutifaris C, Alvero R, Robinson RD, Casson P, Christman GM, Ager J, Huang H, Hansen KR, Baker V, Usadi R, Seungdamrong A, Bates GW, Rosen RM, Haisenleder D, Krawetz SA, Barnhart K, Trussell JC, Ohl D, Jin Y, Santoro N, Eisenberg E, Zhang H. Letrozole, gonadotropin, or clomiphene for unexplained infertility. *N Engl J Med* 2015; **373**: 1230–1240.
70. Sharma S, Ghosh S, Singh S, Chakravarty A, Ganesh A, Rajani S, Chakravarty BN. Congenital malformations among babies born following letrozole or clomiphene for infertility treatment. *PLoS One* 2014; **9**: e108219.
71. Tulandi T, Martin J, Al-Fadhli R, Kabli N, Forman R, Hitkari J, Librach C, Greenblatt E, Casper RF. Congenital malformations among 911 newborns conceived after infertility treatment with letrozole or clomiphene citrate. *Fertil Steril* 2006; **85**: 1761–1765.
72. Forman R, Gill S, Moretti M, Tulandi T, Koren G, Casper R. Fetal safety of letrozole and clomiphene citrate for ovulation induction. *J Obstet Gynaecol Can* 2007; **29**: 668–671.

SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Detailed search strategy

Table S2 List of excluded studies

Table S3 Summary of results of meta-analysis

Figure S1 Assessment of risk of bias. (a) Risk of bias summary for each included study: low risk of bias (+); high risk of bias (−); unclear risk of bias (?). (b) Risk of bias graph for each risk of bias item presented as percentages across all included studies.

Figure S2 Sensitivity analysis for endometrial thickness in comparison between CC and letrozole, CC + metformin and tamoxifen.

Figure S3 Additional funnel plots for CC *vs* letrozole. (a) Live birth. (b) Pregnancy rate. (c) Ovulation rate.

Figure S4 Funnel plots for CC *vs* letrozole. (a) Endometrial thickness. (b) Ovulation rate. (c) Pregnancy rate.

