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Clomiphene and other antioestrogens for ovulation induction in polycystic ovarian syndrome (Review)

Brown J, Farquhar C

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[Intervention Review]

Clomiphene and other antioestrogens for ovulation induction in polycystic ovarian syndrome

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ABSTRACT

Background

Subfertility due to anovulation is a common problem in women. First-line oral treatment is with antioestrogens such as clomiphene citrate, but resistance may be apparent with clomiphene. Alternative and adjunctive treatments have been used including tamoxifen, dexamethasone, and bromocriptine. The effectiveness of these is to be determined.

Objectives

To determine the relative effectiveness of antioestrogen agents including clomiphene alone or in combination with other medical therapies in women with subfertility associated with anovulation, possibly caused by polycystic ovarian syndrome.

Search methods

We conducted a search of the Cochrane Gynaecology and Fertility Group Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, PsycINFO, and CINAHL (all from inception to August 2016) to identify relevant randomised controlled trials (RCTs). We searched the United Kingdom National Institute for Clinical Excellence (NICE) guidelines and the references of relevant reviews and RCTs. We also searched the clinical trial registries for ongoing trials (inception until August 2016).

Selection criteria

We considered RCTs comparing oral antioestrogen agents for ovulation induction (alone or in conjunction with medical therapies) in anovulatory subfertility. We excluded insulin-sensitising agents, aromatase inhibitors, and hyperprolactinaemic infertility.

Data collection and analysis

Two review authors independently performed data extraction and quality assessment. The primary outcome was live birth; secondary outcomes were pregnancy, ovulation, miscarriage, multiple pregnancy, ovarian hyperstimulation syndrome, and adverse effects.

Main results

This is a substantive update of a previous review. We identified an additional 13 studies in the 2016 update. The review now includes 28 RCTs (3377 women) and five RCTs awaiting classification. Five of the 28 included trials reported live birth/ongoing pregnancy. Secondary outcomes were poorly reported.

The quality of the evidence ranged from low to very low. The primary reasons for downgrading the evidence were imprecision and risk of bias associated with poor reporting.

Antioestrogen versus placebo

Live birth rate, miscarriage rate, multiple pregnancy rate, and ovarian hyperstimulation syndrome (OHSS)

No data were reported for these outcomes.

Clinical pregnancy rate

Clomiphene citrate was associated with an increased chance of a clinical pregnancy compared with placebo, though the size of the benefit was very uncertain (odds ratio (OR) 5.91, 95% confidence interval (CI) 1.77 to 19.68; 3 studies; 133 women; low-quality evidence). If the chance of a clinical pregnancy was 5% in the placebo group, then between 8% and 50% of women would have a clinical pregnancy in the clomiphene group.

Clomiphene citrate versus tamoxifen

Live birth rate

There was no clear evidence of a difference in the chance of a live birth between the clomiphene citrate and tamoxifen groups (OR 1.24, 95% CI 0.59 to 2.62; 2 studies; 195 women; low-quality evidence). If 20% of women in the tamoxifen group had a live birth, then between 13% and 40% of women in the clomiphene citrate group would have a live birth.

Miscarriage rate

There was no clear evidence of a difference in the chance of a miscarriage between the clomiphene citrate and tamoxifen groups (OR 1.81, 95% CI 0.80 to 4.12; 4 studies; 653 women; low-quality evidence). If 3% of women in the tamoxifen group had a miscarriage, then between 2% and 10% in the clomiphene citrate group would have a miscarriage.

Clinical pregnancy rate

There was no clear evidence of a difference in the chance of a clinical pregnancy between the clomiphene citrate and tamoxifen groups (OR 1.30, 95% CI 0.92 to 1.85; 5 studies; 757 women; I^2 = 69%; low-quality evidence). If 22% of women in the tamoxifen group had a clinical pregnancy, then between 21% and 35% in the clomiphene citrate group would have a clinical pregnancy.

Multiple pregnancy rate

There was insufficient evidence of a difference in the chance of a multiple pregnancy between the clomiphene citrate group (OR 2.34, 95% CI 0.34 to 16.04; 3 studies; 567 women; very low-quality evidence). If 0% of women in the tamoxifen group had a multiple pregnancy, then between 0% and 0.5% of women in the clomiphene group would have a multiple pregnancy.

OHSS

There were no instances of OHSS in either the clomiphene citrate or the tamoxifen group reported from three studies.

Clomiphene citrate with tamoxifen versus tamoxifen alone

Clinical pregnancy rate

There was insufficient evidence to determine whether there was a difference between groups (OR 3.32, 95% CI 0.12 to 91.60; 1 study; 20 women; very low-quality evidence). No data were reported for the other outcomes.

Other comparisons of interest

Limited evidence suggested that compared with a gonadotropin, clomiphene citrate was associated with a reduced chance of a pregnancy, ongoing pregnancy, or live birth, with no clear evidence of a difference in multiple pregnancy rates.

The comparison of clomiphene citrate plus medical adjunct versus clomiphene alone was limited by the number of trials reporting the comparison and poor reporting of clinical outcomes relevant to this systematic review and by the number of adjuncts reported (ketoconazole, bromocriptine, dexamethasone, combined oral contraceptive, human chorionic gonadotropin, hormone supplementation). The addition of dexamethasone or combined oral contraceptive suggested a possible benefit in pregnancy outcomes, but findings were very uncertain and further research is required to confirm this.

There was limited evidence suggesting that a 10-day regimen of clomiphene citrate improves pregnancy outcomes compared with a 5-day regimen. Data for early versus late regimens of clomiphene citrate were insufficient to be able to make a judgement on differences for pregnancy outcomes.

Authors' conclusions

We found evidence suggesting that clomiphene citrate improves the chance of a clinical pregnancy compared with placebo, but may reduce the chance of live birth or ongoing pregnancy when compared with a gonadotropin. Due to low event rates, we advise caution interpreting these data.

The comparison of clomiphene citrate plus medical adjunctive versus clomiphene alone was limited by the number of trials reporting the comparison. The evidence was very low quality and no firm conclusions could be drawn, but very limited evidence suggested a benefit from adjunctive dexamethasone or combined oral contraceptives. Low-quality evidence suggested that a 10-day regimen of clomiphene citrate improves pregnancy rates compared with a 5-day regimen, but further research is required.

PLAIN LANGUAGE SUMMARY

Clomiphene and other antioestrogens for subfertility associated with anovulation

Review question

Do antioestrogens including clomiphene improve fertility in women with anovulation associated with polycystic ovary syndrome?

Background

Subfertility due to the absence of ovulation is a common problem in women. Medical treatment may help these women ovulate. For example, oral antioestrogens such as clomiphene cause increased stimulation of the ovaries and aid ovulation.

Study characteristics

We added 13 new studies in the 2016 update, and the review now includes 28 trials (3377 women). Five of the 28 included trials reported live birth. Miscarriage, multiple pregnancy rates, and adverse events such as ovarian hyperstimulation syndrome were poorly reported. The evidence is current to August 2016.

Key results

We found evidence suggesting that clomiphene citrate improves the chance of a clinical pregnancy compared with placebo.

There was no evidence of a difference between clomiphene and tamoxifen, a similar antioestrogen drug. Women treated with clomiphene citrate were less likely to get pregnant or have a live baby compared with women who had received gonadotropins; there was no evidence for a difference in the chance of a multiple pregnancy. The numbers of women getting pregnant in these trials were very small, therefore we cannot be certain of the results.

Both dexamethasone (a steroid) and combined oral contraceptives are used to supplement clomiphene and show promise, but more studies are needed to confirm this. Few studies reported beyond the establishment of early pregnancy; given the reported risks of miscarriage with clomiphene treatment, no definitive conclusions can be drawn about effective treatment. We found evidence suggesting that a 10-day regimen of clomiphene citrate improved pregnancy outcomes when compared with a 5-day regimen, although the volume of data is limited and further research is required. There were insufficient data reported for early versus late regimens of clomiphene citrate to be able to make a judgement on differences for pregnancy outcomes.

Quality of the evidence

The quality of the evidence ranged from low to very low. The primary reasons for downgrading evidence were imprecision and risk of bias.

Summary of findings for the main comparison. Antioestrogen versus placebo

Antioestrogen versus placebo

Patient or population: ovulation induction in polycystic ovarian syndrome

Setting: USA/Canada. 1 trial took place in a department of obstetrics and gynaecology; details of setting for 2 trials not provided.
Intervention: antioestrogen
Comparison: no treatment or placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no treatment or placebo	Risk with antioestrogen				
Live birth rate - not reported	See comment	See comment	Not estimable	-	-	No data for live birth reported for this comparison
Miscarriage rate - not reported	See comment	See comment	Not estimable	-	-	No data for miscarriage reported for this comparison
Clinical pregnancy rate	48 per 1000	228 per 1000 (81 to 496)	OR 5.91 (1.77 to 19.68)	133 (3 RCTs)	⊕⊕⊖⊖ LOW [1,2]	Low event rates and small sample size observed in included trials
Multiple pregnancy rate - not reported	See comment	See comment	Not estimable	-	-	No data for multiple pregnancy reported for this comparison
Ovarian hyperstimulation syndrome (OHSS) - not reported	See comment	See comment	Not estimable	-	-	No data for OHSS reported for this comparison

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio; **RCT:** randomised controlled trial

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: 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: 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: the true effect is likely to be substantially different from the estimate of effect.

[1]Wide confidence intervals with low event rates and small sample size suggest imprecision - downgraded one level.
[2]There was insufficient detail for multiple aspects of risk of bias to be able to make a judgement in any of the included studies, none of the studies reported on live birth - downgraded one level.

Summary of findings 2. Antioestrogen versus antioestrogen

Antioestrogen versus antioestrogen

Patient or population: ovulation induction in polycystic ovarian syndrome

Setting: Egypt, USA/Canada, Iran (2 trials), Italy. Trials conducted in outpatient department, infertility clinic (2 trials), private clinic, and 1 trial did not report setting.
Intervention: antioestrogen
Comparison: antioestrogen

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with antioestrogen	Risk with antioestrogen				
Clomiphene citrate versus tamoxifen - Live birth rate	204 per 1000	241 per 1000 (131 to 402)	OR 1.24 (0.59 to 2.62)	195 (2 RCTs)	⊕⊕⊖⊖ LOW [1 2]	Low event rates and small sample size observed in the included studies
Clomiphene citrate versus tamoxifen - Miscarriage rate	27 per 1000	49 per 1000 (22 to 104)	OR 1.81 (0.80 to 4.12)	653 (4 RCTs)	⊕⊕⊖⊖ LOW [2 3]	Low event rates observed in included studies
Clomiphene citrate versus tamoxifen - Clinical pregnancy rate	221 per 1000	270 per 1000 (207 to 345)	OR 1.30 (0.92 to 1.85)	757 (5 RCTs)	⊕⊕⊖⊖ LOW [4 5]	
Clomiphene citrate versus tamoxifen - Multiple pregnancy	4 per 1000	8 per 1000 (1 to 54)	OR 2.34 (0.34 to 16.04)	567 (3 RCTs)	⊕⊖⊖⊖ VERY LOW [6 7]	Low event rates observed in included studies
Clomiphene citrate versus tamoxifen - ovarian hyperstimulation syndrome (OHSS)	Not pooled	Not pooled	Not estimable	567 (3 studies)	-	No events of OHSS reported in either intervention or control group in the included studies
Clomiphene citrate plus tamoxifen versus clomiphene citrate - Clinical pregnancy rate	0 per 1000	0 per 1000 (0 to 0)	OR 3.32 (0.12 to 91.60)	20 (1 RCT)	⊕⊖⊖⊖ VERY LOW [7 8 9]	Very low event rates and very small sample size (n = 20 women) observed in this study

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio; **RCT:** randomised controlled trial

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: 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: 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: the true effect is likely to be substantially different from the estimate of effect.

[1]Low event rates and small sample size increase the chance of imprecision - downgraded one level.
[2]Wide confidence intervals crossing the line of no effect and low event rates suggest imprecision - downgraded one level.
[3]There was insufficient detail to be able to make a judgement regarding randomisation in three of four studies, blinding of researchers/women in two of four studies, and blinding of outcome assessors in three of four studies - downgraded one level.
[4]I^2 statistic was greater than 50% - downgraded one level.
[5]Insufficient data to be able to make judgements on risk of bias for allocation concealment, random allocation, and blinding - downgraded one level.
[6]Insufficient data to be able to make judgments on risk of bias for randomisation and blinding - downgraded one level.
[7]Wide confidence intervals crossing the line of no effect suggesting substantive benefit and substantive harm. Event rates are low, suggesting high risk of imprecision - downgraded one level.
[8]Evidence is based on data from a single small study (n = 20 women) - downgraded one level.
[9]Insufficient detail for all aspects of risk of bias to be able to make a judgement. Live birth was not reported - downgraded one level.

Summary of findings 3. Antioestrogen plus medical adjunct versus antioestrogen alone

Antioestrogen plus medical adjunct versus antioestrogen alone

Patient or population: ovulation induction in polycystic ovarian syndrome

Setting: Four studies from Iran, three from USA, two from Egypt, one from Turkey and one from India. Studies conducted in a University clinic, infertility outpatient clinic, Women's hospital clinic, Infertility and Reproductive Health Centre, private infertility clinic, Women's Health Research Institute, Infertiltiy Clinic and Research Clinic; three studies provided no information.
Intervention: antioestrogen plus medical adjunct
Comparison: antioestrogen alone

Comparison	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with antioestrogen alone	Risk with antioestrogen plus medical adjunct				
Clomiphene citrate plus keto-	Miscarriage rate				⊕⊖⊖⊖ VERY LOW [1 2 3]	Low event rates and small sample size in this single study

conazole versus clomiphene citrate	27 per 1000	8 per 1000 (0 to 164)	OR 0.28 (0.01 to 7.08)	80 (1 RCT)		
	Clinical pregnancy rate				⊕⊝⊝⊝ VERY LOW [1 2 3]	Low event rates and small sample size in this single study
	216 per 1000	395 per 1000 (195 to 638)	OR 2.37 (0.88 to 6.40)	80 (1 RCT)		
	Multiple pregnancy				⊕⊝⊝⊝ VERY LOW [1 2 3]	Low event rates and small sample size in this single study
	162 per 1000	186 per 1000 (67 to 423)	OR 1.18 (0.37 to 3.78)	80 (1 RCT)		
Clomiphene citrate plus bromocriptine versus clomiphene citrate - Clinical pregnancy rate	187 per 1000	191 per 1000 (99 to 337)	OR 1.03 (0.48 to 2.21)	174 (2 RCTs)	⊕⊕⊝⊝ LOW [2 3]	Low event rates and small sample size observed in the included studies
Clomiphene citrate plus dexamethasone versus clomiphene citrate	Clinical pregnancy rate				⊕⊝⊝⊝ VERY LOW [3 5 6]	
	81 per 1000	355 per 1000 (163 to 608)	OR 6.20 (2.20 to 17.48)	434 (4 RCTs)		
	Multiple pregnancy rate				⊕⊕⊝⊝ LOW [2 3]	Low event rates and small sample size observed in these studies. One study had no events in the intervention or the control group.
	0 per 1000	0 per 1000 (0 to 0)	OR 7.71 (0.38 to 155.64)	144 (2 RCTs)		
Clomiphene citrate plus combined oral contraceptive versus clomiphene citrate - Miscarriage rate	Miscarriage rate				⊕⊝⊝⊝ VERY LOW [1 2 3]	Low event rates and small sample size observed in this single study
	42 per 1000	42 per 1000 (3 to 425)	OR 1.00 (0.06 to 16.97)	48 (1 RCT)		
	Clinical pregnancy rate				⊕⊝⊝⊝ VERY LOW [3 8]	Low event rates and small sample size observed in this single study
	42 per 1000	542 per 1000 (120 to 911)	OR 27.18 (3.14 to 235.02)	48 (1 RCT)		
	Multiple pregnancy				⊕⊝⊝⊝ VERY LOW [1 2 3]	Low event rates and small sample size observed in this single study
	0 per 1000	0 per 1000	OR 7.98	48		

		(0 to 0)	(0.39 to 163.33)	(1 RCT)		
Clomiphene citrate plus hCG versus clomiphene citrate alone	Ongoing pregnancy rate				⊕⊝⊝⊝ VERY LOW [1 3 9]	Low event rates and small sample size observed in this single study
	277 per 1000	334 per 1000 (189 to 517)	OR 1.31 (0.61 to 2.80)	125 (1 RCT)		
	Miscarriage rate				⊕⊕⊕⊝ MODERATE [2]	Low event rates and small sample size observed in the included studies
	61 per 1000	44 per 1000 (12 to 146)	OR 0.70 (0.19 to 2.62)	192 (2 RCTs)		
	Clinical pregnancy rate				⊕⊕⊕⊝ MODERATE [9]	Low event rates and small sample size observed in the included studies
	235 per 1000	266 per 1000 (153 to 420)	OR 1.18 (0.59 to 2.36)	192 (2 RCTs)		
	Multiple pregnancies				⊕⊝⊝⊝ VERY LOW [1 2 3]	Low event rates and small sample size observed in this single study
	15 per 1000	33 per 1000 (3 to 281)	OR 2.21 (0.19 to 24.98)	125 (1 RCT)		
Clomiphene citrate plus hormone supplementation versus clomiphene citrate alone	Miscarriage rate				⊕⊝⊝⊝ VERY LOW [1 2 3]	Low event rates and small sample size observed in this single study
	21 per 1000	21 per 1000 (1 to 259)	OR 1.00 (0.06 to 16.46)	96 (1 RCT)		
	Clinical pregnancy rate				⊕⊕⊝⊝ LOW [3 9]	Low event rates and small sample size observed in these studies
	220 per 1000	186 per 1000 (94 to 331)	OR 0.81 (0.37 to 1.76)	161 (2 RCTs)		
	Multiple pregnancy rate				-	No events of multiple pregnancy were observed in either the intervention or control group in this single study.
	0 per 1000	0 per 1000 (0 to 0)	Not estimable	96 (1 RCT)		
	OHSS				-	No events of OHSS were observed in either the intervention or control group in this single study.
	0 per 1000	0 per 1000 (0 to 0)	Not estimable	96 (1 RCT)		

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **hCG:** human chorionic gonadotropin; **OR:** odds ratio; **RCT:** randomised controlled trial

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: 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: 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: the true effect is likely to be substantially different from the estimate of effect.

[1]Evidence is based on data from a single small study - downgraded one level.
[2]Wide confidence intervals crossing the line of no effect, low event rates, and small sample size suggest imprecision - downgraded one level.
[3]Insufficient detail to be able to make judgements on risk of bias. Live birth was not reported - downgraded one level.
[4]Wide confidence interval and small sample size suggest imprecision - downgraded one level.
[5]Wide confidence intervals observed - downgraded one level.
[6]I^2 statistic was greater than 50% - downgraded one level.
[7]I^2 statistic was greater than 80% - downgraded two levels.
[8]Wide confidence intervals, low event rates, and small sample size observed.
[9]Low event rates and small sample size increase the likelihood of imprecision.

Summary of findings 4. Antioestrogen regimens

Antioestrogen regimens

Patient or population: ovulation induction in polycystic ovarian syndrome

Setting: Three studies took place in Egypt and one in Iran. One was conducted in a University Fertility Clinic, one in an Infertility Research Centre and one in a gynaecology outpatient department. The fourth research setting was not specified.
Intervention: clomiphene citrate regimen A
Comparison: clomiphene citrate regimen B

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with clomiphene citrate regimen B	Risk with clomiphene citrate regimen A				
Live birth - Clomiphene citrate 5 days versus clomiphene citrate 10 days	155 per 1000	18 per 1000 (4 to 76)	OR 0.10 (0.02 to 0.45)	220 (1 RCT)	⊕⊕⊖⊖ LOW [1,2]	
Clinical pregnancy - Clomiphene citrate 5 days versus clomiphene citrate 10 days	173 per 1000	36 per 1000 (12 to 103)	OR 0.18 (0.06 to 0.55)	220 (1 RCT)	⊕⊕⊖⊖ LOW [1,2]	

Multiple pregnancy - Clomiphene citrate 5 days versus clomiphene citrate 10 days	27 per 1000	9 per 1000 (1 to 82)	OR 0.33 (0.03 to 3.20)	220 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1 4]
Miscarriage rate - Early versus late clomiphene citrate	29 per 1000	36 per 1000 (8 to 147)	OR 1.25 (0.27 to 5.70)	212 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1 3 4]
Clinical pregnancy - Early versus late clomiphene citrate	195 per 1000	405 per 1000 (198 to 653)	OR 2.81 (1.02 to 7.75)	78 (1 RCT)	⊕⊕⊖⊖ LOW [4]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio; **RCT:** randomised controlled trial

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: 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: 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: the true effect is likely to be substantially different from the estimate of effect.

[1]Evidence is based on a single study - downgraded one level for serious imprecision.
[2]Event rates are low, which may increase the likelihood of imprecision - downgraded one level.
[3]Insufficient data to allow judgement of risk of bias - downgraded one level for serious risk of bias.
[4]Wide confidence intervals, low event rates, and small sample size observed in this single study - downgraded one level for serious imprecision.

BACKGROUND

Description of the condition

Anovulation and oligo-ovulation are estimated to be the cause 21% of female infertility. The World Health Organization (WHO) splits the causes into the following three categories (NICE 2013).

- Group 1: hypothalamic pituitary failure or hypogonadotropic hypogonadism, accounting for around 10% of ovulatory disorders
- Group 2: hypothalamic pituitary dysfunction or eugonadotropic, 85% of ovulatory disorders
- Group 3: ovarian failure or hypergonadotropic hypogonadism, 4% to 5% of ovulatory disorders

Group 2 is the subject of this review. This group consists predominantly of women with polycystic ovary syndrome (PCOS) but may also include women with hyperprolactinaemia and those with unexplained anovulation. PCOS is a common condition of uncertain aetiology occurring in 4% to 7% of women of reproductive age (Lobo 2000). The syndrome was first described in 1935 and was first known as Stein-Leventhal syndrome. In the past the diagnostic criteria for PCOS have varied. A recent consensus meeting between the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine decided on the criteria, based upon majority opinion and not clinical trial data (ESHRE/ASRM 2003). Two of the following three factors are required for diagnosis of PCOS, with exclusion of other aetiologies such as congenital adrenal hyperplasia, androgen-secreting tumours, hyperprolactinaemia, and Cushing's syndrome:

- oligo-ovulation or anovulation;
- clinical or biochemical signs of hyperandrogenism, or both;
- polycystic ovaries as seen on ultrasound scanning.

Common symptoms and signs of PCOS include hirsutism, acne, irregular menstrual bleeding, and obesity. Investigations of women with PCOS may show raised luteinising hormone (LH) and free testosterone levels. Features on ultrasound scanning are enlarged ovaries (volume greater than 10 mL) or equal to or greater than 12 follicles 2 mm to 9 mm or greater in size diffusely distributed on one or both ovaries, or both (ESHRE/ASRM 2003). Women with PCOS may be at increased risk of pregnancy loss and complications and endometrial carcinoma. Their cardiovascular risk is also raised due to an increased risk of type 2 diabetes mellitus, hypertension, and altered serum lipid profiles (Fauser 2012; Hart 2015; Lobo 2000). Women with PCOS are more likely to be diagnosed with infertility and to undergo in vitro fertilisation (Hart 2015).

During normal menstruation, oestrogen levels are low, while follicle-stimulating hormone (FSH) and LH levels begin to rise. This stimulates the development of an ovarian follicle which produces androgens (male sex hormones), some of which are bound to sex hormone binding globulin and some of which circulate freely in the bloodstream. Some androgens are converted to oestrogens. This causes a rise in the level of oestrogen, which in turn causes a fall in FSH and LH levels. The oestrogen levels continue to rise, eventually causing an LH surge, which triggers ovulation. Following ovulation a corpus luteum is formed which produces progesterone as well as oestrogen. The purpose of the corpus luteum is to prepare the endometrium for embryo implantation and for the maintenance of early pregnancy.

In PCOS there is a state of chronic anovulation characterised by small ovarian cysts, elevated ovarian production of androgens, and sometimes hypersecretion of LH. PCOS is the most common cause of anovulatory infertility. With the new criteria being wider than previously accepted definitions, its diagnosis is even more frequent (ESHRE/ASRM 2003).

Hyperprolactinaemia (which is included in the WHO group 2 category) is not included in this review.

Description of the intervention

A number of treatment options, used alone or in conjunction with other medical therapies, are available for the treatment of subfertility associated with anovulation.

Clomiphene citrate and tamoxifen

Medical ovulation induction with clomiphene citrate is currently the first-line treatment for anovulatory women. Clomiphene citrate is an antioestrogen and competes for receptor-binding sites with endogenous oestrogens. Recently published United Kingdom National Institute for Clinical Excellence (NICE) guidelines state that first-line treatment for WHO group 2 anovulation should be clomiphene citrate (or tamoxifen) for up to 12 months (NICE 2013). The recommended daily dose of clomiphene citrate is 50 mg to 100 mg with a maximum of 250 mg. However, clomiphene resistance (failure to ovulate after taking clomiphene) is common, occurring in approximately 15% to 40% of women with PCOS (Kousta 1997; Pritts 2002; Wolf 2000). Definitions of clomiphene resistance vary, but the NICE definition is: "Anovulatory women who do not ovulate while receiving the 150 mg dose of clomiphene citrate" (NICE 2013). Resistance is associated with an increased body mass index, and weight loss programmes improve the success rates of clomiphene citrate therapy (Kousta 1997). Alternative and adjunctive treatments have been sought due to the high incidence of clomiphene resistance.

Dexamethasone as an adjunct

Addition of oral dexamethasone, a steroid hormone, to clomiphene citrate has been advocated in order to improve the chances of ovulation and subsequent pregnancy (Haas 2013).

Bromocriptine as an adjunct

Bromocriptine, a dopamine agonist used to treat hyperprolactinaemia, has been studied as an adjunctive treatment to clomiphene-induced ovulation in anovulatory women with PCOS.

Aromatase inhibitors

The use of aromatase inhibitors (AIs) to treat anovulatory infertility is a new indication. Proponents of AIs believe that they are superior to, and safer than, clomiphene citrate. The latest form of these drugs ('third generation' anastrozole, letrozole, and exemestane) are currently being used as a treatment for breast cancer (Mitwally 2004). Aromatase inhibitors are not included in this review, as they are the subject of a separate review (Franik 2014).

CYP17a inhibitors

Ketoconazole is a CYP17a inhibitor. It inhibits a different part of the cytochrome P450 complex to AIs. Ketoconazole inhibits aromatase activity in the gonads (Hassan 2001; Parsanezhad 2003), and therefore may have similar effects to AIs with added antiandrogenic effects.

Metformin and other insulin-sensitising agents alone or as an adjunct

A feature of PCOS is hyperinsulinaemia due to insulin resistance. This is thought to increase androgen production by the ovaries. Metformin and other insulin-sensitising agents (e.g. troglitazone, rosiglitazone, pioglitazone, and D-chiro-inositol) are thought to help correct this and therefore increase ovulation and pregnancy rates in women with PCOS (Tang 2012). Use of insulin-sensitising agents such as metformin are not included in this review, as they are the subject of a separate review (Tang 2012).

Gonadotropins

Gonadotropins are a long-standing treatment for clomiphene-resistant women. A variety of injectable drugs are available (human menopausal gonadotropins (hMG), urinary FSH, and recombinant FSH). These all have problems related to cost, risk of multiple pregnancy, and ovarian hyperstimulation syndrome (OHSS) (Weiss 2015).

Pulsatile gonadotropin-releasing hormone (GnRH) is also sometimes used. This involves pulsatile GnRH infusion by intravenous or subcutaneous route using a portable pump. Cost and effect are likely similar to that of hMG treatment (Bayram 2004), but there may be a reduced risk of multiple pregnancy and OHSS (Tan 1996).

How the intervention might work

Clomiphene citrate and tamoxifen

By blocking receptors in the hypothalamus and pituitary, clomiphene citrate interferes with the feedback mechanism of endogenous oestrogen on the pituitary and hypothalamus. The result is an increase in FSH and LH secretion by the pituitary, which stimulates the production of ovarian follicles and ovulation. Estimates for numbers of women conceiving with clomiphene therapy vary from 30% to 50%, in Kousta 1997, to 15% (NICE 2013). Approximately 7% of pregnancies resulting from clomiphene-induced ovulation are twin pregnancies, and 0.5% are triplet pregnancies (Wolf 2000). Miscarriage rates of 13% to 25% have been reported with clomiphene-induced conceptions (Kousta 1997). This proportion may be higher than in women with normal fertility and unassisted conception, but this is uncertain (Haas 2013). A more advanced age may be responsible, and beyond that it is not possible to separate the adverse effects of treatment from the underlying process leading to subfertility. OHSS has been reported rarely following clomiphene citrate use. Tamoxifen has been used to induce ovulation but is used much less frequently than clomiphene citrate (Messinis 1982); its mode of action is similar to that of clomiphene citrate.

Dexamethasone as an adjunct

The proposed mechanism of action of dexamethasone in PCOS is suppression of the adrenal production of androgens, which should augment the action of clomiphene. It has also been suggested that dexamethasone may facilitate the growth of ovarian follicles by causing an increase in FSH levels. A third mechanism of action may be to reduce the high pulsatile levels of LH seen in PCOS and which contributes to anovulation (Brann 1991).

Bromocriptine as an adjunct

Dopamine can reduce elevated LH levels in PCOS and has also been reported to lead to a return in cyclical ovarian activity in normoprolactinaemic women with PCOS (Leblanc 1976; Siebel 1984).

Why it is important to do this review

We reviewed the available literature in an attempt to establish the effectiveness and complications of antioestrogen agents, alone or in combination with adjunctive treatments, in ovulation induction for women with anovulatory infertility.

This review has superseded the review on clomiphene citrate for ovulation induction (Hughes 1996), and covers WHO group 2 women (excluding hyperprolactinaemia).

OBJECTIVES

To determine the relative effectiveness of antioestrogen agents alone or in combination with other medical therapies in women with subfertility associated with anovulation, possibly caused by polycystic ovarian syndrome (PCOS).

METHODS

Criteria for considering studies for this review

Types of studies

Published and unpublished randomised controlled trials (RCTs) were eligible for inclusion. We did not include cross-over trials unless phase-one data were available.

Types of participants

Women of reproductive age with WHO group 2 anovulation. Anovulation was defined as a lack of evidence of serum progesterone in the luteal range for the reference laboratory or a failure of basal body temperature to rise by more than 0.4 °C for 10 days or more. Age was as determined by trial authors.

Exclusion criteria

We excluded women with hyperprolactinaemia or Cushing's syndrome, or both, and trials which reported that women with these two conditions had been included. We excluded trials including women with WHO group 1 anovulation.

Types of interventions

The following interventions and comparisons were eligible for inclusion:

Antioestrogen versus no treatment or placebo

For example:

- clomiphene citrate;
- tamoxifen;
- other.

Antioestrogen versus antioestrogen

For example:

- clomiphene citrate versus tamoxifen;
- clomiphene citrate versus other;
- tamoxifen versus other;
- other.

Antioestrogen versus gonadotropin

- Follicle-stimulating hormone (FSH)
- Human menopausal gonadotropin (hMG)

Antioestrogen plus other medical therapy versus antioestrogen alone

For example:

- dopamine agonist - bromocriptine;
- dopamine agonist - cabergoline;
- corticosteroid - dexamethasone;
- other.

Antioestrogen plus other medical therapy versus antioestrogen plus other medical therapy

We excluded trials utilising intrauterine insemination, as they are not relevant to the objective of this review. We included trials utilising natural intercourse or timed intercourse.

We did not include insulin-sensitising agents such as metformin and aromatase inhibitors in this review, as they are the subject of separate reviews (El Daly 2006; Tang 2012).

Clomiphene citrate regimens

- Regimen A versus Regimen B.

Types of outcome measures

Primary outcomes

1. Live birth/ongoing pregnancy rate (per woman).
2. Miscarriage rate (per woman), where miscarriage was defined as the involuntary loss of a pregnancy before 20 weeks gestation.

Secondary outcomes

1. Clinical pregnancy rate (per woman), where pregnancy was defined as evidence of intrauterine gestation on ultrasound; this includes pregnancies in the pre-treatment phase.
2. Incidence of multiple pregnancy (per woman), where multiple pregnancy was defined as greater than one intrauterine pregnancy.
3. Incidence of ovarian hyperstimulation syndrome (OHSS) (per woman), defined according to the definition adopted by the reporting authors.
4. Incidence of women reported adverse effects (per woman), defined according to the definition of the reporting authors.

Search methods for identification of studies

This is a substantive update of the previous review, and we searched the following sources for relevant studies.

Electronic searches

We searched for all published and unpublished RCTs of clomiphene citrate and antioestrogens for ovulation induction in women with PCOS without language restriction and in consultation with the Cochrane Gynaecology and Fertility Group Information Specialist (from database inception until 2 August 2016).

We searched the following electronic databases and trial registers on 2 August 2016.

(1) Cochrane Gynaecology and Fertility Group Specialised Register (Appendix 1), Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Register of Studies Online) (Appendix 2), MEDLINE (Appendix 3), Embase (Appendix 4), PsycINFO (Appendix 5), and CINAHL (Appendix 6).

We combined the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying RCTs, which appears in the *Cochrane Handbook of Systematic Reviews of Interventions* (Version 5.0.2, Chapter 6, 6.4.11)(Higgins 2011). The Embase, CINAHL, and PsycINFO searches were combined with trial filters developed by the Scottish Intercollegiate Guidelines Network (www.sign.ac.uk/methodology/filters.html#random).

(2) We also searched the following trials registers to identify ongoing and registered clinical trials (17th August 2016).

- ClinicalTrials.gov (a service of the US National Institutes of Health) (www.clinicaltrials.gov)
- World Health Organization Clinical Trials Registry Platform (WHO ICTRP) (www.who.int/trialsearch/Default.aspx).

We used the key words 'anovulation' and 'clomiphene citrate'.

Searching other resources

We handsearched the reference lists of included studies.

Data collection and analysis

Selection of studies

In the update of this review, the two review authors independently selected potentially eligible trials in accordance with the aforementioned criteria. We excluded trials from the systematic review if they made comparisons other than those prespecified above. Disagreements were resolved by discussion.

Data extraction and management

The two review authors independently extracted and verified study characteristics and outcome data from eligible studies using forms designed according to Cochrane guidelines. We sought additional information on trial methodology and actual trial data from the authors of six trial reports (Boonstanfar 2001; Branigan 2003; Hassan 2001; Parsanezhad 2002a; Parsanezhad 2002b; Vegetti 1999), but received no reply. We were unable to contact the authors of five trial reports (Cudmore 1966; Daly 1984; Garcia 1985; Johnson 1966; Suginami 1993). Where studies had multiple publications, we collated the reports of the same study so that each study, rather than each report, was the unit of interest for the review, and such studies had a single identifier with multiple references.

Pregnancies that occurred in the pre-treatment phase were included as a success in the analysis.

Assessment of risk of bias in included studies

The two review authors independently assessed the included studies for risk of bias using the Cochrane 'Risk of bias' assessment tool, which addresses the following domains: selection bias (randomisation and allocation concealment); performance bias (blinding of participants and personnel); detection bias (blinding of outcome assessors); attrition bias (incomplete outcome data); reporting bias (selective reporting); and other bias (Higgins 2011). Disagreements were resolved through discussion. We have fully described all judgements and summarised our conclusions in the 'Risk of bias' table in the Characteristics of included studies.

Measures of treatment effect

For dichotomous data (all of the outcome measures in this review), we used the numbers of events in the intervention and control groups of each study to calculate the Mantel-Haenszel odds ratios. We presented 95% confidence intervals for all outcomes. Where data to calculate odds ratios were not available, we utilised the most detailed numeric data available that could facilitate similar analyses of included studies.

Unit of analysis issues

The primary analysis was per woman randomised. Per-cycle data were not pooled, but if reported were included in an additional table. Where per-cycle data were reported, we contacted the authors of the primary study and requested per-woman randomised data. We counted multiple live birth such as twins and higher-order births as a single live birth event. We included only the first arm of cross-over trials in a pooled analysis.

Dealing with missing data

Where possible, we analysed the data on an intention-to-treat basis, and attempted to contact the original study authors for missing data.

Assessment of heterogeneity

We considered whether the clinical and methodological characteristics of the included studies were sufficiently similar for meta-analysis to provide a clinically meaningful summary. We assessed statistical heterogeneity by the I^2 statistic, taking an I^2 value above 50% to indicate substantial heterogeneity (Higgins 2002).

Assessment of reporting biases

In the view of the difficulty of detecting and correcting for publication bias and other reporting biases, we aimed to minimise their potential impact by ensuring a comprehensive search for eligible studies and being alert for duplication of data. We had planned that if there were 10 or more trials in an analysis, we would produce a funnel plot to explore the possibility of small-study effects. We were unable to make this assessment in this update of the review. In future updates we will seek to explore publication bias where sufficient trials are available.

Data synthesis

Where studies were sufficiently similar, we combined the data using a fixed-effect model in the following comparisons.

- Antioestrogen versus placebo
  - Clomiphene citrate versus placebo
- Antioestrogen versus antioestrogen
  - Clomiphene citrate versus tamoxifen
  - Clomiphene citrate plus tamoxifen versus clomiphene
- Antioestrogen versus gonadotropin
  - Clomiphene citrate versus FSH
  - Clomiphene citrate versus hMG
- Antioestrogen plus medical adjunct versus antioestrogen alone
  - Clomiphene citrate plus ketaconazole versus clomiphene
  - Clomiphene citrate plus bromocriptine versus clomiphene
  - Clomiphene citrate plus dexamethasone versus clomiphene
  - Clomiphene citrate plus combined oral contraceptive versus clomiphene
  - Clomiphene citrate plus human chorionic gonadotropin versus clomiphene
  - Clomiphene citrate plus hormone supplement versus clomiphene
- Clomiphene citrate regimens
  - Clomiphene citrate 5 days versus clomiphene citrate 10 days
  - Early clomiphene citrate versus late clomiphene citrate

Subgroup analysis and investigation of heterogeneity

If we detected substantial heterogeneity, we tried to explain it through subgroup analysis by comparing specific regimens (drug doses) where data were available.

Sensitivity analysis

We did not conduct any sensitivity analyses in this review update. In future updates we will conduct sensitivity analyses if there is evidence of substantial statistical heterogeneity. We will conduct sensitivity analysis on the primary outcome measure of live birth. We included studies with adequate evidence of allocation concealment. We undertook a random-effects analysis to assess sensitivity to choice of model.

'Summary of findings' table

We prepared a 'Summary of findings' table using GRADEpro GDT software for the main comparisons of the review (GRADEpro GDT 2014). The two review authors independently evaluated the overall quality of the evidence for the main outcomes of the review (live birth rate, miscarriage rate, clinical pregnancy rate, multiple pregnancy rate, and OHSS per woman randomised) using GRADE criteria (risk of bias, consistency, imprecision, indirectness, publication bias) (Atkins 2004).

We included 'Summary of findings' tables for the following comparisons.

- Antioestrogen versus placebo
- Antioestrogen versus antioestrogen
- Antioestrogen plus medical adjunct versus antioestrogen alone
- Antioestrogen regimens

The remaining comparisons of antioestrogen versus gonadotropin is discussed within the text of the review.

Timeline

The review authors intend that a new search for RCTs will be performed every two years and the review updated accordingly.

RESULTS

Description of studies

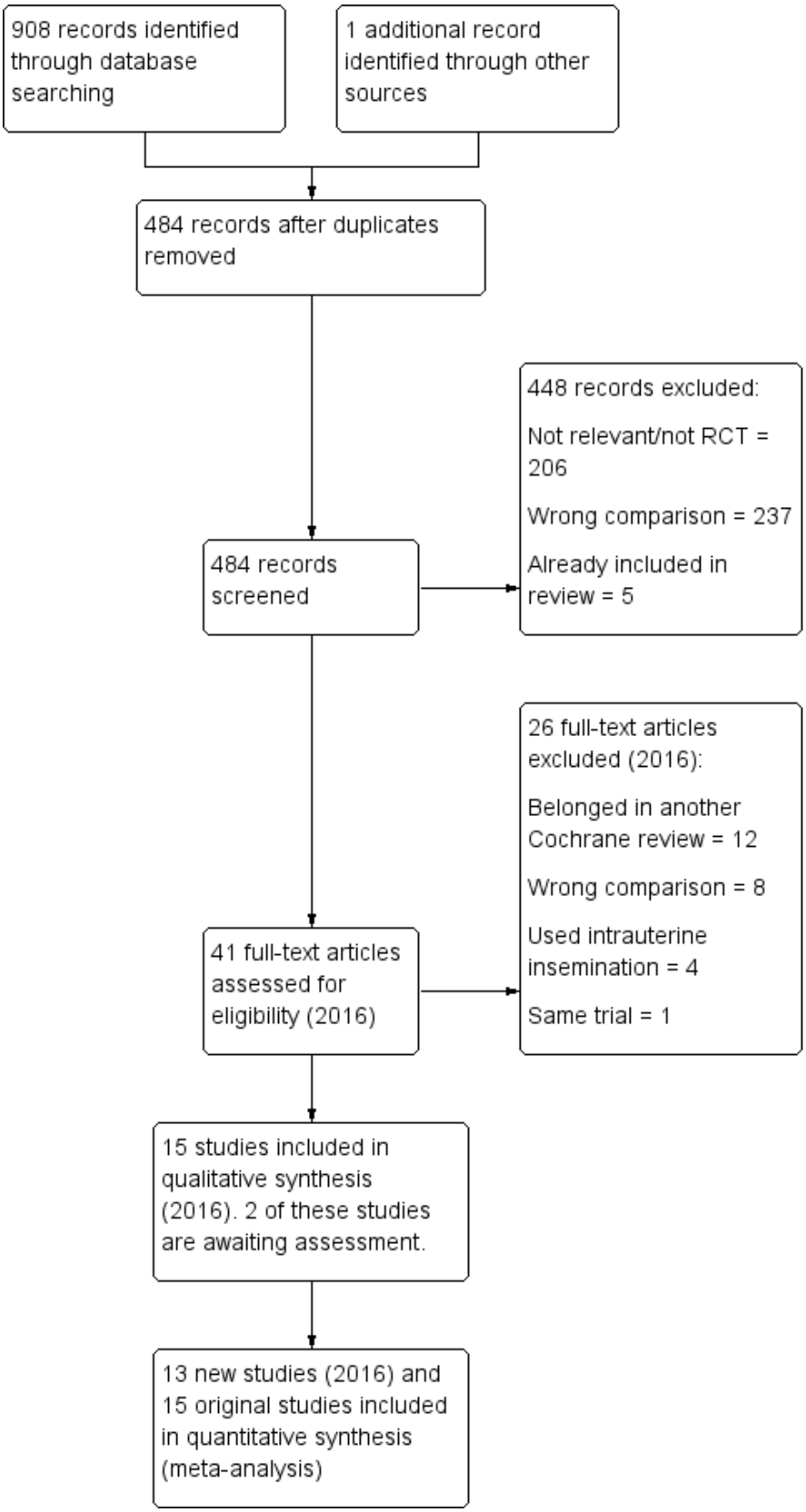
Results of the search

See Characteristics of included studies and Characteristics of excluded studies.

The previous version of this review included 15 trials.

The searches in the 2016 review update resulted in the retrieval of 41 full-text papers (Figure 1). We included 13 new studies (Characteristics of included studies). We excluded 25 studies (Characteristics of excluded studies). Two studies are awaiting classification, as it is unclear if intrauterine insemination was used, which is an exclusion criterion (Craig 2015; Neuhausser 2011); we have contacted the authors and await a response. We moved one study from the excluded studies to the included studies, as it was eligible for the new comparison of antioestrogen versus gonadotropin (Badawy 2008).

Figure 1. Study flow diagram for update 2016.



Included studies

We included a total of 28 studies in this 2016 update of the systematic review. Thirteen new studies were included (Badawy 2009; Badawy 2011; Dehbashi 2006; Elsedeek 2014; Esmaeilzadeh 2011; Ghafourzadeh 2004; Homburg 2012; Lopez 2004; Moslemizadeh 2008; Omran 2011; Seyedoshohadaei 2012; Tripathy 2013). We moved one study from the excluded studies to the included studies, as it was eligible for the new comparison of antioestrogen versus gonadotropin (Badawy 2008).

Design

Twenty-four studies were parallel-design RCTs (Badawy 2008; Badawy 2009; Badawy 2011; Boonstanfar 2001; Branigan 2003; Branigan 2005; Daly 1984; Dehbashi 2006; Elkind-Hirsch 2005; Elnashar 2006; Elsedeek 2014; Esmaeilzadeh 2011; Ghafourzadeh 2004; Hassan 2001; Homburg 2012; Lopez 2004; Moslemizadeh 2008; Omran 2011; Parsanezhad 2002a; Parsanezhad 2002b; Seyedoshohadaei 2012; Tripathy 2013; Vegetti 1999; Yilmaz 2006), and four studies were cross-over trials where phase-one data were available (Cudmore 1966; Garcia 1985; Johnson 1966; Suginami 1993).

Setting

A variety of different settings were used to recruit women into the studies.

- Not stated (Boonstanfar 2001; Cudmore 1966; Daly 1984; Hassan 2001; Homburg 2012; Johnson 1966; Omran 2011; Suginami 1993).
- Infertility clinic (Branigan 2003; Branigan 2005; Elsedeek 2014; Ghafourzadeh 2004; Lopez 2004; Moslemizadeh 2008; Vegetti 1999; Yilmaz 2006).
- Outpatient department (Badawy 2008; Badawy 2009; Badawy 2011; Elnashar 2006; Tripathy 2013).
- Department of obstetrics and gynaecology (Garcia 1985).
- Division of reproductive endocrinology (Parsanezhad 2002a; Parsanezhad 2002b).
- Women's health institute (Elkind-Hirsch 2005).
- Infertility and reproductive health centre/infertility research centre (Dehbashi 2006; Esmaeilzadeh 2011).
- Private clinic (Seyedoshohadaei 2012).

Country

The included studies were conducted in the following countries.

- Turkey (Yilmaz 2006).
- USA and Canada (Boonstanfar 2001; Branigan 2003; Branigan 2005; Cudmore 1966; Daly 1984; Elkind-Hirsch 2005; Garcia 1985; Johnson 1966).
- Japan (Suginami 1993).
- Italy (Vegetti 1999).
- Iran (Dehbashi 2006; Esmaeilzadeh 2011; Ghafourzadeh 2004; Moslemizadeh 2008; Parsanezhad 2002a; Parsanezhad 2002b; Seyedoshohadaei 2012).
- Egypt (Badawy 2008; Badawy 2009; Badawy 2011; Elnashar 2006; Elsedeek 2014; Hassan 2001; Omran 2011).
- India (Tripathy 2013).
- Spain (Lopez 2004).
- Multicentre (Homburg 2012).

Participants

The women ranged in age from 18 to 39 years. Daly 1984 and Omran 2011 did not state age.

Cycles of treatment

The number of treatment cycles ranged from one to six-plus in the included trials, however in some trials this was not stated.

- Not stated (Badawy 2008; Boonstanfar 2001; Daly 1984; Ghafourzadeh 2004; Omran 2011; Vegetti 1999).
- One (Badawy 2011; Branigan 2005; Elkind-Hirsch 2005; Elnashar 2006; Elsedeek 2014; Esmaeilzadeh 2011; Johnson 1966; Moslemizadeh 2008; Suginami 1993; Yilmaz 2006).
- Up to two (Dehbashi 2006).
- Up to three (Cudmore 1966; Homburg 2012; Lopez 2004; Tripathy 2013).
- Up to four (Badawy 2009).
- One to five (Garcia 1985).
- Six or more, or to pregnancy (Branigan 2003; Parsanezhad 2002a).
- Three to six (Hassan 2001).

Inclusion criteria

The main inclusion criteria reported in the trials are listed. Anovulatory PCOS was the principal inclusion criterion.

- Anovulatory (Boonstanfar 2001; Branigan 2003; Cudmore 1966; Daly 1984; Garcia 1985; Homburg 2012; Johnson 1966; Lopez 2004; Seyedoshohadaei 2012; Suginami 1993; Vegetti 1999).
- PCOS (Badawy 2008; Badawy 2011; Branigan 2005; Elnashar 2006; Hassan 2001; Lopez 2004; Moslemizadeh 2008; Tripathy 2013).
- Insulin resistance (Hassan 2001).
- Secondary amenorrhoea (longer than two years) or oligomenorrhoeic (Cudmore 1966; Daly 1984; Elkind-Hirsch 2005; Yilmaz 2006).
- No previous exposure to clomiphene or ovulation induction (Daly 1984; Yilmaz 2006).
- No fertility treatment in previous three months (Cudmore 1966).
- No other causes of infertility (Boonstanfar 2001; Branigan 2003; Cudmore 1966; Tripathy 2013; Yilmaz 2006).
- Clomiphene-resistant PCOS (Elsedeek 2014; Esmaeilzadeh 2011; Ghafourzadeh 2004; Parsanezhad 2002a).
- Normoprolactinaemia (Suginami 1993; Tripathy 2013; Yilmaz 2006).
- Tubal patency (Badawy 2008; Badawy 2011; Branigan 2003; Homburg 2012; Moslemizadeh 2008; Seyedoshohadaei 2012; Tripathy 2013).
- Specified ages (Branigan 2003; Branigan 2005; Elkind-Hirsch 2005; Elnashar 2006; Homburg 2012; Lopez 2004; Yilmaz 2006).
- No medication for previous two months (Elnashar 2006).
- Duration of primary infertility longer than two years (Elnashar 2006; Yilmaz 2006).
- Normal semen analysis (Badawy 2008; Badawy 2011; Branigan 2005; Dehbashi 2006; Ghafourzadeh 2004; Homburg 2012; Lopez 2004; Seyedoshohadaei 2012; Yilmaz 2006).

- Normal results on hysterosalpingogram (Branigan 2005; Dehbashi 2006; Ghafourzadeh 2004; Seyedoshohadaei 2012; Yilmaz 2006).
- Normal endocrine function (Branigan 2005; Dehbashi 2006; Elnashar 2006; Lopez 2004; Seyedoshohadaei 2012; Yilmaz 2006).
- Body mass index between 18 and 38 (Elkind-Hirsch 2005), body mass index 20 to 30 kg/m^2 (Tripathy 2013).
- Comorbid disease (tuberculosis, abnormal glucose tolerance test) (Tripathy 2013).
- No history of pelvic surgery or pelvic inflammatory disease (Lopez 2004).
- No details (Badawy 2009; Omran 2011).

Interventions

Antioestrogen versus no treatment or placebo

Clomiphene citrate versus placebo

Three trials compared clomiphene citrate to placebo (Cudmore 1966; Garcia 1985; Johnson 1966), all of which were of cross-over design (phase-one data only). Doses varied from a 50 mg fixed dose to a variable dose of up to 250 mg (dependent on ovulatory response). Phase one of the trials lasted from one to five cycles. The total number of women was 133, 63 randomised to the control group and 70 to the treatment group.

Antioestrogen versus antioestrogen

Clomiphene citrate versus tamoxifen

Five trials compared clomiphene citrate to tamoxifen (Badawy 2011; Boonstanfar 2001; Moslemizadeh 2008; Seyedoshohadaei 2012; Vegetti 1999). In the Boonstanfar 2001 and Vegetti 1999 trials, the doses of clomiphene citrate ranged from 50 mg to 200 mg, as both trials varied dose dependent on ovulatory response. The Seyedoshohadaei 2012 trial used an initial dose of 50 mg, increasing by 50 mg per cycle to a maximum of 150 mg. The Badawy 2011 and Moslemizadeh 2008 trials used a dose of 100 mg daily. In the Boonstanfar 2001 and Vegetti 1999 trials, the doses of tamoxifen ranged from 20 mg to 60 mg, again as both trials varied the dose. The Badawy 2011 and Moslemizadeh 2008 trials used a dose of 20 mg of tamoxifen per day. The Seyedoshohadaei 2012 trial used an initial dose of 10 mg per day, increasing by 10 mg per cycle to a maximum of 30 mg per day. Boonstanfar 2001 and Vegetti 1999 did not state duration of treatment. Badawy 2011 and Moslemizadeh 2008 treated women for a single cycle. The total number of cycles of treatment was between 91 and 129 for women on clomiphene citrate and between 113 and 133 for women on tamoxifen. The Boonstanfar 2001 trial appears to have continued after publication in 2001; an abstract of a larger trial was published in 2002 that appears to include the women from Boonstanfar 2001. We have excluded this abstract from analysis while awaiting author clarification. A total of 657 women participated, of which 332 were randomised to clomiphene treatment and 325 to tamoxifen.

Clomiphene citrate plus tamoxifen versus clomiphene citrate

Suginami 1993 compared clomiphene citrate plus tamoxifen to clomiphene citrate alone. The trial was of cross-over design with phase-one data available. The dose of clomiphene citrate was 100 mg when used alone and 50 mg when used in combination with 20 mg tamoxifen. Up to three cycles of treatment were given in the first phase. Of the 20 participants, 10 were randomised to clomiphene citrate plus tamoxifen and 10 to clomiphene citrate alone.

Ghafourzadeh 2004 compared clomiphene citrate plus tamoxifen to clomiphene citrate alone in 100 women. The dose of clomiphene citrate was 100 mg when used alone and 50 mg when used in combination with 20 mg tamoxifen. The number of cycles of treatment was unclear.

Antioestrogen versus gonadotropin

Clomiphene citrate versus hMG

Badawy 2008 compared clomiphene citrate with hMG in 318 women. The dose of clomiphene citrate was 100 mg. The number of cycles of treatment was unclear.

Clomiphene citrate versus FSH

Homburg 2012 and Lopez 2004 compared clomiphene citrate with FSH in 378 women. In both trials the starting dose of clomiphene citrate was 50 mg, increasing to a maximum of 150 mg in subsequent cycles. Both trials used up to three cycles of treatment.

Antioestrogen plus other medical therapy versus antioestrogen alone

Clomiphene citrate plus bromocriptine versus clomiphene citrate

Parsanezhad 2002b and Tripathy 2013 compared clomiphene citrate plus bromocriptine to clomiphene citrate. In the Parsanezhad 2002b trial, the control group was given 200 mg clomiphene citrate and placebo continuously. The treatment group was given 200 mg clomiphene citrate plus 7.5 mg bromocriptine continuously. Both groups were administered human chorionic gonadotropin (hCG) (10,000 U) to trigger ovulation and were treated for up to six cycles. The dose of bromocriptine or placebo was gradually introduced before commencing clomiphene citrate. All 100 women had clomiphene-resistant PCOS. In the Tripathy 2013 trial, the control group was given 50 mg of clomiphene citrate daily from Day 3 to Day 7. The treatment group was given clomiphene citrate 50 mg from Day 3 to Day 7 and bromocriptine 2.5 mg from Day 1 to Day 30. All of the women had a diagnosis of PCOS.

Clomiphene citrate plus dexamethasone versus clomiphene

Four trials compared clomiphene citrate plus dexamethasone to clomiphene citrate (Daly 1984; Elnashar 2006; Esmaeilzadeh 2011; Parsanezhad 2002a). The control groups were given 50 mg to 150 mg clomiphene citrate on Days 5 to 9 (Daly 1984); 200 mg clomiphene citrate on Days 5 to 9 and placebo from Day 5 to Day 14 (Parsanezhad 2002a); 100 mg clomiphene citrate on Days 3 to 7 and placebo from Days 3 to 12 (Elnashar 2006); or 100 mg clomiphene citrate on Days 3 to 7 and placebo from Days 5 to 14 (Esmaeilzadeh 2011). Treatment groups were given 50 mg to 150 mg clomiphene citrate plus 0.5 mg dexamethasone on Days 5 to 9 (Daly 1984); 200 mg clomiphene citrate on Days 5 to 9 plus 2 mg dexamethasone on Days 5 to 14 (Parsanezhad 2002a); 100 mg clomiphene citrate on Days 3 to 7 plus 2 mg dexamethasone on Days 3 to 12 (Elnashar 2006); or 100 mg of clomiphene citrate on Days 3 to 7 plus 2 mg dexamethasone on Days 5 to 14 (Esmaeilzadeh 2011). Parsanezhad 2002a and Elnashar 2006 administered hCG to both groups to trigger ovulation. Both groups were treated for up to six cycles in Parsanezhad 2002a and for only one cycle in Elnashar 2006 and Esmaeilzadeh 2011.

Clomiphene citrate plus ketoconazole versus clomiphene

Hassan 2001 compared clomiphene citrate plus ketoconazole versus clomiphene. The control group was given up to 150 mg clomiphene for three to six cycles. The treatment group was given 400 mg per day ketoconazole for 85 days and then 100 mg to 150 mg clomiphene for three to six cycles. In both groups "patients who persistently failed to respond to clomiphene 150 mg per day (clomiphene resistant) were shifted to hMG". The 97 women were all insulin resistant and had PCOS; 48 were randomised to the control group and 49 to the treatment group.

Clomiphene citrate plus combined oral contraceptive versus clomiphene citrate

Branigan 2003 compared clomiphene citrate plus combined oral contraceptive to clomiphene citrate. The control group had no treatment for 38 to 56 days (two cycles), in particular no progestin to induce menstruation, while the treatment group was given combined oral contraceptive (0.03 mg ethinyl estradiol and 0.15 mg desogestrel (Desogen)) continuously for 42 to 50 days. In the following cycle, each group received 100 mg clomiphene citrate on Days 5 to 9, with ovulation triggered by 10,000 U of hCG. Those women who ovulated but did not become pregnant in this cycle (from either group) repeated the clomiphene citrate dose for up to six cycles. It was unclear what treatment or follow-up was provided to women who did not ovulate. The 51 participants were all clomiphene resistant; 25 were randomised to the control group and 26 to the treatment group.

Clomiphene citrate plus *hCG* versus clomiphene citrate alone

Two studies made this comparison (Branigan 2005; Yilmaz 2006). In the study by Branigan 2005, the experimental group received clomiphene citrate 100 mg daily on Days 5 to 9 with daily doses of 200 IU hCG intramuscularly; the control group received 150 mg clomiphene citrate daily on Days 5 to 9. Yilmaz 2006 administered 50 mg clomiphene citrate on Days 5 to 9 with 10,000 IU hCG administered when the follicle reached greater than 18 mm in diameter; the control group received clomiphene citrate only.

Clomiphene citrate plus hormone supplementation versus clomiphene citrate alone

Two trials made this comparison (Elkind-Hirsch 2005; Moslemizadeh 2008). The control and experimental groups both received clomiphene citrate 100 mg daily on Days 3 to 7 in the Elkind-Hirsch 2005 trial and on Days 3 to 9 in the Moslemizadeh 2008 trial. The experimental group received oral estradiol 1.5 mg twice daily commencing on Day 8 and discontinued when a LH surge was detected in the Elkind-Hirsch 2005 trial. In the Moslemizadeh 2008 trial, 2 mg of estradiol was given daily from Day 8 to the hCG injection. A total of 167 women were randomised.

Clomiphene citrate regimen A versus clomiphene citrate regimen B

Two trials reported this comparison (Elsedeek 2014; Omran 2011). The trials compared clomiphene citrate 200 mg per day for 5 days with clomiphene citrate 100 mg per day for 10 days in women with clomiphene-resistant PCOS.

Dehbashi 2006 compared clomiphene citrate 100 mg starting Day 1 of menstrual cycle for 5 days with clomiphene citrate 100 mg starting Day 5 of menstrual cycle for 5 days for a maximum of 3 cycles in 78 women with PCOS.

Badawy 2009 used an early (100 mg clomiphene citrate starting on the date after finishing medroxyprogesterone for five days) versus late (100 mg clomiphene citrate daily for five days starting on Day 3 of menses) regimen.

We found no RCTs for the following comparisons.

- Tamoxifen versus placebo.
- Any antioestrogen plus cabergoline versus antioestrogen.
- Any antioestrogen plus medical adjunct versus antioestrogen plus medical adjunct.

Outcomes

Five trials reported live birth/ongoing pregnancy (Boonstanfar 2001; Elsedeek 2014; Homburg 2012; Lopez 2004; Seyedoshohadaei 2012).

Fifteen trials reported adverse events including miscarriage (Badawy 2008; Badawy 2009; Badawy 2011; Boonstanfar 2001; Branigan 2003; Cudmore 1966; Elkind-Hirsch 2005; Elnashar 2006; Hassan 2001; Homburg 2012; Lopez 2004; Moslemizadeh 2008; Seyedoshohadaei 2012; Vegetti 1999; Yilmaz 2006).

All of the trials reported pregnancy. Ghafourzadeh 2004 and Badawy 2008 reported a positive pregnancy test result and no data for any other pregnancy outcome measure (clinical pregnancy, ongoing pregnancy, live birth).

Thirteen trials reported incidence of multiple pregnancy (Badawy 2008; Badawy 2011; Boonstanfar 2001; Branigan 2003; Daly 1984; Elnashar 2006; Elsedeek 2014; Hassan 2001; Homburg 2012; Lopez 2004; Moslemizadeh 2008; Seyedoshohadaei 2012; Yilmaz 2006).

Seven trials reported incidence of OHSS (Badawy 2008; Badawy 2011; Boonstanfar 2001; Lopez 2004; Moslemizadeh 2008; Seyedoshohadaei 2012; Suginami 1993).

Excluded studies

See Characteristics of excluded studies.

We excluded 37 initially identified trials from the review. Six of these were excluded in the 2016 update of the review (Dura 2015 (two publications); Kosar 2014; Moini 2015; Topcu 2010; Yari 2010). The primary reasons for exclusion of the studies were inclusion criteria and interventions.

Risk of bias in included studies

See Characteristics of included studies; Figure 2; Figure 3.

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

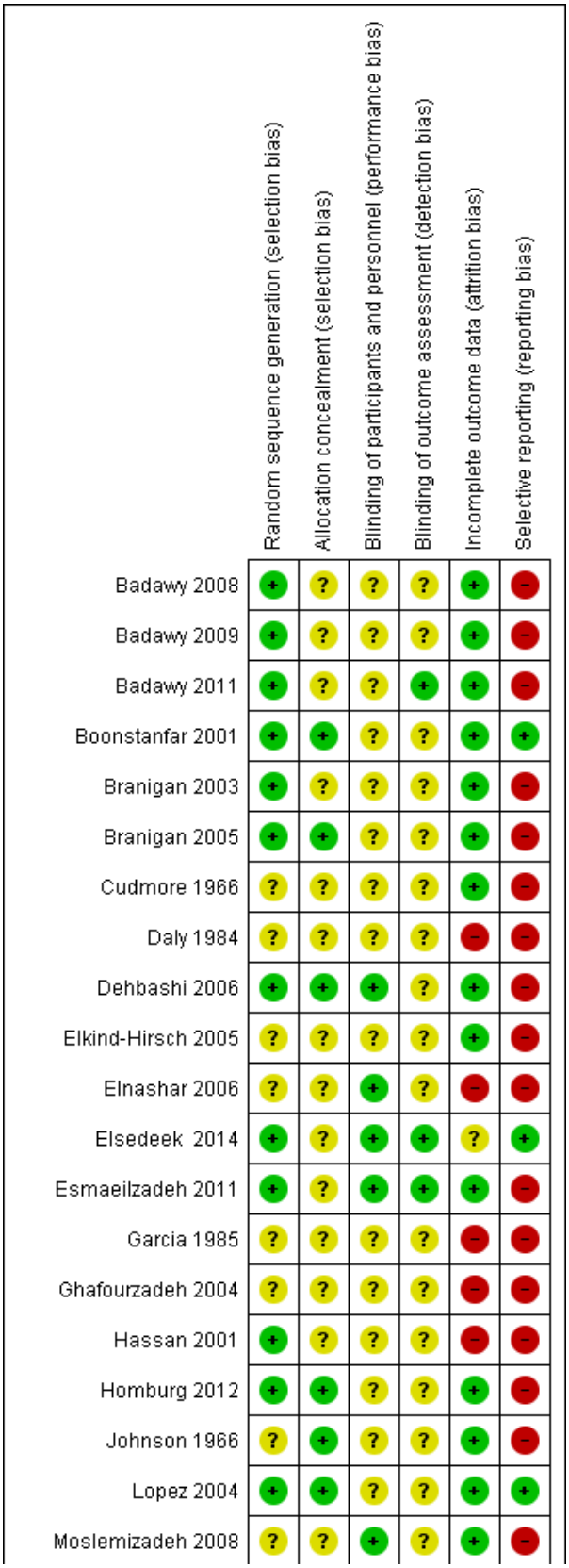


Figure 2. (Continued)

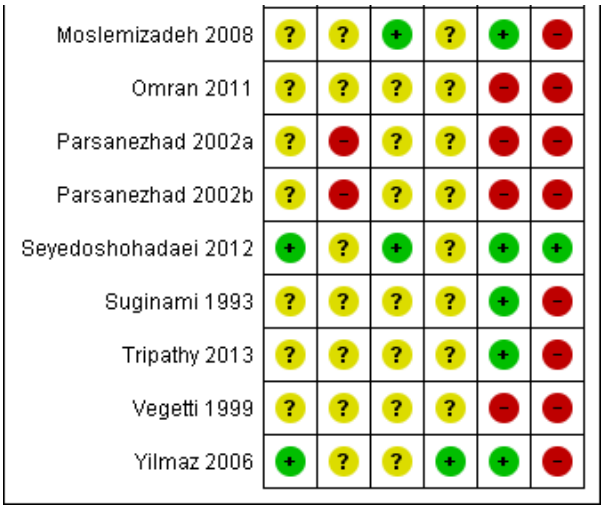
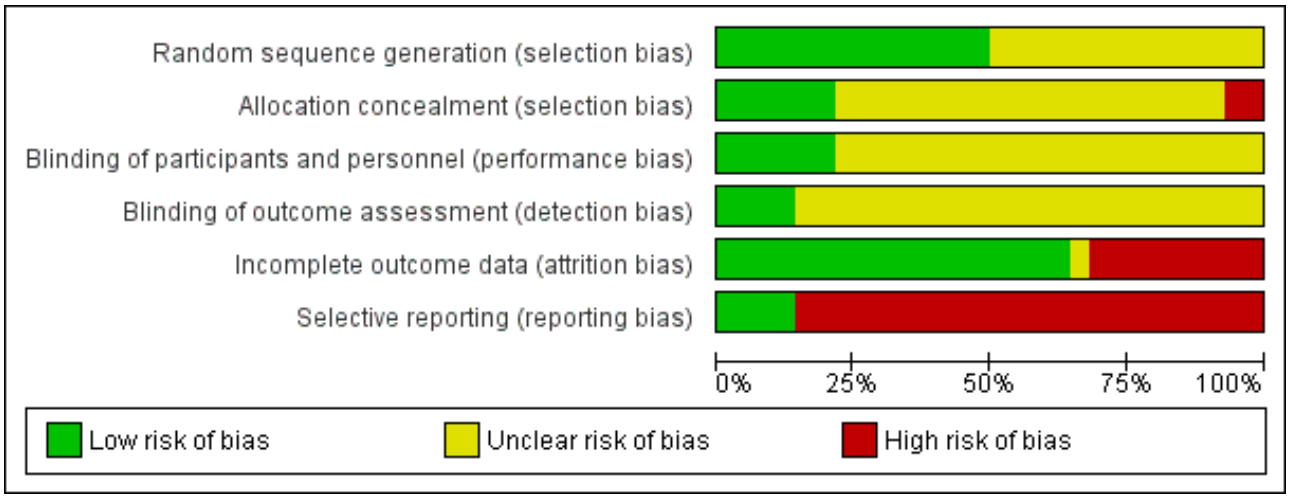


Figure 3. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Allocation

We judged 13 trials to be at low risk of bias for random sequence generation (Badawy 2008; Badawy 2009; Badawy 2011; Boonstanfar 2001; Branigan 2003; Branigan 2005; Dehbashi 2006; Elsedeek 2014; Esmaeilzadeh 2011; Hassan 2001; Homburg 2012; Lopez 2004; Seyedoshohadaei 2012; Yilmaz 2006). All 13 trials used random number tables. We judged random sequence generation to be unclear in the remaining studies due to inadequate details.

We judged only six trials to be at low risk of bias for allocation concealment (Boonstanfar 2001; Branigan 2005; Dehbashi 2006; Homburg 2012; Johnson 1966; Lopez 2004). We considered two trials to be at high risk of bias for allocation concealment, as allocation was conducted by a third party (pharmacist) using odd-even numbers. The remaining studies were at unclear risk of bias for allocation concealment.

Blinding

Performance bias

We judged six studies that reported blinding of participants or personnel, or both to be at low risk of performance bias (Dehbashi 2006; Elnashar 2006; Elsedeek 2014; Esmaeilzadeh 2011; Moslemizadeh 2008; Seyedoshohadaei 2012).

The remaining studies provided insufficient detail to make a judgement and were considered to be at unclear risk of performance bias (Badawy 2008; Badawy 2009; Badawy 2011; Boonstanfar 2001; Branigan 2003; Branigan 2005; Cudmore 1966; Daly 1984; Elkind-Hirsch 2005; Garcia 1985; Ghafourzadeh 2004; Hassan 2001; Homburg 2012; Johnson 1966; Lopez 2004; Omran 2011; Parsanezhad 2002a; Parsanezhad 2002b; Suginami 1993; Tripathy 2013; Vegetti 1999; Yilmaz 2006).

Detection bias

We judged four studies that reported blinding of outcome assessors to be at low risk of detection bias (Badawy 2011; Elsedeek 2014; Esmaeilzadeh 2011; Yilmaz 2006).

The remaining studies provided insufficient detail to make a judgement and were considered to be at unclear risk of detection bias (Badawy 2008; Badawy 2009; Boonstanfar 2001; Branigan 2003; Branigan 2005; Cudmore 1966; Daly 1984; Dehbashi 2006; Elkind-Hirsch 2005; Elnashar 2006; Garcia 1985; Ghafourzadeh 2004; Hassan 2001; Homburg 2012; Johnson 1966; Lopez 2004; Moslemizadeh 2008; Omran 2011; Parsanezhad 2002a; Parsanezhad 2002b; Seyedoshohadaei 2012; Suginami 1993; Tripathy 2013; Vegetti 1999).

Incomplete outcome data

For the purposes of this review we defined a withdrawal as a woman who stopped taking the assigned trial drug but was followed up by the trial. We defined a loss to follow-up as a woman who stopped participating in the trial and was not followed up. The number of dropouts was both these figures together. However, these terms are often used interchangeably by trial authors, without being defined.

Only Garcia 1985 and Esmaeilzadeh 2011 performed an intention-to-treat analysis; for Garcia 1985 the phase-one data contained results for all but three women (who were lost to follow-up). Thirteen studies reported no dropouts or all women randomised were analysed, or both (Badawy 2008; Badawy 2009; Badawy 2011; Cudmore 1966; Dehbashi 2006; Elnashar 2006; Esmaeilzadeh 2011; Homburg 2012; Lopez 2004; Moslemizadeh 2008; Seyedoshohadaei 2012; Suginami 1993; Tripathy 2013); we considered these studies to be at low risk of attrition bias.

We considered a rate of less than 10% of women dropping out to be an acceptable attrition rate; six studies reported rates from 4.3% to 10% (Boonstanfar 2001; Branigan 2003; Branigan 2005; Elkind-Hirsch 2005; Johnson 1966; Yilmaz 2006). We considered these studies to be at low risk of attrition bias.

A rate of more than 10% of women dropping out may be cause for concern. Three studies had high dropout rates: Daly 1984 (17%); Garcia 1985 (43%, though 94% of women were analysed in phase-one data); and Hassan 2001 (21%). The reasons are detailed in the 'Risk of bias' tables. We considered these studies to be at high risk of attrition bias.

Five trials provided no details on attrition and were considered to be at high risk of bias (Ghafourzadeh 2004; Omran 2011; Parsanezhad 2002a; Parsanezhad 2002b; Vegetti 1999). Parsanezhad 2002b presented outcome rates as percentages; an attempt to calculate actual participant numbers from group sizes reported at randomisation indicated that women may have been lost to follow-up. Elsedeek 2014 reported that 230 women were included in their study. Their power calculation required a minimum of 220 participants and they only report data for 220 participants. They do not explain how these 220 were selected from the 230 women included. We judged this study to be unclear risk of bias.

Selective reporting

Only five of 28 included trials reported on live birth (Boonstanfar 2001; Elsedeek 2014; Homburg 2012; Lopez 2004; Seyedoshohadaei 2012), and reporting of adverse effects was limited in all of the included trials.

There were differences in the number of cycles of treatment (one to six-plus), and therefore the duration of follow-up. This was detailed in a previous section of the review (see Characteristics of included studies for details).

The definitions used for some of the outcomes varied, which may have influenced reporting on PCOS, pregnancy, ovulation rate, and clomiphene resistance (see Characteristics of included studies for details).

We judged 21 trials in which no data were reported for live birth or outcomes were reported that were not prespecified, or both, to be at high risk of selective reporting bias (Badawy 2008; Badawy 2009; Badawy 2011; Branigan 2003; Branigan 2005; Cudmore 1966; Elkind-Hirsch 2005; Elnashar 2006; Esmaeilzadeh 2011; Garcia 1985; Ghafourzadeh 2004; Hassan 2001; Homburg 2012; Johnson 1966; Moslemizadeh 2008; Omran 2011; Parsanezhad 2002a; Parsanezhad 2002b; Suginami 1993; Vegetti 1999; Yilmaz 2006).

One study did not prespecify or define outcomes (Tripathy 2013), and two studies did not prespecify any outcomes (Daly 1984; Dehbashi 2006); we judged these studies to be at high risk of selective reporting bias.

Other potential sources of bias

None of the trials performed compliance monitoring to assess adherence to the treatment regimen.

Effects of interventions

See: **Summary of findings for the main comparison** Antioestrogen versus placebo; **Summary of findings 2** Antioestrogen versus antioestrogen; **Summary of findings 3** Antioestrogen plus medical adjunct versus antioestrogen alone; **Summary of findings 4** Antioestrogen regimens

1 Antioestrogen versus no treatment or placebo

Clomiphene citrate (50 mg to 250 mg) versus placebo

There were three trials in this comparison (Cudmore 1966; Garcia 1985; Johnson 1966).

Primary outcomes

Live birth rate

No data were reported for this comparison.

Miscarriage rate

No data were reported for this comparison.

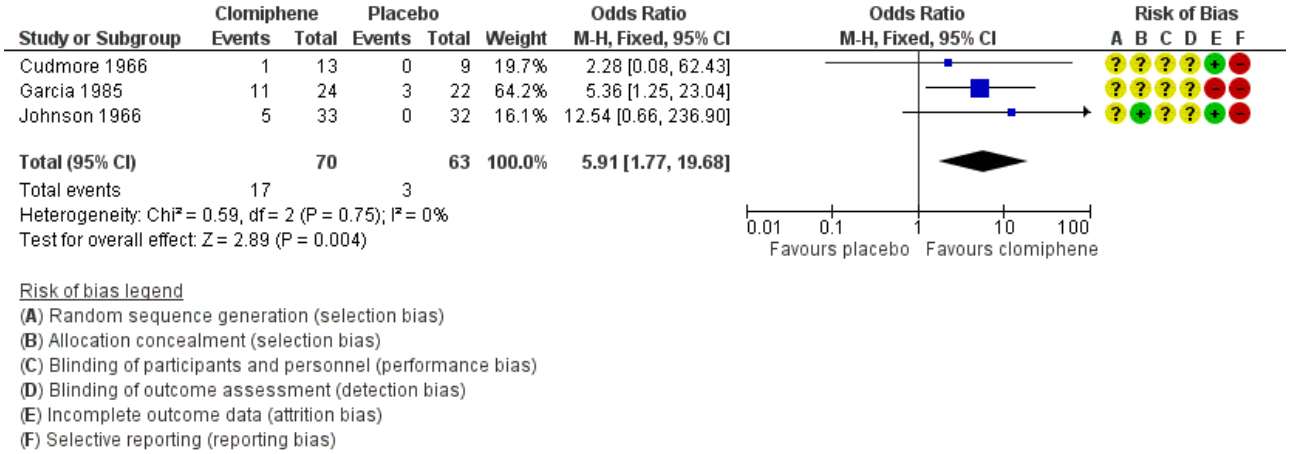
Secondary outcomes

Clinical pregnancy rate

Clomiphene citrate was associated with an increased chance of a clinical pregnancy compared with placebo (odds ratio (OR) 5.91, 95% confidence interval (CI) 1.77 to 19.68; 3 studies; 133 women; low-quality evidence; Analysis 1.1; Figure 4). If the chance of a clinical pregnancy was 5% in the placebo group, then between 8% and 50% of women in the clomiphene group would have a clinical pregnancy. We downgraded the evidence for imprecision

and insufficient methodological information to be able to judge risk of bias (Summary of findings for the main comparison).

Figure 4. Forest plot of comparison: 1 Antioestrogen versus no treatment or placebo, outcome: 1.1 Clinical pregnancy rate (per woman randomised).



Multiple pregnancy

No data were reported for this comparison.

OHSS

No data were reported for this comparison.

Adverse effects

No data were reported for this comparison.

2 Antioestrogen versus antioestrogen

Clomiphene citrate (50 mg to 200 mg) versus tamoxifen (20 mg to 60 mg)

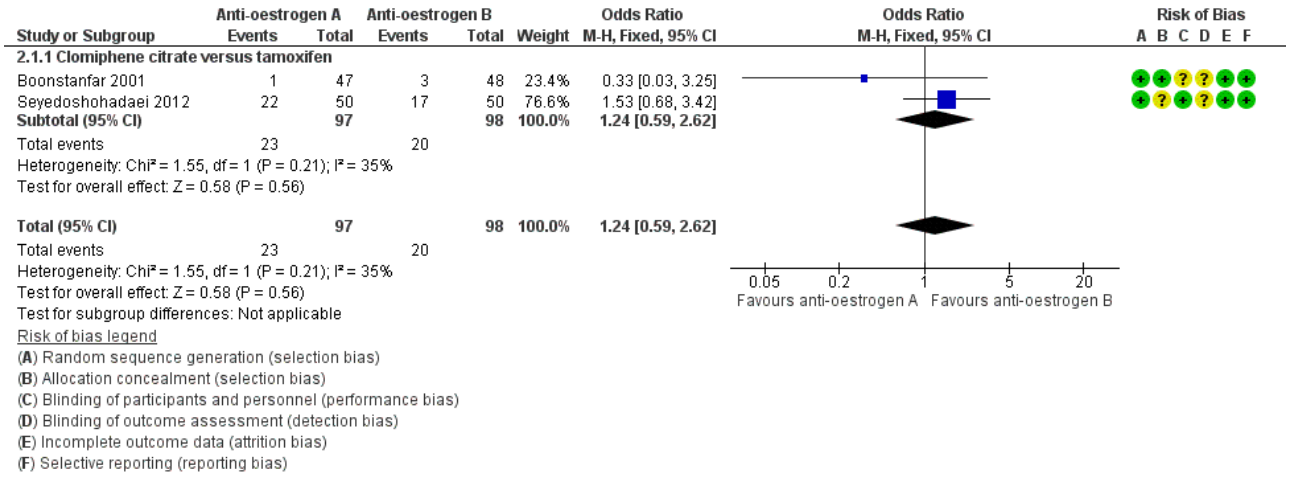
There were five studies in this comparison (Badawy 2011; Boonstanfar 2001; Moslemizadeh 2008; Seyedoshohadaei 2012; Vegetti 1999).

Primary outcomes

Live birth

Two studies reported on live birth (Boonstanfar 2001; Seyedoshohadaei 2012). There was no evidence of a difference in the chance of a live birth between the clomiphene citrate and tamoxifen groups (OR 1.24, 95% CI 0.59 to 2.62; 2 studies; 195 women; low-quality evidence; Analysis 2.1; Figure 5). If 20% of women in the tamoxifen group had a live birth, then between 13% to 40% of women in the clomiphene citrate group would have a live birth. We downgraded the evidence for imprecision (Summary of findings 2).

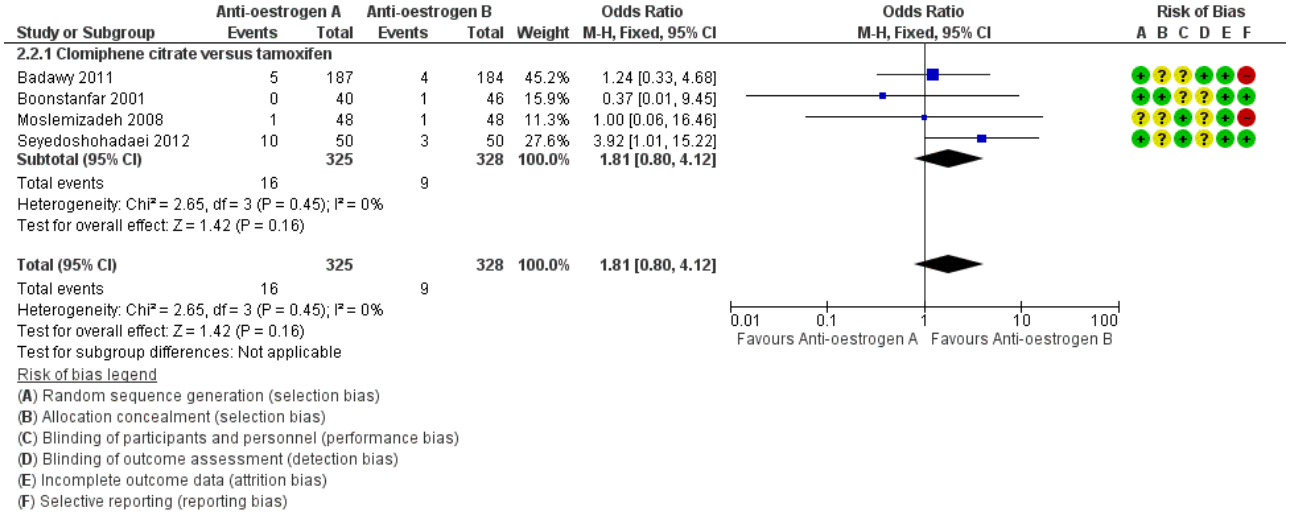
Figure 5. Forest plot of comparison: 2 Antioestrogen versus antioestrogen, outcome: 2.1 Live birth rate (per woman).



Miscarriage

Four studies reported on miscarriage (Badawy 2011; Boonstanfar 2001; Moslemizadeh 2008; Seyedoshohadaei 2012). There was no evidence of a difference in the chance of a miscarriage between the clomiphene citrate and tamoxifen groups (OR 1.81, 95% CI 0.80 to 4.12; 4 studies; 653 women; low-quality evidence; Analysis 2.2; Figure 6). If 3% of women in the tamoxifen group had a miscarriage, then between 2% and 10% of women in the clomiphene citrate group would have a miscarriage (Summary of findings 2). We downgraded the evidence for imprecision and risk of bias.

Figure 6. Forest plot of comparison: 2 Antioestrogen versus antioestrogen, outcome: 2.2 Miscarriage rate (per woman).



Secondary outcomes

Clinical pregnancy

All five studies reported data on clinical pregnancy (Badawy 2011; Boonstanfar 2001; Moslemizadeh 2008; Seyedoshohadaei 2012; Vegetti 1999). There was no evidence of a difference in the chance of a clinical pregnancy between the clomiphene citrate and tamoxifen groups (OR 1.30, 95% CI 0.92 to 1.85; 5 studies; 757 women; I^2 = 69%; low-quality evidence; Analysis 2.3). If 22% of women in the tamoxifen group had a clinical pregnancy, then between 21% and 35% of women in the clomiphene citrate group would have a clinical pregnancy (Summary of findings 2). We downgraded the evidence for inconsistency (heterogeneity) and risk of bias. The observed heterogeneity is most likely due to differences in study protocols; there were differences in number of cycles of treatment, dose of clomiphene citrate and tamoxifen, and start and end day of treatment in the menstrual cycles (refer to Characteristics of included studies).

Multiple pregnancy

Three studies reported on multiple pregnancy (Badawy 2011; Moslemizadeh 2008; Seyedoshohadaei 2012). There was insufficient evidence to determine whether there was a difference in the chance of a multiple pregnancy between the clomiphene citrate group (3 out of 285; 1%) and tamoxifen group (1 out of 282; < 1%) (OR 2.34, 95% CI 0.34 to 16.04; 3 studies; 567 women; very low-quality evidence). The data suggests that if 0% of women in the tamoxifen group had a multiple pregnancy, then between 0% and 0.5% of women in the clomiphene group would have a multiple pregnancy (Summary of findings 2). We downgraded the evidence for risk of bias and imprecision.

OHSS

There were no instances of OHSS in either the clomiphene citrate or the tamoxifen group (Badawy 2011; Boonstanfar 2001; Moslemizadeh 2008).

Adverse effects

No data were reported for this comparison.

Clomiphene citrate (50 mg) plus tamoxifen (20 mg) versus clomiphene citrate (100 mg)

Two trials reported on this comparison (Ghafourzadeh 2004; Suginami 1993).

Primary outcomes

Live birth

No data were reported for this comparison.

Miscarriage

No data were reported for this comparison.

Secondary outcomes

Clinical pregnancy

One small study reported on clinical pregnancy (Suginami 1993). There was insufficient evidence to determine whether there was a difference between the clomiphene citrate plus tamoxifen group and the clomiphene-alone group (OR 3.32, 95% CI 0.12 to 91.60; 1 study; 20 women). Caution is required in interpreting these data as they have high levels of imprecision with wide confidence intervals, small event rates, and small sample size (Analysis 2.3).

Multiple pregnancy

No data were reported for this comparison.

OHSS

No data were reported for this comparison.

Adverse effects

No data were reported for this comparison.

3 Antioestrogen versus gonadotropin

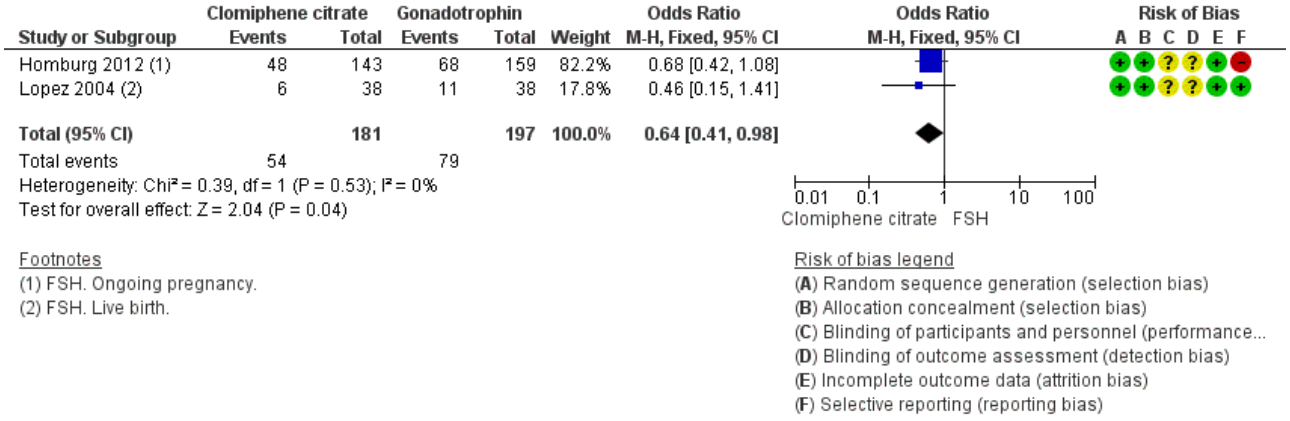
Three trials reported on this comparison. Two trials reported data for clomiphene citrate versus FSH (Homburg 2012; Lopez 2004), and one trial reported data for clomiphene citrate versus hMG (Badawy 2008).

Primary outcomes

Live birth/ongoing pregnancy

The evidence suggests that live birth/ongoing pregnancy is reduced with clomiphene citrate compared with gonadotropins (OR 0.64, 95% CI 0.41 to 0.98; 2 studies; 378 women; I^2 = 0%; Analysis 3.1, Figure 7). Lopez 2004 reported on live birth, and Homburg 2012 reported on ongoing pregnancy. Both trials used FSH as the gonadotropin. The Badawy 2008 trial only reported data for biochemical pregnancy and was therefore not included in the meta-analysis.

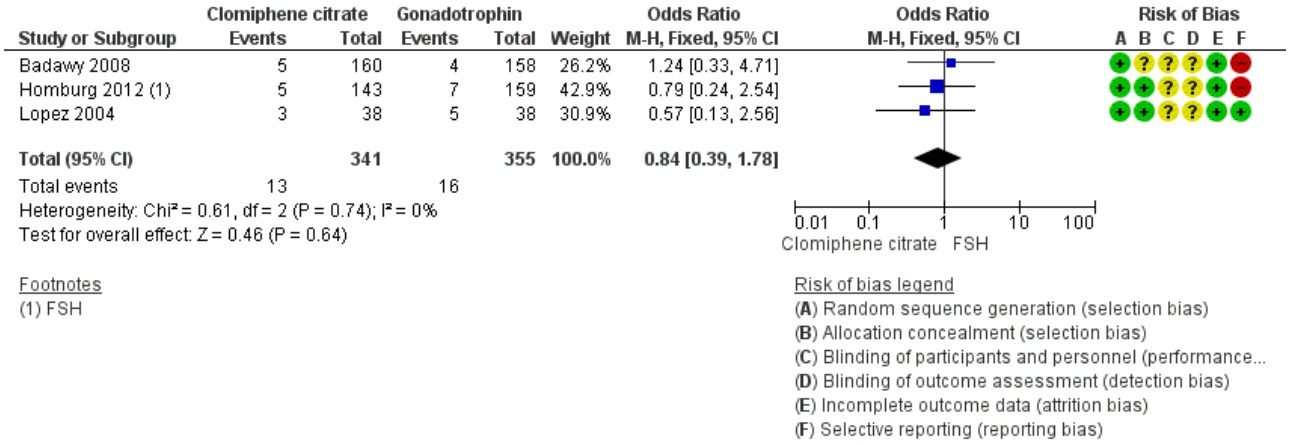
Figure 7. Forest plot of comparison: 3 Antioestrogen versus gonadotropin, outcome: 3.1 Live birth/ongoing pregnancy.



Miscarriage

There was no evidence of a difference between clomiphene citrate and gonadotropin for chance of miscarriage (OR 0.84, 95% CI 0.39 to 1.78; 3 studies; 696 women; I^2 = 0%; Analysis 3.2, Figure 8). Homburg 2012 and Lopez 2004 used FSH, and Badawy 2008 used hMG.

Figure 8. Forest plot of comparison: 3 Antioestrogen versus gonadotropin, outcome: 3.2 Miscarriage rate (per woman).



Secondary outcomes

Clinical pregnancy

The evidence suggests that clinical pregnancy is reduced with clomiphene citrate compared with gonadotropins (OR 0.61, 95% CI 0.40 to 0.93; 2 studies; 378 women; $I^2 = 0\%$). Both trials used FSH as the gonadotropin.

Multiple pregnancy

There was no evidence of a difference for chance of a multiple pregnancy between clomiphene citrate (2 out of 341; < 1%) and gonadotropins (9 out of 355; 3%) (OR 0.26, 95% CI 0.06 to 1.06; 3 studies; 696 women; $I^2 = 0\%$). Homburg 2012 and Lopez 2004 both used FSH, and Badawy 2008 used hMG. Caution is advised in interpreting these data due to low event rates.

OHSS

There was no evidence of a difference between groups for chance of developing OHSS (OR 0.19, 95% CI 0.02 to 1.67; 2 studies; 394 women; $I^2 = 0\%$). Lopez 2004 used FSH, and Badawy 2008 used hMG.

Adverse effects

No data were reported for this comparison.

4 Antioestrogen plus other medical therapy versus antioestrogen alone

Clomiphene citrate (up to 150 mg) plus ketoconazole (400 mg) versus clomiphene citrate (up to 150 mg)

One study reported this comparison (Hassan 2001).

Primary outcomes

Live birth

No data were reported for this comparison.

Miscarriage

One instance of miscarriage was reported in the clomiphene citrate-alone group in the Hassan 2001 study. There were no events in the clomiphene citrate plus ketoconazole group (OR 0.28, 95% CI 0.01 to 7.08; 1 study; 80 women; very low-quality evidence; Summary of findings 3). The evidence suggests that if 2.7% of women in the clomiphene group had a miscarriage, then between 0% and 16% of women the in the clomiphene plus ketoconazole group would have a miscarriage. We downgraded the evidence for low event rates, small sample size, and the evidence being based on a single study (imprecision) (Summary of findings 3).

Secondary outcomes

Clinical pregnancy

There was no evidence of a difference between clomiphene citrate plus ketoconazole and clomiphene citrate alone for chance of a clinical pregnancy (OR 2.37, 95% CI 0.88 to 6.40; 1 study; 80 women; very low-quality evidence; Summary of findings 3). The evidence suggests that if 22% of women in the clomiphene group had a clinical pregnancy, then between 20% and 64% of women in the clomiphene plus ketoconazole group would have a clinical pregnancy. We downgraded the evidence for low event rates, small sample size, and the evidence being based on a single study (imprecision) (Summary of findings 3).

Multiple pregnancy

There was no evidence of a difference for chance of a multiple pregnancy between clomiphene plus ketoconazole (8 out of 43; 19%) and clomiphene alone (6 out of 37; 16%) (OR 1.18, 95% CI 0.37 to 3.78; 1 study; 80 women; very low-quality evidence; Summary of findings 3). The evidence suggests that if 16% of women in the clomiphene group had a multiple pregnancy, then between 7% and 42% of women in the clomiphene plus ketoconazole group would have a multiple pregnancy. We downgraded the evidence for low event rates, small sample size, and the evidence being based on a single study (imprecision) (Summary of findings 3).

OHSS

No data were reported for this comparison.

Adverse effects

No data were reported for this comparison.

Clomiphene citrate (50 mg to 200 mg) plus bromocriptine (2.5 mg to 7.5 mg) versus clomiphene citrate (50 mg to 200 mg)

Two trials reported this comparison (Analysis 4.2) (Parsanezhad 2002b; Tripathy 2013).

Primary outcomes

Live birth

No data were reported for this comparison.

Miscarriage

No data were reported for this comparison.

Secondary outcomes

Clinical pregnancy

There was no evidence of a difference in chance of a clinical pregnancy between clomiphene citrate plus bromocriptine compared with clomiphene citrate alone (OR 1.03, 95% CI 0.48 to 2.21; 2 studies; 174 women; low-quality evidence). The evidence suggests that if 19% of women in the clomiphene group had a clinical pregnancy, then between 10% and 34% of women in the clomiphene plus bromocriptine group would have a clinical pregnancy. We downgraded the evidence for low event rate and small sample size (imprecision) (Summary of findings 3).

Multiple pregnancy

No data were reported for this comparison.

OHSS

No data were reported for this comparison.

Adverse effects

No data were reported for this comparison.

Clomiphene (50 mg to 200 mg) plus dexamethasone (0.5 mg to 2.0 mg) versus clomiphene citrate (50 mg to 200 mg)

Four trials reported on this comparison (Analysis 4.3) (Daly 1984; Elnashar 2006; Esmaeilzadeh 2011; Parsanezhad 2002a).

Primary outcomes

Live birth

No data were reported for this comparison.

Miscarriage

No data were reported for this comparison.

Secondary outcomes

Clinical pregnancy

All four trials reported on clinical pregnancy. Clomiphene plus dexamethasone was associated with an increase in the chance of a clinical pregnancy (average OR 6.20, 95% CI 2.20 to 17.48; 4 studies; 434 women; random-effects I^2 = 64%; very low-quality evidence). Three trials used a 2 mg dose of dexamethasone (Elnashar 2006; Esmaeilzadeh 2011; Parsanezhad 2002a), and one trial used a 0.5 mg dose (Daly 1984). The removal of the Daly 1984 trial did not affect the direction of the treatment effect or the statistical significance. The evidence suggests that if 8% of women in the clomiphene group had a clinical pregnancy, then between 16% and 61% of women in the clomiphene plus dexamethasone group would have a clinical pregnancy. We downgraded the evidence for risk of bias, imprecision, and inconsistency (Summary of findings 3).

Multiple pregnancy

There was no evidence of a difference in the incidence of multiple pregnancy per woman between clomiphene citrate plus dexamethasone compared with clomiphene citrate alone (OR 7.71, 95% CI 0.38 to 155.64; 2 studies; 144 women; low-quality evidence) (Daly 1984; Elnashar 2006). We could not calculate absolute risk, as no events were reported in either group in one of the trials. Three multiple pregnancies were reported in the clomiphene plus dexamethasone group (Daly 1984); no other cases of multiple pregnancy were reported. The Daly 1984 trial used a 0.5 mg dose of dexamethasone, and the Elnashar 2006 trial used a 2 mg dose of dexamethasone. It is unclear if the dosage of dexamethasone influenced the outcome due to the small number of events, if any, that were reported.

OHSS

No data were reported for this comparison.

Adverse effects

No side effects were reported by Elnashar 2006 in either group.

Clomiphene citrate (100 mg) plus combined oral contraceptive versus clomiphene citrate (100 mg)

One study reported on this comparison (Branigan 2003).

Primary outcomes

Live birth

No data were reported for this comparison.

Miscarriage

There was no evidence of a difference in miscarriage rate between women treated with clomiphene citrate plus combined oral contraceptive and women treated with clomiphene citrate alone (OR 1.0, 95% CI 0.06 to 16.97; 1 study; 48 women; very low-quality evidence). The evidence suggests that if 4% of women in the clomiphene citrate group had a miscarriage, then between 0% and 43% of women in the clomiphene citrate plus oral contraceptive group would have a miscarriage. We downgraded the evidence for low event rate and small sample size and the evidence being based on a single study (imprecision) (Summary of findings 3).

Secondary outcomes

Clinical pregnancy

Clomiphene citrate plus combined oral contraceptive was associated with an increased chance of a clinical pregnancy compared with clomiphene citrate alone (OR 27.18, 95% CI 3.14 to 235.02; 1 study; 48 women; very low-quality evidence). The evidence suggests that if 4% of women in the clomiphene citrate group had a clinical pregnancy, then between 12% and 91% of women in the clomiphene citrate plus combined oral contraceptive group would have a clinical pregnancy. We downgraded the evidence for low event rate and small sample size and the evidence being based on a single study (imprecision) (Summary of findings 3).

Multiple pregnancy

There was no evidence of a difference in the chance of a multiple pregnancy between clomiphene citrate plus combined oral contraceptive and clomiphene citrate alone (OR 7.98, 95% CI 0.39 to 163.33; 1 study; 48 women; very low-quality evidence). We could not calculate absolute risk estimates, as there were no events in the control group. We downgraded the evidence for low event rate and small sample size and the evidence being based on a single study (imprecision) (Summary of findings 3).

OHSS

No data were reported for this comparison.

Adverse effects

No data were reported for this comparison.

Clomiphene citrate plus hCG versus clomiphene citrate

Two trials reported this comparison (Analysis 4.5) (Branigan 2005; Yilmaz 2006).

Primary outcomes

Live birth/ongoing pregnancy rate

There was no evidence of a difference between groups for ongoing pregnancy reported by Yilmaz 2006 (OR 1.31, 95% CI 0.61 to 2.80; 1 study; 125 women; very low-quality evidence). The evidence suggests that if 28% of women had an ongoing pregnancy in the clomiphene citrate group, then between 19% and 52% of women in the clomiphene citrate plus hCG group would have an ongoing pregnancy. We downgraded the evidence for low event rate and small sample size and the evidence being based on a single study (imprecision) (Summary of findings 3).

Miscarriage

There was no evidence of a difference in the chance of miscarriage between clomiphene citrate plus hCG and clomiphene citrate alone (OR 0.70, 95% CI 0.19 to 2.62; 2 studies; 192 women; moderate-quality evidence). The evidence suggests that if 6% of women in the clomiphene citrate group had a miscarriage, then between 1%

and 15% of women in the clomiphene citrate plus hCG group would have a miscarriage. We downgraded the evidence for low event rate and small sample size (imprecision) (Summary of findings 3).

Secondary outcomes

Clinical pregnancy rate

There was no evidence of a difference in the chance of a clinical pregnancy between clomiphene citrate plus hCG and clomiphene citrate alone (OR 1.18, 95% CI 0.59 to 2.36; 2 studies; 192 women; moderate-quality evidence). The evidence suggests that if 24% of women in the clomiphene group had a clinical pregnancy, then between 15% and 42% of women in the clomiphene plus hCG group would have a clinical pregnancy. We downgraded the evidence for low event rate and small sample size (imprecision) (Summary of findings 3).

Multiple pregnancy rate

Only Yilmaz 2006 reported on multiple pregnancies, and there was no evidence of a difference between clomiphene citrate plus hCG (2 out of 60; 3%) and clomiphene citrate alone (1 out of 65; 2%) (OR 2.21, 95% CI 0.19 to 24.98; 1 study; 125 women; very low-quality evidence). The evidence suggests that if 2% of women in the clomiphene group had a multiple pregnancy, then between 0% and 28% of women in the clomiphene plus hCG group would have a multiple pregnancy. We downgraded the evidence for low event rate and small sample size and the evidence being based on a single study (imprecision) (Summary of findings 3).

OHSS

No data were reported for this comparison.

Adverse effects

No data were reported for this comparison.

Clomiphene citrate plus hormone supplementation versus clomiphene citrate

Two trials reported this comparison (Analysis 4.6) (Elkind-Hirsch 2005; Moslemizadeh 2008).

Primary outcomes

Live birth rate

No data were reported for this comparison.

Miscarriage rate

One event of miscarriage was reported for both the clomiphene citrate plus hormone supplementation and the clomiphene citrate-alone groups. There was no statistical difference between the groups (OR 1.00, 95% CI 0.06 to 16.46; 1 study; 96 women; very low-quality evidence). The evidence suggests that if 2% of women in the clomiphene citrate group had a miscarriage, then between 0% and 26% of women in the clomiphene citrate plus hormone supplementation group would have a miscarriage. We downgraded the evidence for low event rates and small sample size and the evidence being based on a single trial (imprecision) (Summary of findings 3).

Secondary outcomes

Clinical pregnancy rate

There was no evidence of a difference in the chance of a clinical pregnancy between the clomiphene citrate plus hormone supplementation and the clomiphene citrate-alone groups (OR 0.81, 95% CI 0.37 to 1.76; 2 studies; 161 women; low-quality evidence). The evidence suggests that if 22% of women in the clomiphene citrate group had a clinical pregnancy, then between 9% and 33% of women in the clomiphene citrate plus hormone supplementation group would have a clinical pregnancy. We downgraded the evidence for low event rates and small sample size (imprecision) (Summary of findings 3).

Multiple pregnancy rate

There were no events of multiple pregnancy in either the clomiphene citrate plus hormone supplementation or the clomiphene citrate-alone group, reported in one trial of 96 women (Moslemizadeh 2008), therefore we could not calculate absolute risk.

OHSS

There were no events of OHSS in either the clomiphene citrate plus hormone supplementation or the clomiphene citrate-alone group, reported in one trial of 96 women (Moslemizadeh 2008), therefore we could not calculate absolute risk.

Adverse effects

There were no reports of adverse effects in either the clomiphene citrate plus hormone supplementation or the clomiphene citrate-alone group (OR 0.21, 95% CI 0.01 to 4.47; 1 study; 65 women). Caution is required in interpreting these data due to low event rates and small sample size, which increases the risk of imprecision. There were wide confidence intervals that cross the line of no effect.

5 Antioestrogen plus other medical therapy versus antioestrogen plus other medical therapy

No trials were found reporting data for this comparison.

6 Clomiphene citrate regimens

Clomiphene citrate for 5 days versus clomiphene citrate for 10 days

Two trials reported this comparison (Elsedeek 2014; Omran 2011). Both trials used a regimen of 200 mg clomiphene citrate per day for 5 days or 100 mg clomiphene citrate per day for 10 days.

Primary outcomes

Live birth rate

One trial reported that clomiphene citrate for 10 days was associated with an increased chance of a live birth compared with the 5-day regimen (OR 0.10, 95% CI 0.02 to 0.45; 1 study; 220 women; low-quality evidence) (Elsedeek 2014). The evidence suggests that if 16% of women in the 10-day regimen group had a live birth, then between 0% and 8% of women in the 5-day regimen group would have a live birth. We downgraded the evidence for low event rates and the evidence being based on a single trial (imprecision) (Summary of findings 4).

Miscarriage rate

No data were reported for this comparison.

Secondary outcomes

Clinical pregnancy rate

One trial reported that clomiphene citrate for 10 days was associated with an increased chance of a clinical pregnancy (OR 0.18, 95% CI 0.06 to 0.55; 1 study; 220 women; low-quality evidence) (Elsedeek 2014). The evidence suggests that if 17% of women in the 10-day regimen group had a clinical pregnancy, then between 1% and 10% in the 5-day regimen group would have a clinical pregnancy.We suggest caution when interpreting these data due to low event rates and the evidence being based on a single trial (imprecision) (Summary of findings 4). Further research is needed to confirm this benefit for an extended regimen.

Multiple pregnancy rate

There was no evidence of a difference between the 5-day regimen (1 out of 110; < 1%) and the 10-day regimen (3 out of 110; 3%), reported by Elsedeek 2014 (OR 0.33, 95% CI 0.03 to 3.20; 1 study; 220 women; very low-quality evidence). The evidence suggests that if 3% of women in the 10-day regimen group had a multiple pregnancy, then between 0% and 8% in the 5-day regimen group would have a multiple pregnancy. We downgraded the evidence for low event rates and small sample size and the evidence being based on a single trial (imprecision) (Summary of findings 4.

OHSS

No data were reported for this comparison.

Adverse effects

No data were reported for this comparison.

Early versus late clomiphene citrate

Two trials reported this comparison (Badawy 2009; Dehbashi 2006). Badawy 2009 used a regimen of 5 days of 100 mg per day clomiphene citrate starting on the day after finishing medroxyprogesterone (early regimen) compared with 5 days of 100 mg per day clomiphene citrate starting on Day 3 of menses (late regimen). Dehbashi 2006 used a regimen of 100 mg clomiphene citrate per day on Days 1 to 5 of the menstrual cycle (early regimen) compared with 100 mg clomiphene citrate per day on Days 5 to 9 of the menstrual cycle (late regimen).

Primary outcomes

Live birth

No data were reported for this comparison.

Miscarriage

One trial reported no evidence of a difference in chance of a miscarriage between early and late clomiphene citrate regimens (OR 1.25, 95% CI 0.27 to 5.70; 1 study; 212 women; very low-quality evidence) (Badawy 2009). The evidence suggests that if 3% of women in the late-regimen group had a miscarriage, then between 1% and 15% of women in the early-regimen group would have a miscarriage. We downgraded the evidence for being based on a single trial (imprecision) and risk of bias (Summary of findings 4).

Secondary outcomes

Clinical pregnancy

One trial reported that an early regimen of clomiphene citrate was associated with an increased chance of a clinical pregnancy compared with a late regimen of clomiphene citrate (OR 2.81, 95% CI 1.02 to 7.75; 1 study; 78 women; low-quality evidence) (Dehbashi 2006). The evidence suggests that if 20% of women in the late-regimen group had a clinical pregnancy, then between 20% and 65% of women in the early-regimen group would have a clinical pregnancy. We downgraded the evidence for being based on a single trial (imprecision) (Summary of findings 4).

Multiple pregnancy

No data were reported for this comparison.

OHSS

No data were reported for this comparison.

Adverse effects

No data were reported for this comparison.

DISCUSSION

Summary of main results

Clomiphene citrate versus placebo

Analysis of the three trials comparing clomiphene with placebo showed that clomiphene improves the chance of pregnancy (Summary of findings for the main comparison).

Clomiphene citrate versus tamoxifen

Five trials comparing clomiphene with tamoxifen showed no clear evidence of a difference in live birth, clinical pregnancy, miscarriage, or multiple pregnancy rate. No cases of OHSS were reported.

Clomiphene citrate plus tamoxifen versus clomiphene citrate

Two trials compared clomiphene citrate plus tamoxifen with clomiphene citrate alone. The evidence was insufficient to determine whether there was a difference in clinical pregnancy rates. No other outcomes were reported for this comparison (Summary of findings 2).

Clomiphene citrate versus gonadotropin

Three trials compared clomiphene citrate with gonadotropins. Clomiphene citrate was associated with a reduced chance of a clinical pregnancy, ongoing pregnancy, or live birth. There was no evidence of a difference between groups for chance of a multiple pregnancy, although event rates were very low and therefore data should be interpreted with caution.

Clomiphene citrate plus medical adjunct versus clomiphene citrate

Data were reported for six different medical adjuncts used with clomiphene citrate and compared with clomiphene citrate alone (Summary of findings 3).

One small study of 80 women reported limited evidence using ketoconazole as an adjunct. There was no evidence of a difference

between clomiphene plus ketoconazole and clomiphene alone for miscarriage, clinical pregnancy, or multiple pregnancy. Event rates were low and therefore data should be interpreted with caution. The results are open to some misinterpretation, as the trial authors moved women who failed to respond to 150 mg clomiphene to hMG treatment. No data were provided on the numbers from each group, however it would be reasonable to assume that more women from the control group, with its higher rates of clomiphene resistance, required this.

Two trials reported the use of bromocriptine as an adjunct. There was no evidence of a difference for clinical pregnancy rates between groups. No other relevant outcomes were reported.

Four trials reported using dexamethasone as an adjunct. Clomiphene citrate plus dexamethasone was associated with an increased chance of a clinical pregnancy when compared with clomiphene citrate alone. Three of the four trials used a dose of 2 mg dexamethasone. There was no evidence of a difference between groups for multiple pregnancy. None of the trials used the same protocol for treatment, which could explain the observed heterogeneity. Despite this, dexamethasone shows potential as an inexpensive and non-invasive treatment option for women with PCOS, perhaps especially those who have failed to respond to standard therapy.

One small trial reported on combined oral contraceptive (COC) pill used as an adjunct. Clomiphene citrate plus COC was associated with an increase in clinical pregnancy, with no evidence of a difference in miscarriage or multiple pregnancy rate when compared with clomiphene citrate alone. Event rates and sample size (n = 48 women) were small and therefore data should be interpreted with caution. Further trials are needed to establish if COC is indeed a safe and effective adjunct to clomiphene citrate.

The use of hCG as an adjunct showed no evidence of a difference in miscarriage, clinical pregnancy, or multiple pregnancy rate when compared with clomiphene citrate alone.

Two studies reported hormone supplementation as an adjunct, finding no evidence of a difference in miscarriage or clinical pregnancy. No events were reported for multiple pregnancy or OHSS.

Clomiphene citrate regimens

Clomiphene citrate given for 10 days was associated with an increased chance of live birth and clinical pregnancy compared with a 5-day regimen. There was no evidence of a difference for multiple pregnancy (Summary of findings 4).

Data for early versus late regimens were insufficient to be able to draw any conclusions regarding the benefits of one over the other.

Overall completeness and applicability of evidence

We believe we have used rigorous methods to identify published and unpublished trials by searching multiple electronic databases with no restriction on language. Trials were reported from various countries. Many of the comparisons included in this review only had one or two relevant trials, and the sample sizes were small, which increases the risk of imprecision. In particular, data for multiple pregnancies were very limited. The trials that compared an antioestrogen with no treatment or placebo did not report multiple pregnancy as a clinical outcome. There were no data on self reported adverse effects.

Quality of the evidence

Limitations of the review

All of the trials included in this review have methodological flaws, including lack of clarity around randomisation and allocation concealment, lack of blinding, and attrition, which weaken the results.

Using GRADE methodology, we judged the evidence to be of low quality for the comparisons of antioestrogen versus no treatment or placebo (Summary of findings for the main comparison) and antioestrogen versus antioestrogen (Summary of findings 2). We downgraded much of the evidence for risk of bias and imprecision. More rigorous RCTs are required for all of the interventions.

Live birth rate is the gold-standard primary outcome for RCTs of this nature (Vail 2003). Only five of the 28 included trials in this review reported this outcome (Boonstanfar 2001; Elsedeek 2014; Homburg 2012; Lopez 2004; Seyedoshohadaei 2012). Using pregnancy rate as a surrogate endpoint is of dubious accuracy. Other poorly reported outcomes included adverse effects and incidence of OHSS. OHSS is a rare but potentially life-threatening complication of ovulation induction therapy; it is an important outcome, but if it did not occur in the trial populations it may not have been reported. Multiple pregnancy was poorly reported, and where data were available, event rates were low, making it uncertain if the interventions were influencing the outcome.

Potential biases in the review process

We believe we have conducted a thorough review of the literature searching for relevant published and unpublished trials, unrestricted by date or language. There were insufficient trials (fewer than 10) for each comparison to allow us to investigate publication bias via inspection of funnel plots.

Agreements and disagreements with other studies or reviews

NICE 2013 recommends clomiphene as a first-line treatment option for women with WHO group 2 anovulatory infertility, taking into account potential adverse effects, ease and mode of use, the woman's body mass index, and monitoring needed.

AUTHORS' CONCLUSIONS

Implications for practice

We have not found strong evidence in favour of one antioestrogen or adjunctive agent. We found evidence supporting the effectiveness of the current first-line treatment, clomiphene citrate, in terms of pregnancies, although there is a reduced chance of clinical pregnancy, ongoing pregnancy, or live birth when compared with gonadotropins. It is unclear whether there is a difference in effect between clomiphene plus tamoxifen and clomiphene alone, as the number of women studied was too small to be conclusive. We could find no trials comparing tamoxifen and placebo.

There were insufficient data to determine the place of ketoconazole, tamoxifen, bromocriptine, human chorionic

gonadotropin, or hormone supplementation as an adjunct to clomiphene versus clomiphene alone in anovulatory, normoprolactinaemic women. Due to the limited reporting of multiple pregnancy as a clinical outcome, we are unable to judge the effect of antioestrogens on this outcome and therefore suggest that the monitoring of ovulation induction with serum hormones and preferably vaginal ultrasound should be considered in order to minimise the risk of multiple gestation.

Implications for research

Clomiphene is currently widely accepted as an effective treatment, and it is unlikely that further trials against placebo will be conducted. Large, well-designed randomised controlled trials are needed comparing the long-standing interventions such as clomiphene with the medical adjunctive drugs (in particular dexamethasone), and the newer drugs such as aromatase inhibitors. In addition, studies on the duration of treatment with clomiphene should be planned. Differentiation between results by aetiology of anovulation is also needed in new trials.

We suggest further research is required to confirm the potential benefit in the improved clinical pregnancy rate observed in a single trial comparing a 10-day with a 5-day regimen.

This review reports that currently available trials are often of poor quality and have potentially serious methodological and selective-reporting flaws, primarily due to lack of data on live birth. Randomised controlled trials should follow the CONSORT guidelines (Moher 2001). Trials should be of sufficient duration to have live birth as their primary outcome and should ideally report all secondary outcomes listed in this review, in particular incidence of multiple pregnancy and miscarriage. All rates should be reported per woman, not per cycle, and in actual numbers of participants, not percentages.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Badawy 2008

Methods	Parallel randomised controlled trial
Participants	318 women randomised Inclusion criteria: diagnosed with PCOS, patent fallopian tubes. Normal semen analysis in male partners. Exclusion criteria: Not stated Setting: outpatient clinic in Mansoura University Hospitals, Mansoura University, Egypt and a private practice setting Timing: May 2004 to May 2007
Interventions	Clomiphene citrate - 100 mg of clomiphene citrate daily starting on Day 2 of menses for 9 days (n = 160 women) versus Gonadotropin - human menopausal gonadotropin 75 IU intramuscularly daily for 5 days starting on Day 3 of menses (n = 158 women)
Outcomes	The primary outcome measures were the number of growing and mature follicles, serum oestradiol (pg/mL), serum progesterone (ng/mL), and endometrial thickness (mm). Secondary outcome measures were the occurrence of biochemical pregnancy and miscarriage.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated random table"
Allocation concealment (selection bias)	Unclear risk	Allocated by researcher
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding of participants
Blinding of outcome assessment (detection bias)	Unclear risk	No details

Badawy 2008 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 woman in the gonadotropin group was lost to follow-up.
Selective reporting (reporting bias)	High risk	Only reported data for biochemical pregnancy

Badawy 2009

Methods	Randomised controlled trial
Participants	212 women with PCOS Inclusion criteria: not clear, but included women with patent fallopian tubes and normal semen analysis in partners Exclusion criteria: not stated Setting: gynaecology outpatient clinic in Egypt Timing: November 2004 to March 2007
Interventions	Withdrawal bleeding using 10 mg medroxyprogesterone acetate (MPA) for 10 days before stimulation Early CC - 100 mg clomiphene citrate daily starting the next day after finishing MPA for 5 days (n = 110 women, 227 cycles) Late CC - 100 mg clomiphene citrate daily for 5 days starting on Day 3 of menses (n = 102 women, 211 cycles) hCG 5000 to 10,000 IU given IM when at least 1 follicle was 18 mm or greater in diameter. Women advised to have intercourse 24 to 36 hours after hCG injection.
Outcomes	Primary outcomes: number of growing and mature follicles, serum E2, endometrial thickness Secondary outcomes: pregnancy (biochemical after 2 weeks), miscarriage
Notes	Sample size calculation: no ITT analysis: yes Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomly allocated using computer-generated random table"
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	Unclear risk	No details, but blinding unlikely to have affected outcome

Badawy 2009 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details, but blinding unlikely to have affected outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data reported for all women randomised
Selective reporting (reporting bias)	High risk	Authors state that groups were balanced at baseline for demographics. However FSH and LH levels were significantly higher in the late-CC group and the total number of follicles and the number of follicles ≥14 and 18 mm diameter were greater in the early-CC group. Live birth data were not reported.

Badawy 2011

Methods	Randomised controlled trial
Participants	371 women Age: clomiphene group 25.8 ± 2.1 years, tamoxifen group 26.2 ± 2.2 years Duration of infertility (months): clomiphene group 18.0 ± 7.2, tamoxifen group 16.8 ± 6.0 Inclusion criteria: women diagnosed with PCOS (ESHRE/ASRM 2003), patent fallopian tubes, normal semen analysis Setting: outpatient clinic, Egypt Timing: December 2005 to December 2009
Interventions	Clomiphene citrate (n = 187) - 1 cycle 100 mg/day from Day 3 for 5 days versus Tamoxifen (n = 184) - 1 cycle 20 mg/day from Day 3 for 5 days
Outcomes	Primary: number of follicles, serum E2, endometrial thickness, ovulation rate Secondary: clinical pregnancy rate, miscarriage
Notes	Sample size calculation: yes, based on pregnancy rate ITT: yes Funding: not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Computer generated random table"
Allocation concealment (selection bias)	Unclear risk	"Allocation done by the investigators"; no other details

Badawy 2011 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Neither women nor investigators were blinded, but unlikely to affect outcome.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcome assessors were blinded to allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	High risk	Multiple pregnancy and OHSS reported but not prespecified. Did not report on live birth.

Boonstanfar 2001

Methods	Parallel randomised controlled trial
Participants	95 women (86 analysed) Inclusion criteria: anovulation with no other cause of infertility Age: CC 26.5 ± 4.3, TMX 26.6 ± 4.3 Duration of infertility: CC 3.7 ± 2.5 years, TMX 3.5 ± 2.9 years Exclusion criteria: uterine or adnexal pathology, abnormal HSG, abnormal semen analysis, age > 40 years, hyperprolactinaemia, hypo- or hyperthyroidism, FSH > 20 mIU/mL, progesterone > 3.0 ng/mL, previous exposure to ovulation induction agents, hepatic or renal disease, presence of a contraindication to trial drugs Location: Los Angeles, USA Setting: not stated
Interventions	Treatment(s): Both groups had a progesterone-induced withdrawal bleed and then either 50 mg CC on Days 5 to 9, increased to 100 mg, and then 150 mg if woman remained anovulatory (n = 47); or 20 mg TMX on Days 5 to 9, increased to 40 mg, and then 60 mg if woman remained anovulatory (n = 48). Control or placebo: none Duration: not stated
Outcomes	Relevant outcomes: live birth (incomplete follow-up), pregnancy, ovulation, miscarriage (no definition), multiple birth, OHSS, and women-reported adverse effects
Notes	Contacted authors re: power calculation, blinding, funding, and ongoing pregnancy results; received no reply ITT: no

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random number table
Allocation concealment (selection bias)	Low risk	Adequate - opaque envelopes

Boonstanfar 2001 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding unlikely to have affected outcome
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women accounted for. Of 95 women randomised, 86 analysed, 9 did not return for follow-up.
Selective reporting (reporting bias)	Low risk	All stated outcomes reported on.

Branigan 2003

Methods	Parallel randomised controlled trial
Participants	48 women randomised (48 women analysed) Inclusion criteria: anovulation while receiving ≥ 150 mg clomiphene; under 36 years old; tubal patency (HSG/laparoscopy); normal fasting glucose and insulin; normal prolactin, thyroid-stimulating hormone, and FSH levels; DHEAS ≤ 200 ug/mL; norm oestrogenic; no contraindication to COC use; and partner with normal semen analysis Age: 28.2 ± 3.4 Duration of infertility: 2.4 ± 0.8 Exclusion criteria: not stated Setting: Private tertiary infertility clinic; Bellingham, WA, USA
Interventions	Treatment(s): COC (0.03 mg ethinyl estradiol and 0.15 mg desogestrel (Desogen)) continuously for 42 to 50 days followed by 1 cycle of 100 mg CC (Days 5 to 9); 10,000 IU hCG ovulation trigger Control/placebo: 38 to 56 days no treatment followed by 1 cycle of 100 mg CC (Days 5 to 9); 10,000 IU hCG ovulation trigger Duration: up to 6 cycles of CC for those women who ovulated but did not become pregnant in the first cycle
Outcomes	Relevant outcomes: ovulation, pregnancy, multiple pregnancy, miscarriage (no definition)
Notes	Contacted authors re: randomisation and allocation concealment, treatment protocol, adverse effects, and definitions used; received no reply Power calculation: yes ITT: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised permuted blocks of 4
Allocation concealment (selection bias)	Unclear risk	Adequate - opaque envelopes

Branigan 2003 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details, but blinding unlikely to have affected outcome
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women randomised analysed
Selective reporting (reporting bias)	High risk	No report of live birth

Branigan 2005

Methods	Randomised, parallel, 2-arm study
Participants	70 women randomised (66 women analysed) Inclusion criteria: previously documented dominant follicle or follicles ≥12 mm mean diameter on transvaginal ultrasound follicular monitoring while receiving CC at the 100 mg dose but failed to ovulate; under the age of 40 years; documented normal uterine cavity and patent tubes by either HSG or laparoscopy and hysteroscopy; normal fasting glucose and insulin levels; normal prolactin, thyroid-stimulating hormone, and FSH; DHEAS sulphate levels of 200 µg/mL or less; normal semen analysis according to WHO criteria in male partner Age: mean age of CC + hCG group 34.1 ± 1.1 years, mean age of CC-only group 33.4 ± 1.3 years Duration of infertility: no details Exclusion criteria: not stated Setting: Private tertiary infertility clinic; USA
Interventions	Transvaginal ultrasound follicular monitoring started on Day 12 and was repeated every 1 to 2 days until mean diameter of lead follicle was greater than 20 mm. Treatment(s): CC + hCG: CC 100 mg on Days 5 to 9 plus daily IM injections of 200 IU hCG when the lead follicle was 12 mm or larger until 20 mm or larger was attained. (If the follicle diameter failed to increase by more than 1 mm per day after 14 mm or 14 mm was not achieved, monitoring was ceased and the cycle cancelled) (n =35) Control or placebo: CC-only 150 mg Days 5 to 9 (n = 35) Both groups received 10,000 IU hCG IM injection when lead follicle diameter was 20 mm or greater. Timed intercourse advised on day of hCG injection and following day. Duration: 1 cycle
Outcomes	Relevant outcomes: ovulation rate, endometrial thickness, number of follicles, E2 levels, testosterone levels, P4 levels, pregnancy rate
Notes	Pregnancy confirmed by serum hCG and 7-week gestational ultrasound. BMI group 1: 21.3 ± 0.4, group 2: 21.2 ± 0.3 Power calculation: yes, based on expected ovulation rate ITT: yes

Branigan 2005 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random permuted blocks with a block size of 4 used to generate the 2 groups.
Allocation concealment (selection bias)	Low risk	The group assignments were contained in consecutively numbered, opaque envelopes, which were opened after the women were enrolled in the study.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding unlikely to have affected outcome
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number of women randomised: 70 Number of women analysed: 66 Number of withdrawals and reasons: 1 woman in CC + hCG group and 3 women in CC-only group did not begin the study.
Selective reporting (reporting bias)	High risk	Results section reported on additional relevant outcomes to those stated in the methods section. No details of adverse events, no report of live birth

Cudmore 1966

Methods	Cross-over trial
Participants	22 women randomised (22 women analysed) Inclusion criteria: All women stated as anovulatory. Secondary amenorrhoea (> 2 years) or oligomenorrhoea (no more than 4 periods a year and none in the 3 months prior to study) or anovulatory infertility (> 2 years); no infertility treatment in the 3 months prior to the study; no other cause of infertility found Exclusion criteria: not stated Age: treatment: 18 to 33, placebo: 20 to 29 Duration of infertility: not stated Setting: Halifax, Canada
Interventions	Treatment(s): 50 mg CC (Days 1 to 14) (n = 13) Control or placebo: placebo (Days 1 to 14) (n = 9) Duration: 3 cycles, then 3 cycles
Outcomes	Relevant outcomes: ovulation and women-reported adverse effects, hormonal responses
Notes	Authors not contacted as trial published > 15 years ago. Power calculation: not stated ITT: yes Source of funding: Support and drug supplied by Wm S Merrell Company, Cincinnati, OH, USA

Risk of bias

Cudmore 1966 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Entered treatment group by chance
Allocation concealment (selection bias)	Unclear risk	Coded, but unclear if this was centrally administered
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but not stated who was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind, but not stated who was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women accounted for.
Selective reporting (reporting bias)	High risk	Pregnancy not noted as an outcome in methods but described in results. No adverse events or miscarriage reported, no report of live birth.

Daly 1984

Methods	Parallel randomised controlled trial
Participants	64 women randomised (45 women analysed) Inclusion criteria: either anovulatory as evidenced by basal body temperature charting or oligomenorrhoeic but responsive to progesterone. No previous exposure to clomiphene Age: not stated Duration of infertility: not stated Exclusion criteria: hyperprolactinaemia, hyper- or hypothyroidism, major male factor, tubal disease (HSG) Setting: USA
Interventions	Treatment(s): 50 mg CC (Days 5 to 9) plus 0.5 mg DEX. CC increased up to 150 mg if woman remained anovulatory. Women remaining anovulatory at 150 mg crossed to other arm of trial, as did women who ovulated but had an abnormal postcoital test or endometrial biopsy. Control/placebo: 50 mg CC (Days 5 to 9). CC increased up to 150 mg if woman remained anovulatory. Women remaining anovulatory at 150 mg crossed to other arm of trial, as did women who ovulated but had an abnormal postcoital test or endometrial biopsy. Timed intercourse: no details Duration: not stated
Outcomes	Relevant outcomes: ovulation, pregnancy
Notes	Authors not contacted as trial published > 15 years ago. Power calculation: not stated ITT: yes Source of funding: not stated

Daly 1984 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Pre-randomised schedule
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details of blinding, but unlikely to influence outcomes
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	High risk	9 women (4 CC, 5 CC + DEX) discontinued in the first cycle, and 10 women were found to have other infertility factors, leaving 22 women receiving CC alone and 23 receiving CC + DEX.
Selective reporting (reporting bias)	High risk	No outcome measures were reported in the methods section. No details of adverse events, no report of live birth

Dehbashi 2006

Methods	Parallel randomised controlled trial
Participants	78 infertile women with PCOS. Inclusion criteria: not clearly stated, but included women who were anovulatory with laboratory or clinical evidence of hyperandrogenism with no apparent cause Setting: Infertility Research Centre, Iran Timing: June 2002 to May 2004
Interventions	CC 100 mg starting day 1 of menstrual cycle for 5 days (n = 37 women, 71 cycles) for a maximum of 3 cycles CC 100 mg starting day 5 of menstrual cycle for 5 days (n = 41 women, 78 cycles) for a maximum of 3 cycles If women did not menstruate, then menstrual cycles were induced with a single 200 mg IM dose of progesterone.
Outcomes	Not stated a priori but reported on hormonal levels, follicle number and size, endometrial thickness, ovulation, pregnancy
Notes	Sample size calculation: no ITT: yes Funding: Office for the Vice Chancellor for Research, Shiraz University of Medical Sciences

Dehbashi 2006 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomised", standard random number table
Allocation concealment (selection bias)	Low risk	"Randomization was done by a nurse not aware of the objectives of the study"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double blind"; nurses administering the regimen were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women randomised were analysed.
Selective reporting (reporting bias)	High risk	No outcomes were prespecified.

Elkind-Hirsch 2005

Methods	Parallel randomised controlled trial
Participants	71 women randomised (65 analysed) Inclusion criteria: aged 21 to 35 years, oligo-amenorrhoea, BMI > 18 and < 38 Exclusion criteria: pregnant, known endometrial or uterine anomaly, tubal occlusion, previously failed to ovulate in response to clomiphene, premature ovulation failure Age: median age 28 Duration of infertility: not stated Setting: Women's Health Research Institute (April 2003 to July 2004), USA
Interventions	Treatment(s): CC (100 mg orally for 5 days from Day 3 to 7 of cycle) Control or placebo: CC (100 mg orally for 5 days from Day 3 to 7 of cycle) + HS in the form of estradiol (E2) 1.5 mg (2 tablets) orally twice daily on cycle day 8. On cycle day 10, women commenced monitoring urine LH levels. E2 was discontinued with detection of LH surge. If woman was pregnant, vaginal progesterone was administered daily for an additional 10 weeks. Timed intercourse: encouraged from cycle day 10 Duration: 1 cycle
Outcomes	Relevant outcomes: pregnancy rate, ovulation rate
Notes	Pregnancy assessed as serum hCG 2 weeks following LH surge. Power calculation indicated 458 women per group should have been randomised. Study stopped after 88 participants.

Elkind-Hirsch 2005 *(Continued)*

ITT: yes for women with a P assay
Source of funding: grant from Columbia Laboratories Inc

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised, no details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding, but unlikely to influence outcome
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	6 women had an abnormal scan and were discontinued without receiving treatment.
Selective reporting (reporting bias)	High risk	No details of adverse events, no report of live birth

Elnashar 2006

Methods	Parallel randomised controlled study
Participants	80 women randomised (80 women analysed) All women had PCOS as defined by Rotterdam criteria, without hyperprolactinaemia, clinical evidence of hypercorticism, or thyroid dysfunction. Inclusion criteria: aged 18 to 39 years, period of infertility > 2 years, serum DHEAS within normal levels, no treatment during previous 2 months Age: CC + DEX 23.4 ± 3.6 years, CC + placebo 25.2 ± 2.4 years Duration of infertility: CC + DEX 2.1 ± 0.9 years, CC + placebo 3.2 ± 1.4 years Exclusion criteria: history of pelvic surgery or infertility factor other than anovulation Setting: Women's hospital clinic (March 2004 to December 2004); Egypt
Interventions	Induction of menses using progesterone-in-oil (100 mg); 10,000 IU IM hCG given when at least 1 follicle > 18 mm Treatment(s): CC 100 mg daily from Day 3 to 7 + DEX 2 mg daily orally in 2 divided doses from Day 3 to 12 Control or placebo: CC 100 mg daily from Day 3 to 7 + placebo (folic acid) from Day 3 to 12 Timed intercourse advised 24 to 36 hours after hCG. Duration: 1 cycle
Outcomes	Relevant outcomes: ovulation rate, number of follicles > 18 mm, endometrial thickness, and pregnancy rate

Elnashar 2006 *(Continued)*

Notes	All women had previously received clomiphene and were defined as clomiphene resistant. Clinical pregnancy defined as presence of gestational sac on ultrasound scanning 1 week after missed period. Power calculation: yes, based on results of study by Parsanezhad 2002a; Parsanezhad 2002b ITT: All women randomised were analysed. Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Assigned randomly, no further details
Allocation concealment (selection bias)	Unclear risk	Used closed, dark envelopes and allocated by a 3rd party (nurse)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Women and physician monitoring cycles were blinded to treatment.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	High risk	All women randomised were analysed, no dropouts.
Selective reporting (reporting bias)	High risk	No report of live birth and no details of adverse events

Elsedeek 2014

Methods	Randomised controlled trial
Participants	230 women Age: CC 5-days group 27.67 ± 3.65, CC 10-days group 29.23 ± 4.43 Duration of infertility: CC 5-days group 2.8 ± 1.3, CC 10-days group 2.4 ± 0.9 Inclusion criteria: nulliparous; PCOS using NIH-NICHD definition (presence of chronic anovulation, and clinical and/or biochemical evidence of hyperandrogenism excluding other related disorders); diagnosed as clomiphene resistant (lack of response to clomiphene at 100 mg/day for 5 days within 3 months of inclusion in the study) Exclusion criteria: baseline ovarian cysts or uterine pathology Setting: University infertility clinics, Egypt Timing: January 2009 to January 2012
Interventions	Starting on Day 3 of progestin-induced withdrawal bleeding

Elsedeek 2014 *(Continued)*

	Clomiphene citrate - 1 cycle of 200 mg/day for 5 days Clomiphene citrate - 1 cycle of 100 mg/day for 10 days Women also received 4 placebo tablets for 10 days.
Outcomes	Primary outcome: ovulation Secondary outcomes: number of dominant follicles, endometrial thickness, clinical pregnancy, live birth rate
Notes	Sample size calculation: yes, based on ovulation rate ITT: unclear Funding: no details in paper

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer generated tables"
Allocation concealment (selection bias)	Unclear risk	"Allocation was placed in sealed envelopes opened on the first day of the treatment for each patient by infertility unit administrator". Not clear if envelopes were opaque or if they were handed out sequentially
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"placebo" controlled. Women were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Sonographers assessing follicle size were blinded to allocation.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The authors report including 230 women. The power calculation required 220 women, and that is what they report on. Unclear how these were selected from the 230
Selective reporting (reporting bias)	Low risk	All outcomes prespecified were reported. The authors also reported multiple pregnancy and FSH levels. Adverse effects were not reported.

Esmaeilzadeh 2011

Methods	Randomised controlled trial
Participants	60 women Mean age in CC + DEX group 24.8 ± 3.56 years, in CC + placebo group 23.1 ± 3.45 years Inclusion criteria: diagnosed with PCOS (Rotterdam criteria), age 18 to 35 years, infertility for 1 to 5 years, normal DHEAS level, diagnosed with clomiphene resistance (3 cycles of clomiphene 150 mg daily from Day 3 to 7) Exclusion criteria: hyperprolactinaemia, thyroidism, had a pelvic pathology or surgery, infertility factor other than anovulation

Esmaeilzadeh 2011 *(Continued)*

	Setting: Infertility and Reproductive Health Centre, Babal, Iran Timing: 2008 to 2010
Interventions	No treatments for 3 months prior to trial entry 1 cycle of: CC 100 mg from Day 3 to 7 plus DEX 2 mg/day in divided doses Day 5 to 14 (n = 30) versus CC 100 mg from Day 3 to 7 plus placebo (folic acid 1 mg/day) Day 5 to 14 (n = 30)
Outcomes	Ovulation, clinical pregnancy rate, follicular development, hormonal status
Notes	Power calculation: yes, but unclear on what it was based ITT: yes Funding: Babel University of Medical Science

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated sequence
Allocation concealment (selection bias)	Unclear risk	"Concealed from study participants"; no further details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Women and doctor/nurse were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Data collector was blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals after randomisation
Selective reporting (reporting bias)	High risk	All prespecified outcomes were reported. Did not report on ongoing pregnancies, live births, or adverse effects

Garcia 1985

Methods	Cross-over randomised trial
Participants	49 women randomised (46 women analysed) Inclusion criteria: amenorrhoea (> 6 months), progesterone withdrawal bleeding, and no other known cause of infertility Age: mean 27.6 years Duration of infertility: not stated

Garcia 1985 *(Continued)*

	Exclusion criteria: not stated Setting: Department of Obstetrics and Gynecology; Philadelphia, USA
Interventions	Treatment(s): 50 mg clomiphene, increased by 50 mg if ovulation failed to occur, up to 250 mg (n = 24) Control or placebo: placebo, 1 tablet, increased up to 5 tablets similar to treatment (n = 22) Duration: 5 cycles, then 5 cycles
Outcomes	Relevant outcomes: ovulation and pregnancy
Notes	Authors not contacted as trial published > 15 years ago. Power calculation: not stated ITT: yes Source of funding: National Institute of Child Health and Human Development grant Notes: cross-over trial, phase 1 data only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated.
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, no details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	High risk	49 randomised and 46 analysed (21 withdrawals: 11 difficulty with protocol, 4 ambivalence towards pregnancy at time, 4 with medical difficulties, and 2 left the country)
Selective reporting (reporting bias)	High risk	No details of adverse events, no report of live birth

Ghafourzadeh 2004

Methods	Randomised controlled trial
Participants	100 women Age range 18 to 39 years; mean age clomiphene + tamoxifen 25.53 ± 3.78 years, clomiphene alone 25.59 ± 4.65 years Duration of infertility: clomiphene alone 3.66 ± 1.83, clomiphene + tamoxifen 3.83 ± 2.0 Inclusion criteria: not clearly specified, but appears to be women with PCOS with normal hysterosalpingography, partners with normal semen analysis (WHO criteria), clomiphene resistant (failure with 3 previous cycles)

Ghafourzadeh 2004 *(Continued)*

	Exclusion criteria: Cushing syndrome and adrenal hyperplasia Setting: Infertility clinic, Iran Timing: 2001 to 2003
Interventions	Clomiphene 100 mg/day from Day 5 to 9 (n = 51) versus Clomiphene 50 mg/day + tamoxifen 20 mg/day from Day 5 to 9 (n = 49)
Outcomes	Development of at least 1 dominant follicle, positive pregnancy test
Notes	Power calculation: no ITT: unclear

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised"; no other details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	High risk	Not stated, unclear if data are reported per women or per cycle
Selective reporting (reporting bias)	High risk	Ovulation rate is reported but was not prespecified. No data were reported for clinical pregnancy, live birth, or adverse effects.

Hassan 2001

Methods	Parallel randomised controlled trial
Participants	97 women randomised (80 women analysed) Inclusion criteria: infertile women with PCOS and insulin resistance Exclusion criteria: male factor infertility Age: not stated Duration of infertility: not stated Setting: Alexandria, Egypt

Hassan 2001 *(Continued)*

Interventions	Treatment(s): ketoconazole 400 mg for 85 days pretreatment followed by CC 100 mg to 150 mg, women persistently failing to ovulate on 150 mg CC were shifted to hMG (n = 49) Control/placebo: CC 100 mg to 150 mg, women persistently failing to ovulate on 150 mg CC were shifted to hMG (n = 48) Duration: 3 to 6 cycles
Outcomes	Relevant outcomes: pregnancy, multiple pregnancy, spontaneous abortion (after cord pulse)
Notes	Authors contacted re: power calculation, allocation concealment, blinding, inclusion and exclusion criteria, exclusions and dropouts, age ranges, ITT analysis, hMG treatment, outcome definitions, and side effects; no reply received Incidence of clomiphene resistance: treatment 11.6% (5/43), control 32.4% (12/37) Power calculation: not stated ITT: not stated Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly divided using random number table
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding, but unlikely to influence outcome
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	High risk	Number of women analysed: 80, treatment 43 and control 37 Number of withdrawals and reasons: control 11, treatment 6, reasons not stated
Selective reporting (reporting bias)	High risk	Pregnancy and multiple pregnancy are not specified as outcomes in the methods section, similar to antioestrogenic markers. No details of adverse events, no report of live birth

Homburg 2012

Methods	Parallel randomised controlled trial (multicentre, n = 10)
Participants	302 women randomised Inclusion criteria: < 40 years old; normal uterine cavity and tubal patency; male partners had normal semen analysis; anovulatory or oligo-anovulatory infertility associated with PCOS Exclusion criteria: no details Setting: multicentre across 10 European and South American sites

Homburg 2012 *(Continued)*

	Timing: August 2005 to March 2009
Interventions	3 cycles of: Clomiphene citrate (oral) - starting dose 50 mg/day for 5 days from Day 4 of a progestin-induced or spontaneous menstruation, rising by 50 mg/day up to 150 mg in subsequent cycles if ovulation not achieved (n = 143) versus FSH (s.c.) in a low-dose protocol starting with 50 IU on cycle day 4, with weekly increments of 25 IU to induce a follicular response (n = 159)
Outcomes	Live birth, clinical pregnancy, ongoing pregnancy, miscarriage, multiple pregnancy
Notes	ITT: yes Funding: unrestricted educational grant from Organon, Oss, Netherlands (MSD/Schering-Plough)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer generated randomisation"
Allocation concealment (selection bias)	Low risk	"sealed, opaque envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No evidence of blinding, and this would be unlikely given that one intervention was oral and one was subcutaneous. Blinding unlikely to have influenced fertility outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	In the clomiphene citrate group, 20 women did not complete the full study (5 intercycle, 1 chemical pregnancy, 14 personal reasons). In the FSH group, 27 women did not complete the full study (4 intercycle, 3 chemical pregnancy, 19 personal reasons, 1 following cycle cancellation for OHSS).
Selective reporting (reporting bias)	High risk	Although live birth was prespecified, no data were reported for this outcome. Ectopic pregnancy was reported as an outcome but was not prespecified in the methods.

Johnson 1966

Methods	Cross-over randomised trial (multicentre, n = 5)
Participants	Inclusion criteria: anovulation for > 6 months, adequate endogenous oestrogen, no local or systematic defect that may interfere with CC action Age: not stated Duration of infertility: not stated Exclusion criteria: not stated

Johnson 1966 *(Continued)*

	Setting: USA
Interventions	Treatment(s): 100 mg CC Days 6 to 10 Control or placebo: placebo Days 6 to 10 Duration: 1 cycle, then 1 cycle
Outcomes	Relevant outcomes: pregnancy and ovulation
Notes	Power calculation: not stated ITT: not stated Source of funding: supported by Wm S Merrell Company, Cincinnati, OH, USA Phase 1 data used only. Authors not contacted as trial published > 15 years ago.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details
Allocation concealment (selection bias)	Low risk	Pharmacy coded drug boxes.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind; no details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number of women randomised: 75 Number of women analysed: 65 (33 to CC and 32 to placebo) Number of withdrawals and reasons: 13, 8 failed to return or did not comply with protocol, and 5 became pregnant in the first phase
Selective reporting (reporting bias)	High risk	No details of adverse events, no report of live birth

Lopez 2004

Methods	Parallel randomised controlled trial
Participants	76 women randomised Inclusion criteria: women aged < 40 years with anovulatory infertility due to PCOS of at least 1 year's duration and attending the infertility clinic at the Hospital Virgen de la Arrixaca in Murcia (Spain). Also ultrasonographic appearance of polycystic ovaries, a positive response to the progestin challenge test, normal serum prolactin, DHEAS sulphate, and fasting glucose concentrations, a normal HSG (and laparoscopy when appropriate), and no history of pelvic surgery or pelvic inflammatory disease. Normal semen analysis in male partner Exclusion criteria: previous pregnancy or previous treatment with ovarian stimulation drugs

Lopez 2004 *(Continued)*

	Setting: infertility clinic at the Hospital Virgen de la Arrixaca in Murcia (Spain) Timing: April 2000 to December 2001
Interventions	Up to 3 consecutive cycles Clomiphene citrate (50 to 150 mg/day for 5 days): a daily dose of 50 mg for 5 days, starting on Day 5 following spontaneous or induced menstruation. If ovulation was documented but there was no pregnancy, the same dose was used in the next cycle. If there was no ovulatory response, the daily dose was increased by 50 mg for the subsequent cycle, up to a maximum daily dose of 150 mg in the 3rd treatment cycle (n = 38). versus Recombinant human FSH in a chronic, low-dose, step-up protocol (daily starting dose 75 IU) commenced on Day 3 following spontaneous or induced menstruation. The chronic, low-dose, step-up regimen consisted of a starting dose of 75 IU daily s.c., with dose increments of 37.5 IU daily every 7 days if there was no evidence of ovarian response by ultrasonography (i.e. no follicle > 10 mm in diameter). This stepwise increase was continued until ovarian activity was seen, at which time the dose was maintained. The starting dose of FSH could be modified in successive treatment cycles based on ovarian response in the previous cycle (n = 38).
Outcomes	Cumulative pregnancy, cycle cancellation, ovulation rate per cycle, cumulative ovulation rate, pregnancy rate per cycle, incidence of OHSS, cumulative live birth rate, and multiple birth rate
Notes	Data are reported per cycle rather than per woman randomised.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated randomization table"
Allocation concealment (selection bias)	Low risk	"sealed opaque envelopes each containing a unique study number and prepared independently by a secretary."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding, but unlikely to affect pregnancy outcomes
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 woman in the FSH group withdrew after 1 unsuccessful treatment cycle.
Selective reporting (reporting bias)	Low risk	All outcomes appear to have been reported.

Moslemizadeh 2008

Methods	Randomised controlled trial

Moslemizadeh 2008 *(Continued)*

Participants	157 women enrolled Age of women in clomiphene-alone group 27.6 ± 4.5 years, in tamoxifen group 27.1 ± 4.1 years, in clomiphene + estradiol group 27.3 ± 5.1 years Duration of infertility in clomiphene-alone group 4.2 ± 2.7 years, in tamoxifen group 4.2 ± 2.3 years, in clomiphene + estradiol group 3.5 ± 2.7 years Inclusion criteria: PCOS, tubal patency Exclusion criteria: uterine, kidney, liver, or thyroid disease; uterine anomalies; uterine leiomyoma; male factor infertility; > 35 years old; secondary infertility; duration of infertility > 10 years; hyperprolactinaemia; hyper-/hypothyroidism; FSH > 12 mIU ml^{-1} in the 3rd day of the cycle; BMI > 30 kg/m^2; clomiphene resistance; previous exposure to other ovulation induction agents; interval of earlier treatment with ovulatory agents less than 6 months; contraindication to one of the medications Setting: infertility clinic and research clinic, Sari, Iran Timing: August 2006 to August 2007
Interventions	Clomiphene citrate 2 x 50 mg daily from Day 3 to 9 plus estradiol 2 mg daily from Day 8 to hCG injection day (n = 48) versus Clomiphene citrate 2 x 50 mg daily from Day 3 to 9 (n = 48) versus Tamoxifen 20 mg daily from Day 3 to 9 (n = 48) All groups received placebo.
Outcomes	Ovulation, clinical pregnancy rate
Notes	Sample size calculation: yes, based on ovulation and pregnancy ITT: yes Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly divided"; no other details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Women received placebo and were blinded to allocation. Paper states that the trial was double-blind, but it was unclear who aside from the women was blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias)	Low risk	157 women enrolled, 13 were excluded due to ovulation failure, and 144 who were randomised completed the trial.

Moslemizadeh 2008 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	High risk	Additional outcomes were reported that were not prespecified. No report on live birth

Omran 2011

Methods	Randomised controlled trial
Participants	220 cycles (number of women not reported) Inclusion criteria: not clearly stated, but included women with clomiphene-resistant PCOS Exclusion criteria: not stated Setting: not stated. Egypt Timing: not stated
Interventions	200 mg clomiphene citrate for 5 days 100 mg clomiphene citrate for 10 days
Outcomes	Ovulation rate, time to ovulation, number of follicles, endometrial thickness when largest follicle had a diameter of 18 mm, midluteal progesterone, pregnancy
Notes	Sample size calculation: no ITT: unclear Funding: not reported Conference abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised"; no other details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated double-blind, but unclear who was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	High risk	Conference abstract only, no details on randomisation and attrition rates

Omran 2011 *(Continued)*

Selective reporting (reporting bias)	High risk	Conference abstract only, no data reported

Parsanezhad 2002a

Methods	Parallel randomised controlled trial
Participants	230 women randomised Inclusion criteria: PCOS as defined by a history of oligo- or amenorrhoea, increased basal LH and androgen levels, polycystic ovaries found on ultrasound. Plus clomiphene citrate resistance, defined as failure to ovulate and achieve normal luteal phase with 250 mg dose of CC for 5 days and at least 5 cycles Age: mean age treatment group 23.56 years, control group 23.36 years. Range 19 to 35 for both groups Duration of infertility: treatment mean 4 years, range 2 to 14; control mean 4.25 years, range 3 to 14.5 Exclusion criteria: not stated Setting: Reproductive and endocrinology division, university; Shiraz, Iran
Interventions	Treatment(s): 200 mg CC (Days 5 to 9), 2 mg DEX (Days 5 to 14), hCG (10,000 IU) as an ovulation trigger (n = 111) Control or placebo: 200 mg CC (Days 5 to 9), placebo 4 times a day (Days 5 to 14), hCG (10,000 IU) as an ovulation trigger (n = 119) Duration: up to 6 cycles
Outcomes	Relevant outcomes: ovulation rate, pregnancy
Notes	Authors contacted re: power calculation, randomisation, blinding, exclusion criteria, exclusions and dropouts, and ITT analysis; no reply received. Power calculation: not stated ITT: not stated Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	High risk	Unclear, 3rd party (pharmacist), odd-even numbers given to treatment or control (no further explanation provided by authors)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but no details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	High risk	Follow-up not clear

Parsanezhad 2002a *(Continued)*

Selective reporting (reporting bias)	High risk	No details of adverse events, no report of live birth

Parsanezhad 2002b

Methods	Parallel randomised controlled trial
Participants	100 women randomised Inclusion criteria: PCOS as defined by women with 3 of the following: infertility, oligo- or amenorrhoea, acne or hirsutism, obesity, increased testosterone, increased DHEAS, LH/FSH ratio > 2, polycystic ovaries on ultrasound. Plus clomiphene citrate resistance, defined as failure to ovulate and achieve normal luteal phase with the highest dose of CC for 5 days and at least 5 cycles. Plus normal prolactin (80 to 500 mIU/mL) Age: mean age treatment group 25.02 ± 2.7 years, control group 24.87 ± 2.9 years Duration of infertility: treatment mean 4.53 ± 3.1 years, range 2 to 22; control 4.02 ± 1.9 years, range 2 to 10 Exclusion criteria: not stated Setting: Shiraz, Iran
Interventions	Treatment(s): 200 mg CC on Days 5 to 9, bromocriptine gradual dose increase up to 2.5 mg 3 times a day continuously, hCG (10,000 IU) as an ovulation trigger on Day 16 or 17 (n = 47) Control or placebo: 200 mg CC on Days 5 to 9, placebo 3 times a day continuously, hCG (10,000 IU) as an ovulation trigger on Day 16 or 17 (n = 53) Duration: up to 6 cycles
Outcomes	Relevant outcomes: ovulation rate, pregnancy, women-reported adverse effects
Notes	Authors contacted re: power calculation, randomisation, blinding, exclusion criteria, exclusions and dropouts, and ITT analysis; no reply received. ITT: not stated Source of funding: not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear, no details
Allocation concealment (selection bias)	High risk	Unclear, 3rd party (pharmacist), odd-even numbers given to treatment or control (no further explanation provided by authors)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but no details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	High risk	Follow-up data not clear

Parsanezhad 2002b *(Continued)*

Selective reporting (reporting bias)	High risk	No details of adverse events such as miscarriage, no report of live birth

Seyedoshohadaei 2012

Methods	Randomised controlled trial
Participants	150 women randomised Mean age of clomiphene group 24.7 ± 4.7 years, tamoxifen group 25.4 ± 4.2 years; mean duration of infertility for the clomiphene group 2.95 ± 2.1 years, tamoxifen group 2.99 ± 2.0 years Inclusion criteria: anovulatory women, infertile at least 1 year, menstrual cycle 35 days to 6 months, normal serum prolactin, TSH, FSH, LH. Normal uterus and ovary, no evidence of polycystic ovary or dominant follicle at midcycle in ultrasonography, normal uterus and patent tubes on HSG. Normal semen analysis for partner Exclusion criteria: no details Setting: private clinics in Iran Timing: November 2007 to September 2009
Interventions	Spontaneous or progesterone-induced menses Clomiphene citrate (n = 50 women, 199 cycles) 50 mg daily from Day 3 to 9 (increased by 50 mg per failed cycle to a maximum of 150 mg daily) Tamoxifen (n = 50 women, 174 cycles) 10 mg daily from Day 3 to 9 (increased by 10 mg per cycle to a maximum of 30 mg daily) *Letrozole (n = 50) 2.5 mg daily from Day 3 to 9 (increased by 2.5 mg per failed cycle to a maximum of 7.5 mg daily)* If failed to ovulate after 5 days, then treatment continued up to 7 days. Treatment stopped if pregnant or failure to ovulate after 7 days of treatment or failed to conceive after 6 months despite ovulation, or severe adverse reaction
Outcomes	Primary outcomes: number of follicles 18 mm or more in diameter, endometrial thickness, ovulation rate Secondary outcomes: clinical pregnancy rate, spontaneous miscarriage rate, multiple pregnancy rate, OHSS
Notes	Sample size calculation: no ITT: yes Funding: Kurdistan University of Medical Sciences

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Unclear risk	No details

Seyedoshohadaei 2012 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Women not blinded, but unlikely to affect the outcome. Researchers were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women randomised were analysed.
Selective reporting (reporting bias)	Low risk	All outcomes prespecified were reported.

Suginami 1993

Methods	Randomised cross-over trial
Participants	20 women randomised (20 women analysed) Inclusion criteria: anovulation, normoprolactinaemic Age: Group A: 29.3 ± 3.1 years, Group B: 28.6 ± 3.0 years Duration of infertility: not stated Exclusion criteria: none stated Setting: Ehime, Japan
Interventions	Treatment(s): Both groups received combination pill (0.05 mg ethinyl E2 and 0.5 mg norgestrel) to induce withdrawal bleed, then Gp A - 100 mg CC on Days 5 to 9 for 3 cycles and then 50 mg CC plus 20 mg TMX on Days 5 to 9 for 3 cycles. Gp B - reverse sequence, otherwise identical (n = 10) Control or placebo: None (n = 10) Timed intercourse: normal intercourse encouraged, no details Duration: 3 cycles then 3 cycles
Outcomes	Relevant outcomes: ovulation, pregnancy, and women-reported adverse effects
Notes	Unable to contact authors. Power calculation: not stated ITT: no Source of funding: not stated Notes: cross-over trial, phase 1 data only

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	Unclear risk	Unclear

Suginami 1993 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding, but unlikely to influence outcome
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts; all women randomised were analysed
Selective reporting (reporting bias)	High risk	No details of adverse events such as miscarriage, no report of live birth

Tripathy 2013

Methods	Parallel randomised trial
Participants	74 women randomised (74 women analysed) Inclusion criteria: diagnosed with PCOS (2 out of 3 criteria); serum prolactin ≤ 20 ng/mL, age less than 35 years, BMI 20 to 30 kg/m^2 Exclusion criteria: hyperprolactinaemia (> 20 ng/mL), other causes of infertility (tubal, uterine), comorbid disease (tuberculosis, abnormal glucose tolerance test) Age: clomiphene citrate 25 ± 4.2 years, clomiphene + bromocriptine 25.13 ± 3.5 years Duration of infertility: not reported Setting: infertility outpatient department, Tamil Nadu, India Timing: not reported
Interventions	3 cycles of treatment with: Clomiphene citrate 50 mg Day 3 to 7 (n = 38) versus Clomiphene citrate 50 mg Day 3 to 7 + bromocriptine 2.5 mg Day 1 to 30 (n = 36)
Outcomes	Relevant outcomes: ovulation rate, pregnancy rate
Notes	Power calculation: not stated ITT: yes Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly assigned - no further details
Allocation concealment (selection bias)	Unclear risk	No details

Tripathy 2013 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition, all women randomised were analysed
Selective reporting (reporting bias)	High risk	Outcomes were not specified or defined. Major adverse events such as OHSS were not reported.

Vegetti 1999

Methods	Parallel randomised controlled trial
Participants	95 women randomised (95 women analysed) Inclusion criteria: normogonadotrophic anovulation, infertility for > 1 year, tubal patency shown by HSG or laparoscopy, normal semen analysis Age: not stated Duration of infertility: not stated Source of women: tertiary infertility centre Exclusion criteria: not stated Location: Milan, Italy
Interventions	Treatment(s): 100 mg CC on Days 3 to 7, if woman remained anovulatory for 2 cycles then dose doubled or 20 mg TMX on Days 3 to 7, if woman remained anovulatory for 2 cycles then dose doubled (n = 50) Control or placebo: none (n = 45) Duration: not stated
Outcomes	Relevant outcomes: ovulation (per cycle, CC 108/129, TMX 92/133), pregnancy, and women-reported adverse effects
Notes	Authors contacted re: power calculation, random allocation, blinding, reasons for dropouts, external funding, anovulation definition, exclusion criteria, treatment time limit, ovulation rate per women; no reply received. ITT: not stated Source of funding: not stated Notes: abstract only

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	Unclear risk	Unclear

Vegetti 1999 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	High risk	No reason given for dropouts
Selective reporting (reporting bias)	High risk	No details of adverse events such as miscarriage, no report of live birth

Yilmaz 2006

Methods	Parallel randomised controlled trial
Participants	133 women randomised (125 women analysed) Inclusion criteria: normoprolactinaemic, normogonadotropic, primary infertility with oligomenorrhoea or amenorrhoea, age 20 to 40 years, duration of primary infertility > 2 years, no history of ovulation induction treatment and thyroid disease, normal results on HSG, husband with normal semen analysis according to WHO criteria Age: CC + hCG group 26.2 ± 3.4 years, CC-alone group 26.7 ± 3.2 years Duration of infertility: CC + hCG group 2.91 ± 2.0 years, CC-alone group 2.88 ± 2.0 years Exclusion criteria: no details Setting: Infertility units; Turkey Timing: May 2002 to April 2004
Interventions	Day 1 was start of menses, clomiphene administered on Days 5 to 9 Treatment(s): CC 50 mg + hCG (Pregnyl 10,000 IU IM) when follicles reached 18 mm in diameter as determined by ultrasound (n = 60) Control or placebo: CC 50 mg (n = 65) Timed intercourse was advised 5 days after the last dose of clomiphene citrate for alternate days in both groups. Duration: 1 cycle
Outcomes	Relevant outcomes: ovulation and pregnancy rates, clinical pregnancy rate, fertilisation rate, implantation rate, twin rate, abortion rate (detected chemically but not by ultrasound scan at 7 weeks), corpus luteum function, mid-luteal serum progesterone, and luteal phase length
Notes	Pregnancy test (at 16th day after ovulation by serum ß-hCG), positive foetal heart rate at 7 weeks Power calculation: yes, based on a previous trial ITT: no Source of funding: no details

Risk of bias

Bias	Authors' judgement	Support for judgement

Yilmaz 2006 *(Continued)*

Random sequence generation (selection bias)	Low risk	Random number tables
Allocation concealment (selection bias)	Unclear risk	Opaque envelope technique
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Sonographers evaluating follicle size were blinded to treatment group.
Incomplete outcome data (attrition bias) All outcomes	Low risk	133 randomised, 125 completed the trial and were analysed. 8 women were lost to follow-up.
Selective reporting (reporting bias)	High risk	No details of adverse events, no report of live birth

BMI: body mass index
CC: clomiphene citrate
COC: combined oral contraceptive
DEX: dexamethasone
DHEAS: dehydroepiandrosterone
E2: estradiol
FSH: follicle-stimulating hormone
hCG: human chorionic gonadotropin
hMG: human menopausal gonadotropins
HS: hormone supplementation
HSG: hysterosalpingogram
IM: intramuscular
ITT: intention-to-treat analysis
LH: luteinising hormone
NIH-NICHD: National Institutes of Health - National Institute of Child Health and Human Development
OHSS: ovarian hyperstimulation syndrome
P4: progesterone
PCOS: polycystic ovarian syndrome
s.c.: subcutaneous
TMX: tamoxifen
TSH: thyroid-stimulating hormone
WHO: World Health Organization

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Al-Omari 2002	This was a conference abstract superseded by full paper (see Al-Omari 2004).
Al-Omari 2004	Study using letrozole, excluded in 2009 update
Archer 1989	Women not anovulatory
Armeanu 1992	Not an RCT

Study	Reason for exclusion
Atay 2006	Study using letrozole, excluded in 2009 update
Aygen 2007	Study using letrozole, excluded in 2009 update
Bayer 2006	Study using letrozole, excluded in 2009 update
Connaughton 1974	Cross-over trial, not all women anovulatory, was included in Hughes 1996
Dura 2015	Trial used intrauterine insemination.
Echt 1969	Population selection based on diagnosis of luteal phase defect
el Tabbakh 1988	Did not involve antioestrogen therapy
Gerhard 1979	Not an RCT
Glasier 1989	Women not anovulatory
Greenblatt 1961	Not an RCT
Guedes Neto 2011	Wrong comparison, no adjunct
Ito 1990	Not an RCT
Johnson 1990	Not oral agents
Koloszar 1996	Does not appear to be an RCT
Kosar 2014	Trial used intrauterine insemination.
Kubota 1992	Not an RCT
Lisse 1980	Not an RCT
Lobo 1982	Not an RCT
Mendes 1999	WHO group 1 women only
Mitwally 2001a	Not an RCT
Mitwally 2001b	Not an RCT
Moini 2015	Trial used intrauterine insemination.
Presl 1984	Does not appear to be an RCT
Roozenburg 1997	Does not compare included interventions
Ruiz-Velasco 1978	Not an RCT
Senior 1978a	6/9 women not anovulatory
Singh 1992	Not an RCT
Topcu 2010	Trial used intrauterine insemination.

Study	Reason for exclusion
Trott 1996	Not an RCT
Tsuiki 1984	Not an RCT
Williamson 1973	Not an RCT
Yari 2010	Wrong comparison

RCT: randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Buvat 1987

Methods	Randomised trial
Participants	66 infertile women, infertile for at least 1 year; n = 26 eugonadal anovulation, n = 40 luteal phase inadequacy; no other severe infertility factor
Interventions	Clomiphene citrate 25 to 50 mg/day versus tamoxifen 20 mg/day
Outcomes	Pregnancy, multiple pregnancy, adverse events
Notes	Unable to separate anovulatory data from luteal phase deficiency data. Unable to contact author

Cabau 1990

Methods	Double-blind randomised trial, randomisation using permuted blocks of 10. Numbered boxes from laboratory with no distinguishing marks
Participants	300 women who had to be childless and referred for anovulatory cycles, irregular cycles with or without ovulation, or dysovulatory cycles. Also included women with slight insufficiency of mucus and those with idiopathic sterility. Trying to get pregnant for at least 1 year, or had already received treatment for sterility, or had suffered a miscarriage and tried for at least 6 months to get pregnant again Excluded all women to whom physician did not want to prescribe placebo, > 38 years old, amenorrhoea > 6 months' duration, known tubal sterility, distinctly insufficient or infected mucus, partners presenting with deficiency in semen, women undergoing artificial insemination
Interventions	Cyclofenil 400 mg taken on Days 4 to 8 of menstrual cycle or Days 5 to 8 (n = 114) versus placebo (n = 99)
Outcomes	Live birth, miscarriage, foetal death
Notes	Unable to separate anovulatory data. Unable to contact authors

Craig 2015

Methods	Parallel randomised controlled trial

Craig 2015 *(Continued)*

Participants	160 women Inclusion criteria: 18 to 45 years old, anovulatory infertility Exclusion criteria: none specified Setting: USA Timing: not stated
Interventions	Traditional protocol: clomiphene followed by progestin withdrawal if anovulatory before increasing clomiphene dose (n = 60) versus Stair-step protocol: clomiphene dose increased cycle Days 11 to 14 without progestin withdrawal if no follicle > 12 mm. Clomiphene dose started at 50 mg and increased up to 150 mg (n = 60).
Outcomes	Primary outcome: time to ovulation Secondary outcome: time to pregnancy
Notes	Conference abstract only. Unclear if this is in vitro fertilisation/intracytoplasmic sperm injection or intrauterine insemination

Neuhausser 2011

Methods	Randomised trial
Participants	50 anovulatory women Excluded: women with glucose intolerance on metformin
Interventions	Stair-step protocol: if no dominant follicle clomiphene citrate increased from 50 mg/day to 100 mg for 5 days and then to 150 mg for 5 days versus Standard care: clomiphene citrate increased in 50 mg increments up to a maximum of 150 mg in subsequent menstrual cycles
Outcomes	Unclear from conference abstract, but does include pregnancy outcomes
Notes	It is unclear from the abstract whether or not intrauterine insemination was used.

Senior 1978b

Methods	Randomised cross-over trial
Participants	9 infertile women (3 with anovulation and 6 with suspected luteal phase deficiency)
Interventions	Clomiphene for 2 months, tamoxifen for 2 months, and placebo for 1 month before and 1 month between interventions
Outcomes	Ovulation and pregnancy, hormonal assays

Senior 1978b *(Continued)*

Notes	Unable to extract anovulatory women from luteal deficiency data; unable to contact authors

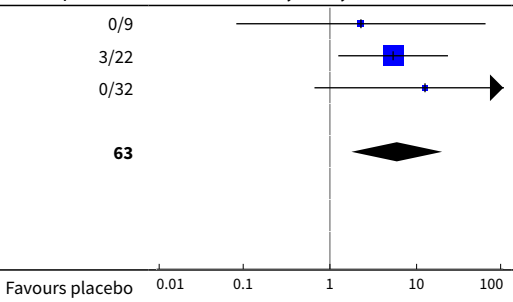
DATA AND ANALYSES

Comparison 1. Antioestrogen versus no treatment or placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical pregnancy rate (per woman randomised)	3	133	Odds Ratio (M-H, Fixed, 95% CI)	5.91 [1.77, 19.68]

Analysis 1.1. Comparison 1 Antioestrogen versus no treatment or placebo, Outcome 1 Clinical pregnancy rate (per woman randomised).

Study or subgroup	Clomiphene n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Cudmore 1966	1/13	0/9		19.71%	2.28[0.08,62.43]
Garcia 1985	11/24	3/22		64.18%	5.36[1.25,23.04]
Johnson 1966	5/33	0/32		16.1%	12.54[0.66,236.9]
Total (95% CI)	**70**	**63**		**100%**	**5.91[1.77,19.68]**
Total events: 17 (Clomiphene), 3 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.59, df=2(P=0.75); I^2=0%					
Test for overall effect: Z=2.89(P=0)					

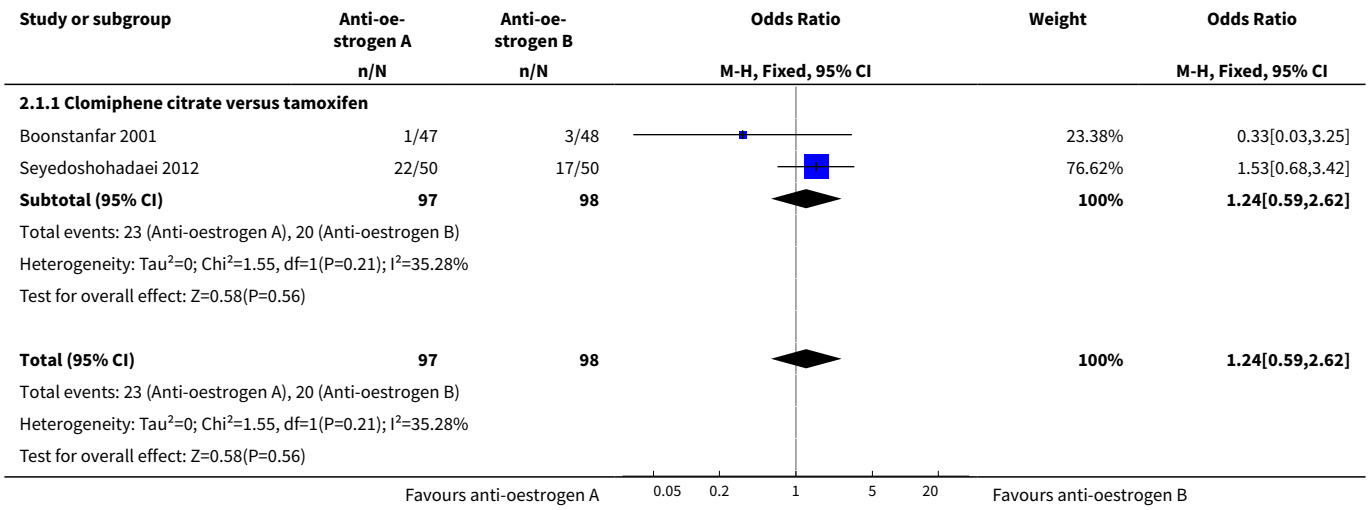


Comparison 2. Antioestrogen versus antioestrogen

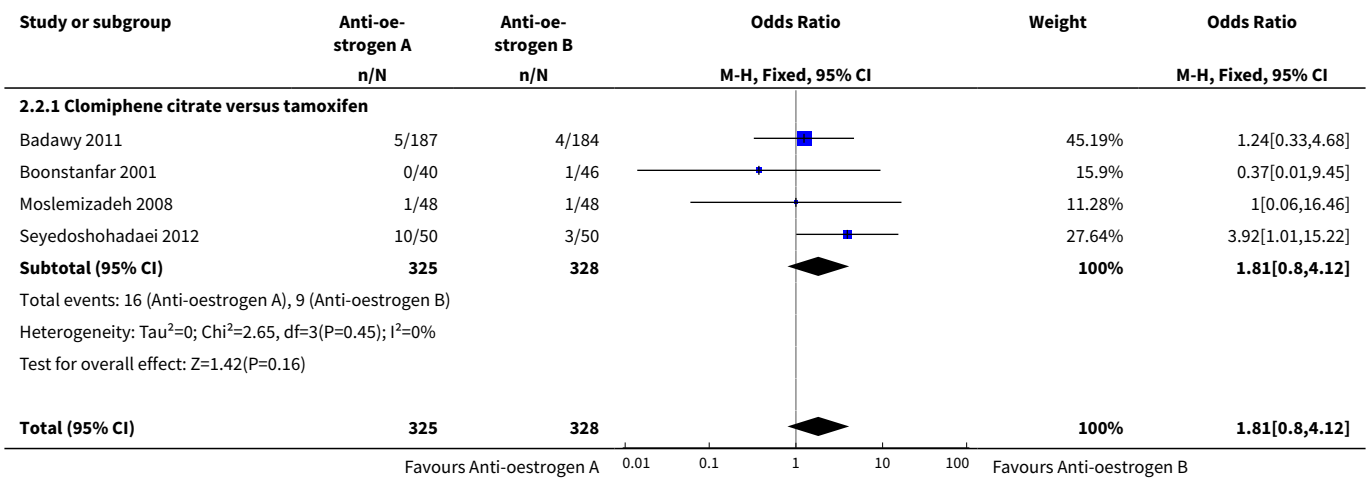
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth rate (per woman)	2	195	Odds Ratio (M-H, Fixed, 95% CI)	1.24 [0.59, 2.62]
1.1 Clomiphene citrate versus tamoxifen	2	195	Odds Ratio (M-H, Fixed, 95% CI)	1.24 [0.59, 2.62]
2 Miscarriage rate (per woman)	4	653	Odds Ratio (M-H, Fixed, 95% CI)	1.81 [0.80, 4.12]
2.1 Clomiphene citrate versus tamoxifen	4	653	Odds Ratio (M-H, Fixed, 95% CI)	1.81 [0.80, 4.12]
3 Clinical pregnancy rate (per woman)	6		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

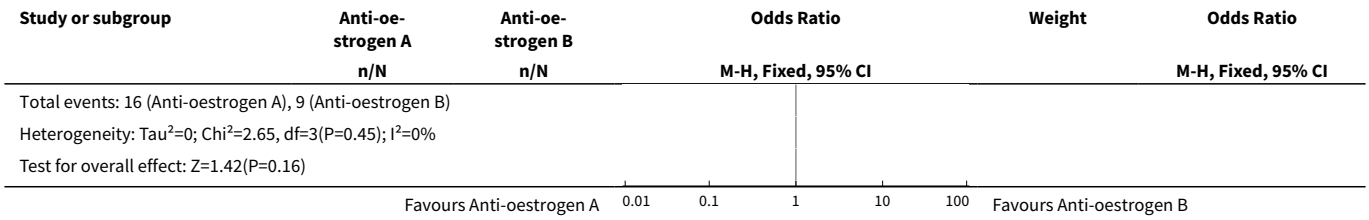
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Clomiphene citrate versus tamoxifen	5	757	Odds Ratio (M-H, Fixed, 95% CI)	1.30 [0.92, 1.85]
3.2 Clomiphene citrate plus tamoxifen versus clomiphene citrate	1	20	Odds Ratio (M-H, Fixed, 95% CI)	3.32 [0.12, 91.60]
4 Multiple pregnancy	3	567	Odds Ratio (M-H, Fixed, 95% CI)	2.34 [0.34, 16.04]
5 OHSS	3	567	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 Antioestrogen versus antioestrogen, Outcome 1 Live birth rate (per woman).

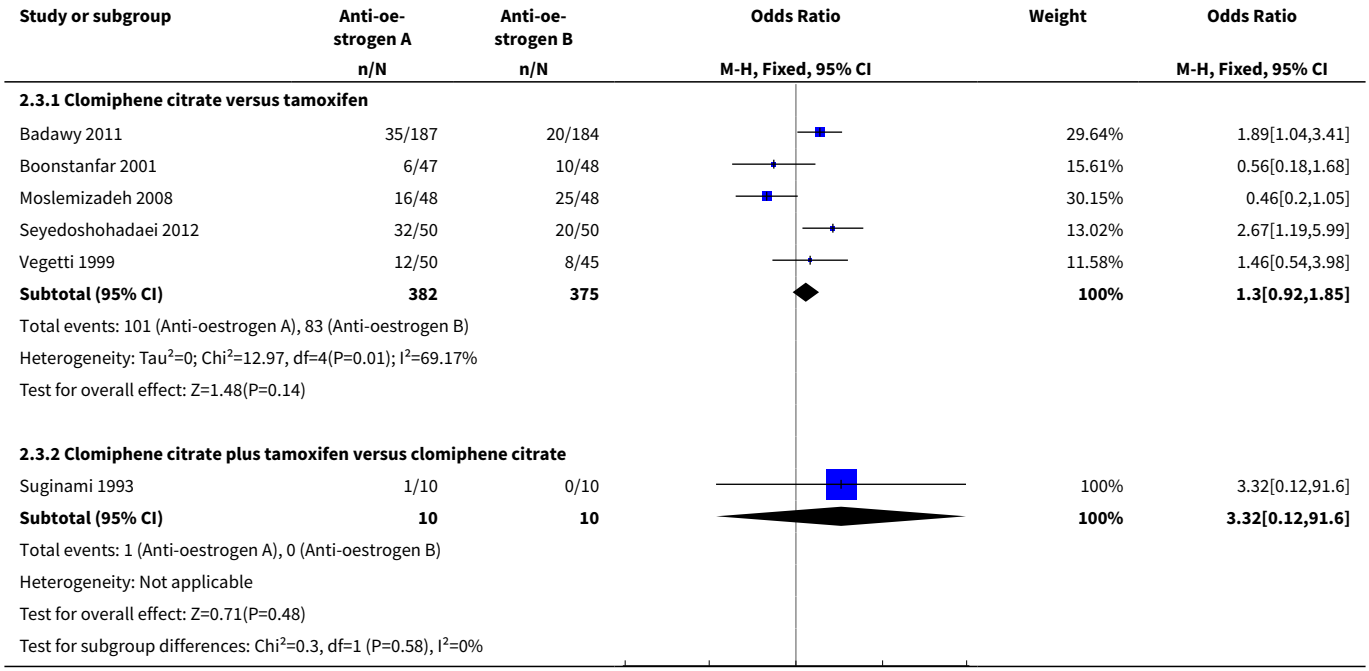


Analysis 2.2. Comparison 2 Antioestrogen versus antioestrogen, Outcome 2 Miscarriage rate (per woman).

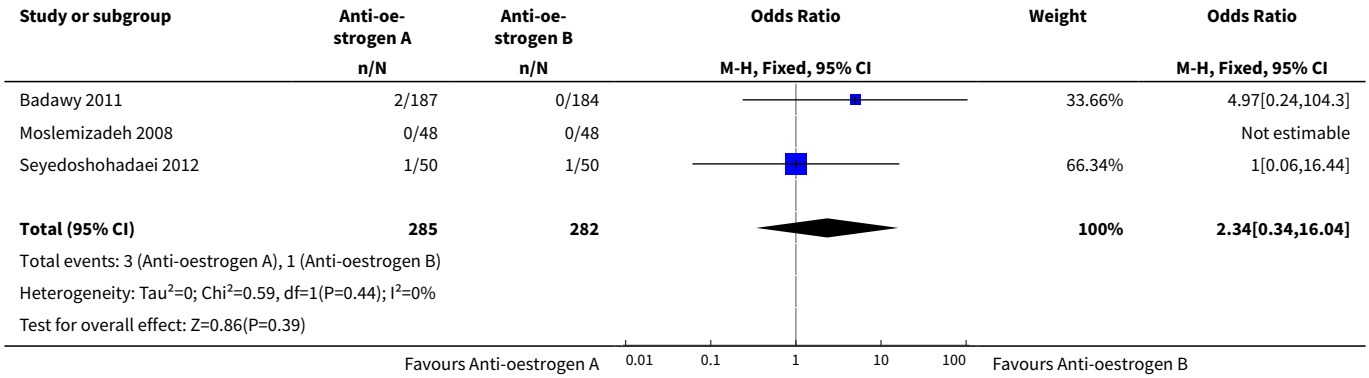




Analysis 2.3. Comparison 2 Antioestrogen versus antioestrogen, Outcome 3 Clinical pregnancy rate (per woman).

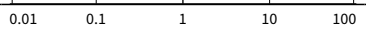


Analysis 2.4. Comparison 2 Antioestrogen versus antioestrogen, Outcome 4 Multiple pregnancy.



Analysis 2.5. Comparison 2 Antioestrogen versus antioestrogen, Outcome 5 OHSS.

Study or subgroup	Anti-oestrogen A n/N	Anti-oestrogen B n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Badawy 2011	0/187	0/184			Not estimable
Moslemizadeh 2008	0/48	0/48			Not estimable
Seyedoshohadaei 2012	0/50	0/50			Not estimable
Total (95% CI)	**285**	**282**			**Not estimable**
Total events: 0 (Anti-oestrogen A), 0 (Anti-oestrogen B)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



Favours Anti-oestrogen A — Favours Anti-oestrogen B

Comparison 3. Antioestrogen versus gonadotropin

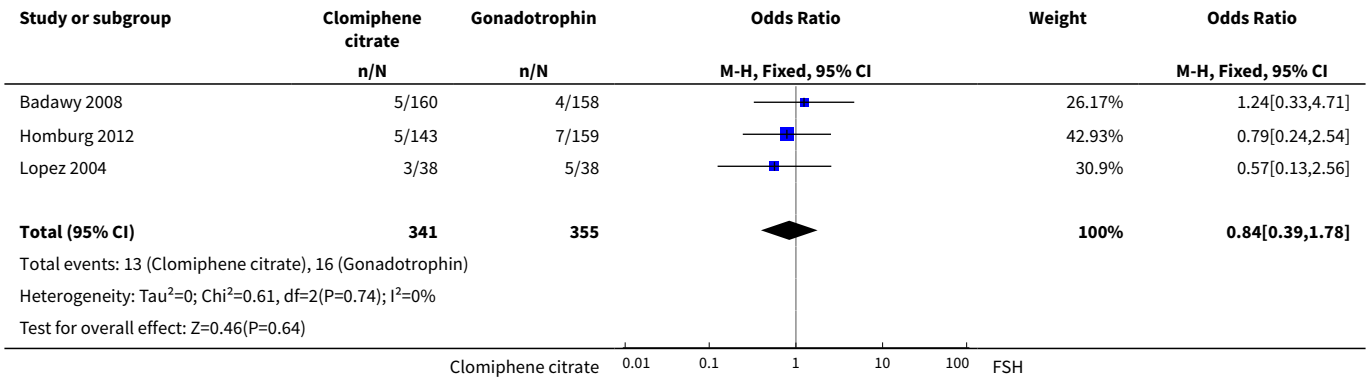
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth/ongoing pregnancy	2	378	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.41, 0.98]
2 Miscarriage rate (per woman)	3	696	Odds Ratio (M-H, Fixed, 95% CI)	0.84 [0.39, 1.78]
3 Clinical pregnancy rate (per woman)	2	378	Odds Ratio (M-H, Fixed, 95% CI)	0.61 [0.40, 0.93]
4 Multiple pregnancy	3	696	Odds Ratio (M-H, Fixed, 95% CI)	0.26 [0.06, 1.06]
5 OHSS	2	394	Odds Ratio (M-H, Fixed, 95% CI)	0.19 [0.02, 1.67]

Analysis 3.1. Comparison 3 Antioestrogen versus gonadotropin, Outcome 1 Live birth/ongoing pregnancy.

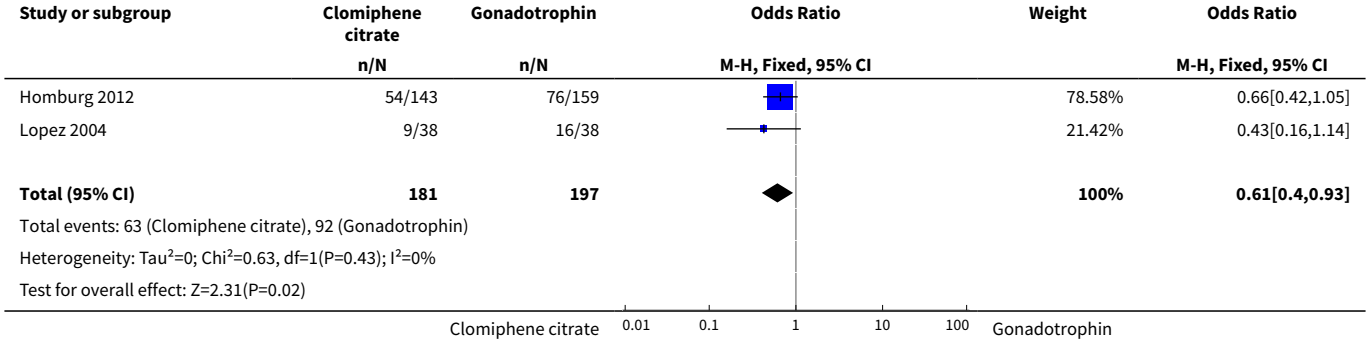
Study or subgroup	Clomiphene citrate n/N	Gonadotrophin n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Homburg 2012	48/143	68/159		82.2%	0.68[0.42,1.08]
Lopez 2004	6/38	11/38		17.8%	0.46[0.15,1.41]
Total (95% CI)	**181**	**197**		**100%**	**0.64[0.41,0.98]**
Total events: 54 (Clomiphene citrate), 79 (Gonadotrophin)					
Heterogeneity: Tau^2=0; Chi^2=0.39, df=1(P=0.53); I^2=0%					
Test for overall effect: Z=2.04(P=0.04)					

Clomiphene citrate — FSH

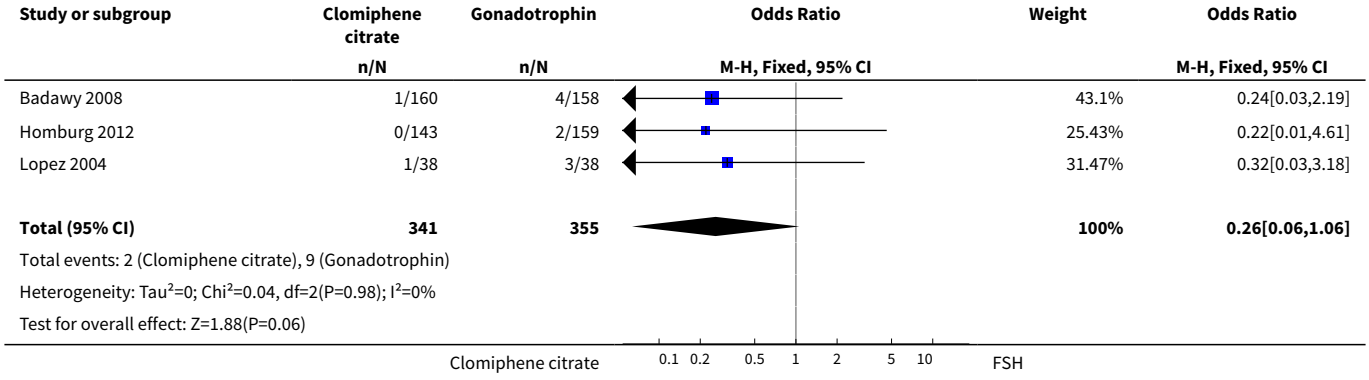
Analysis 3.2. Comparison 3 Antioestrogen versus gonadotropin, Outcome 2 Miscarriage rate (per woman).



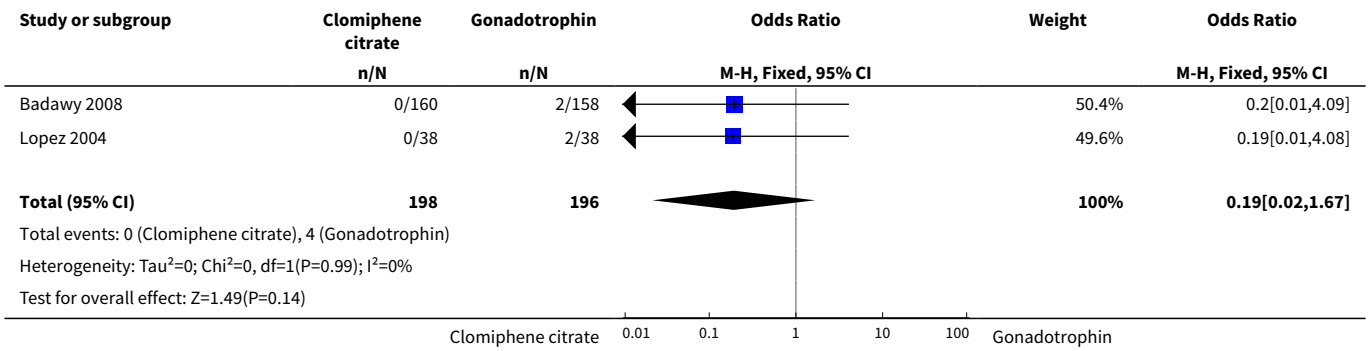
Analysis 3.3. Comparison 3 Antioestrogen versus gonadotropin, Outcome 3 Clinical pregnancy rate (per woman).



Analysis 3.4. Comparison 3 Antioestrogen versus gonadotropin, Outcome 4 Multiple pregnancy.



Analysis 3.5. Comparison 3 Antioestrogen versus gonadotropin, Outcome 5 OHSS.

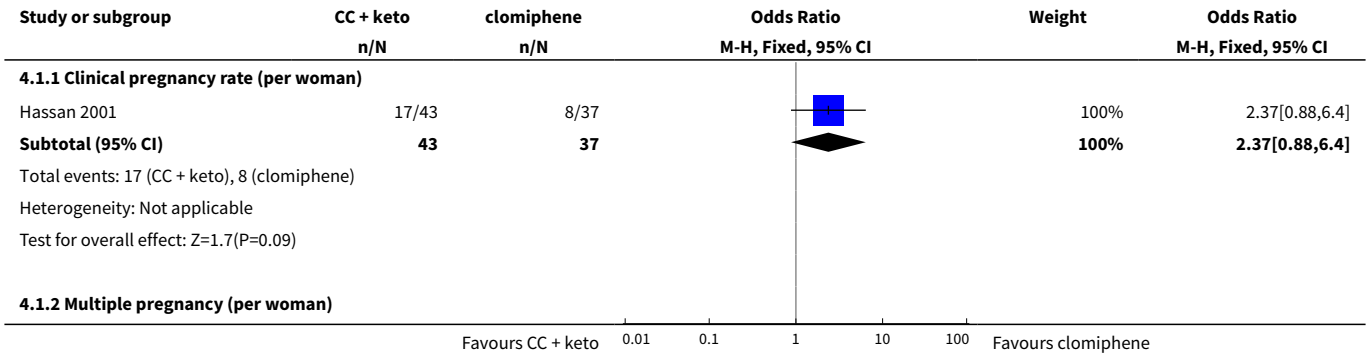


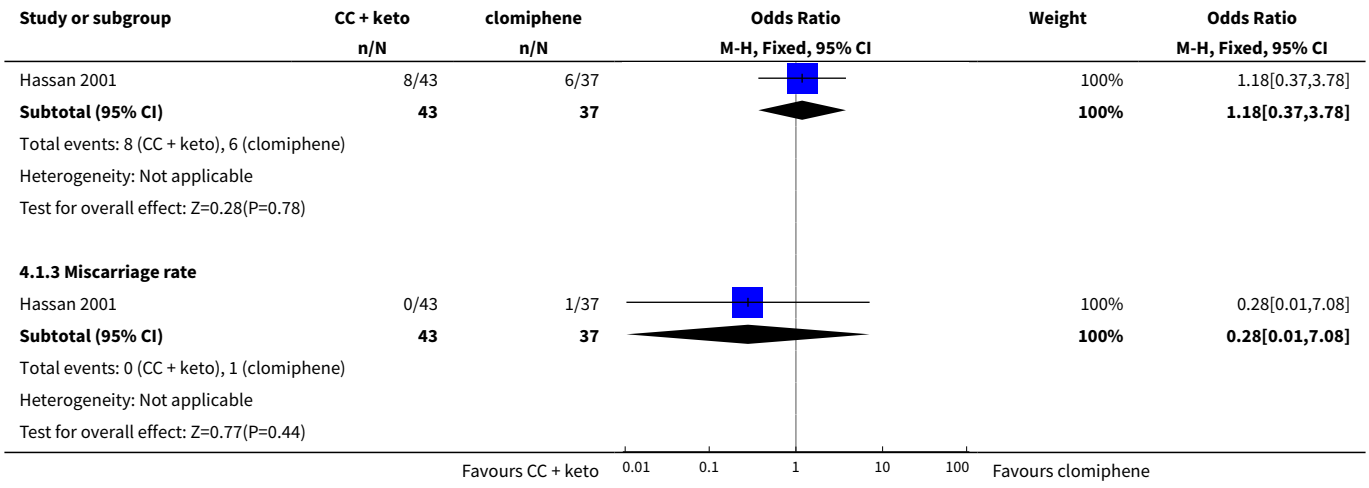
Comparison 4. Antioestrogen plus medical adjunct versus antioestrogen alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clomiphene citrate plus ketoconazole versus clomiphene citrate	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Clinical pregnancy rate (per woman)	1	80	Odds Ratio (M-H, Fixed, 95% CI)	2.37 [0.88, 6.40]
1.2 Multiple pregnancy (per woman)	1	80	Odds Ratio (M-H, Fixed, 95% CI)	1.18 [0.37, 3.78]
1.3 Miscarriage rate	1	80	Odds Ratio (M-H, Fixed, 95% CI)	0.28 [0.01, 7.08]
2 Clomiphene citrate plus bromocriptine versus clomiphene citrate	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Clinical pregnancy rate (per woman)	2	174	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.48, 2.21]
3 Clomiphene citrate plus dexamethasone versus clomiphene citrate	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Clinical pregnancy rate (per woman)	4	434	Odds Ratio (M-H, Random, 95% CI)	6.20 [2.20, 17.48]
3.2 Multiple pregnancy (per woman)	2	144	Odds Ratio (M-H, Random, 95% CI)	7.71 [0.38, 155.64]
4 Clomiphene citrate plus combined oral contraceptive versus clomiphene citrate	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Miscarriage rate (per woman)	1	48	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 16.97]
4.2 Clinical pregnancy rate (per woman)	1	48	Odds Ratio (M-H, Fixed, 95% CI)	27.18 [3.14, 235.02]

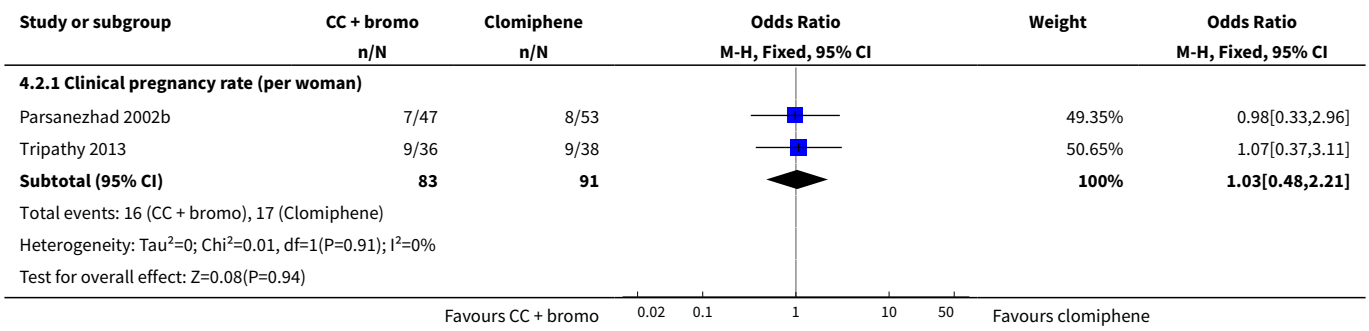
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.3 Multiple pregnancy (per woman)	1	48	Odds Ratio (M-H, Fixed, 95% CI)	7.98 [0.39, 163.33]
5 Clomiphene citrate plus hCG versus clomiphene citrate alone	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Ongoing pregnancy rate (per woman)	1	125	Odds Ratio (M-H, Fixed, 95% CI)	1.31 [0.61, 2.80]
5.2 Miscarriage	2	192	Odds Ratio (M-H, Fixed, 95% CI)	0.70 [0.19, 2.62]
5.3 Clinical pregnancy rate (per woman)	2	192	Odds Ratio (M-H, Fixed, 95% CI)	1.18 [0.59, 2.36]
5.4 Multiple pregnancies (per woman)	1	125	Odds Ratio (M-H, Fixed, 95% CI)	2.21 [0.19, 24.98]
6 Clomiphene citrate plus hormone supplementation versus clomiphene citrate alone	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Miscarriage	1	96	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 16.46]
6.2 Clinical pregnancy rate (per woman)	2	161	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.37, 1.76]
6.3 Multiple pregnancy	1	96	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.4 OHSS	1	96	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.5 Adverse events	1	65	Odds Ratio (M-H, Fixed, 95% CI)	0.21 [0.01, 4.47]

Analysis 4.1. Comparison 4 Antioestrogen plus medical adjunct versus antioestrogen alone, Outcome 1 Clomiphene citrate plus ketoconazole versus clomiphene citrate.

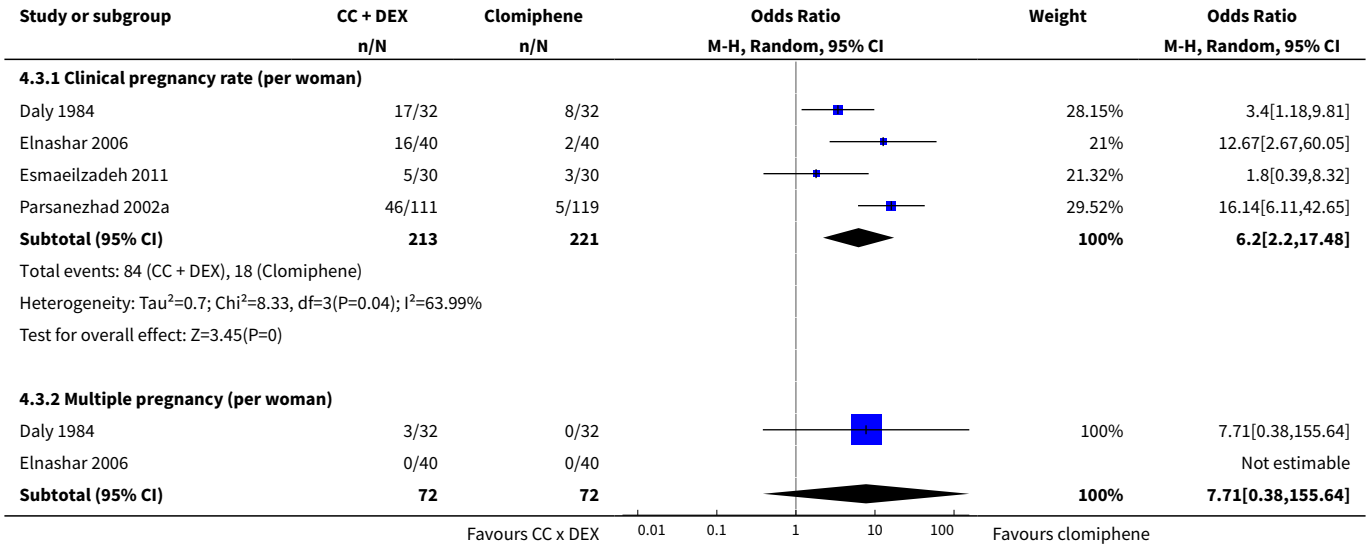


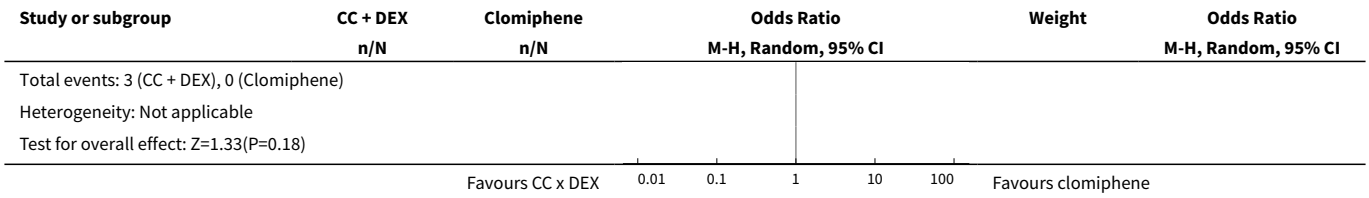


Analysis 4.2. Comparison 4 Antioestrogen plus medical adjunct versus antioestrogen alone, Outcome 2 Clomiphene citrate plus bromocriptine versus clomiphene citrate.

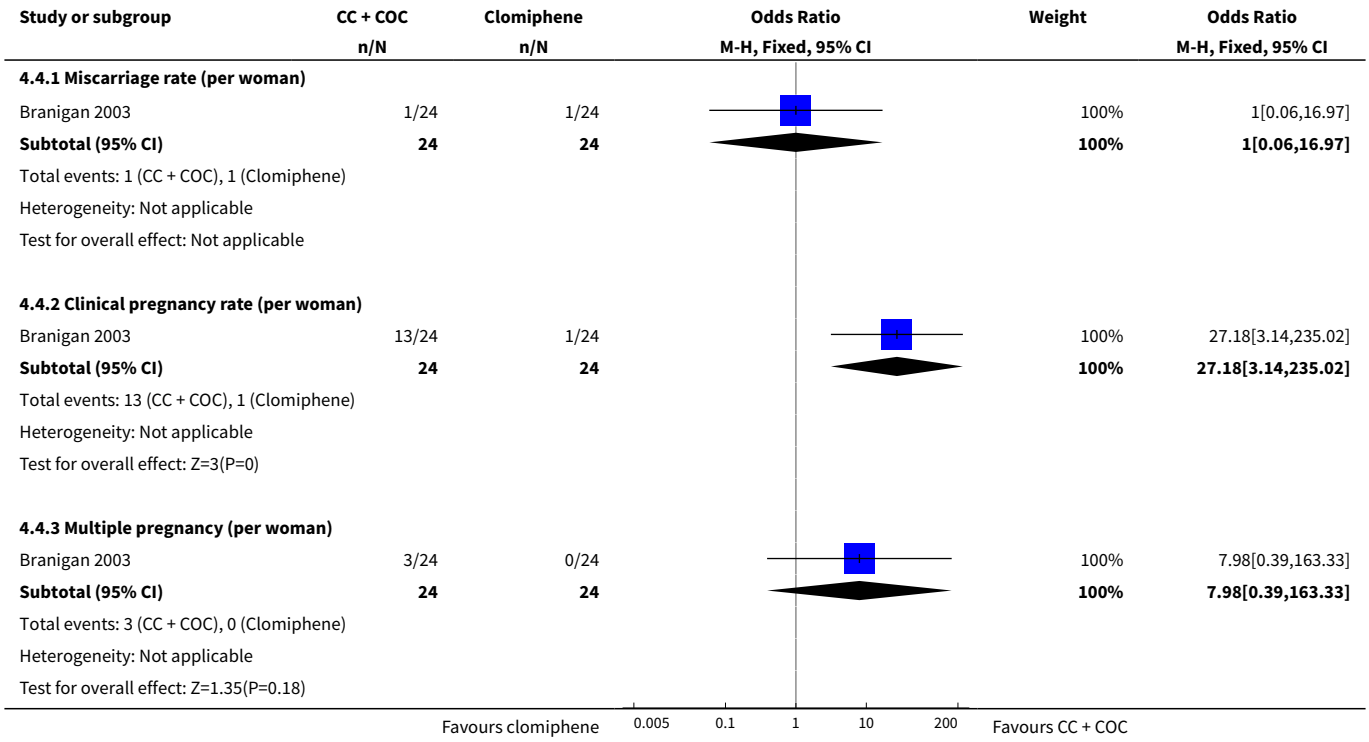


Analysis 4.3. Comparison 4 Antioestrogen plus medical adjunct versus antioestrogen alone, Outcome 3 Clomiphene citrate plus dexamethasone versus clomiphene citrate.

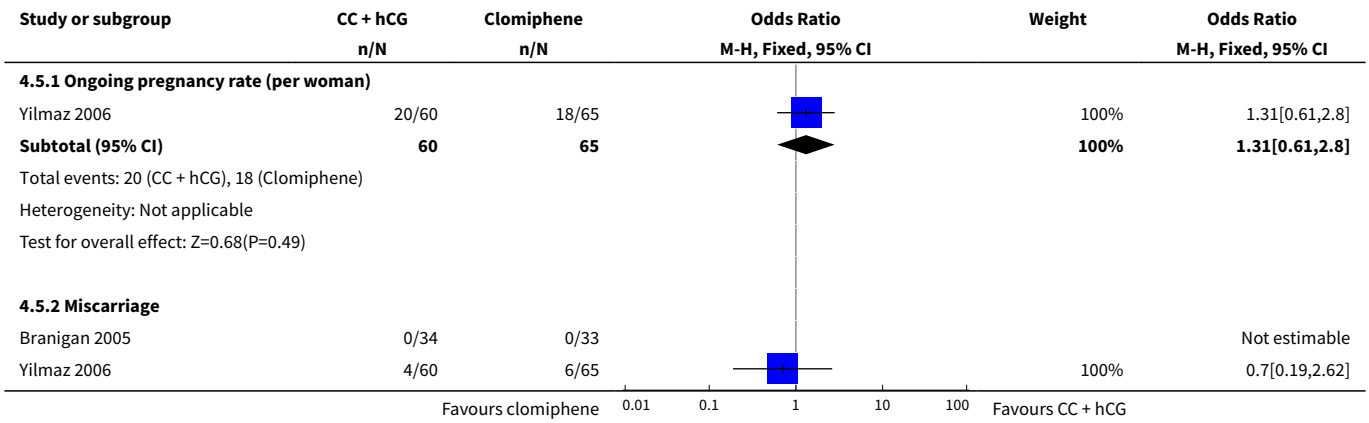


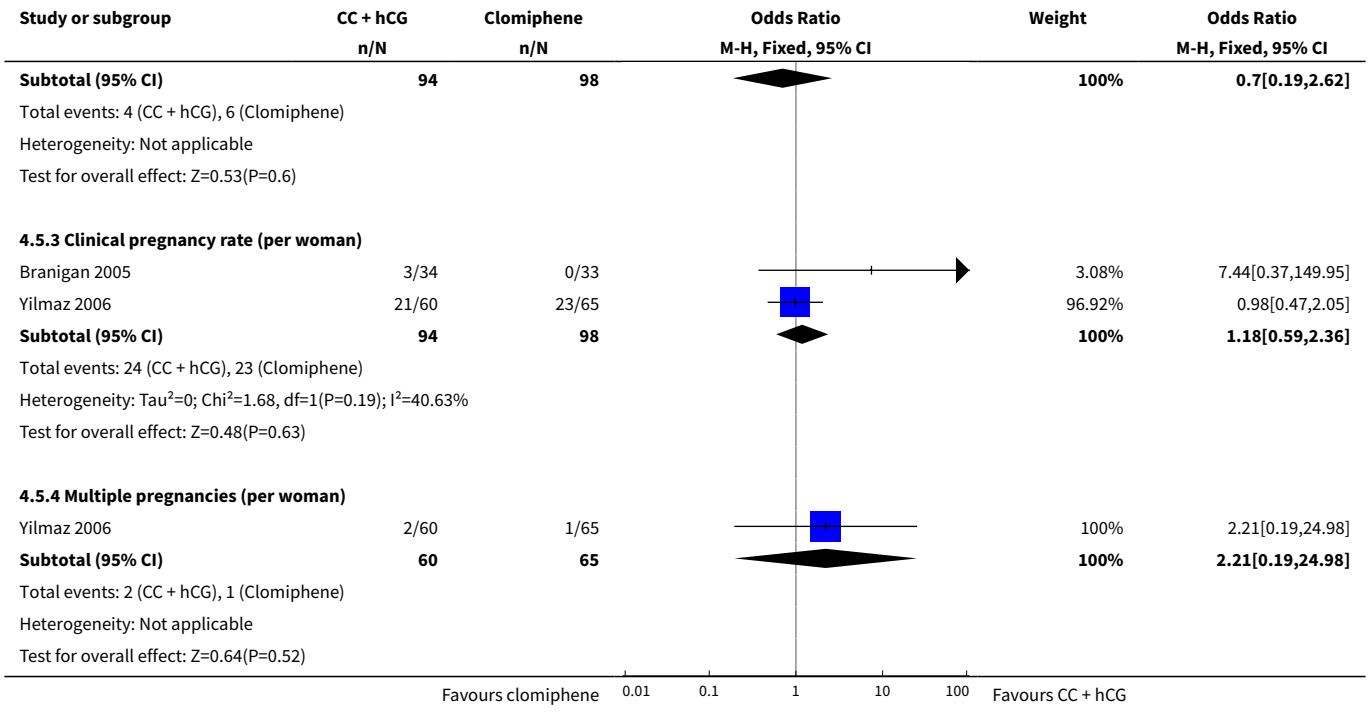


Analysis 4.4. Comparison 4 Antioestrogen plus medical adjunct versus antioestrogen alone, Outcome 4 Clomiphene citrate plus combined oral contraceptive versus clomiphene citrate.

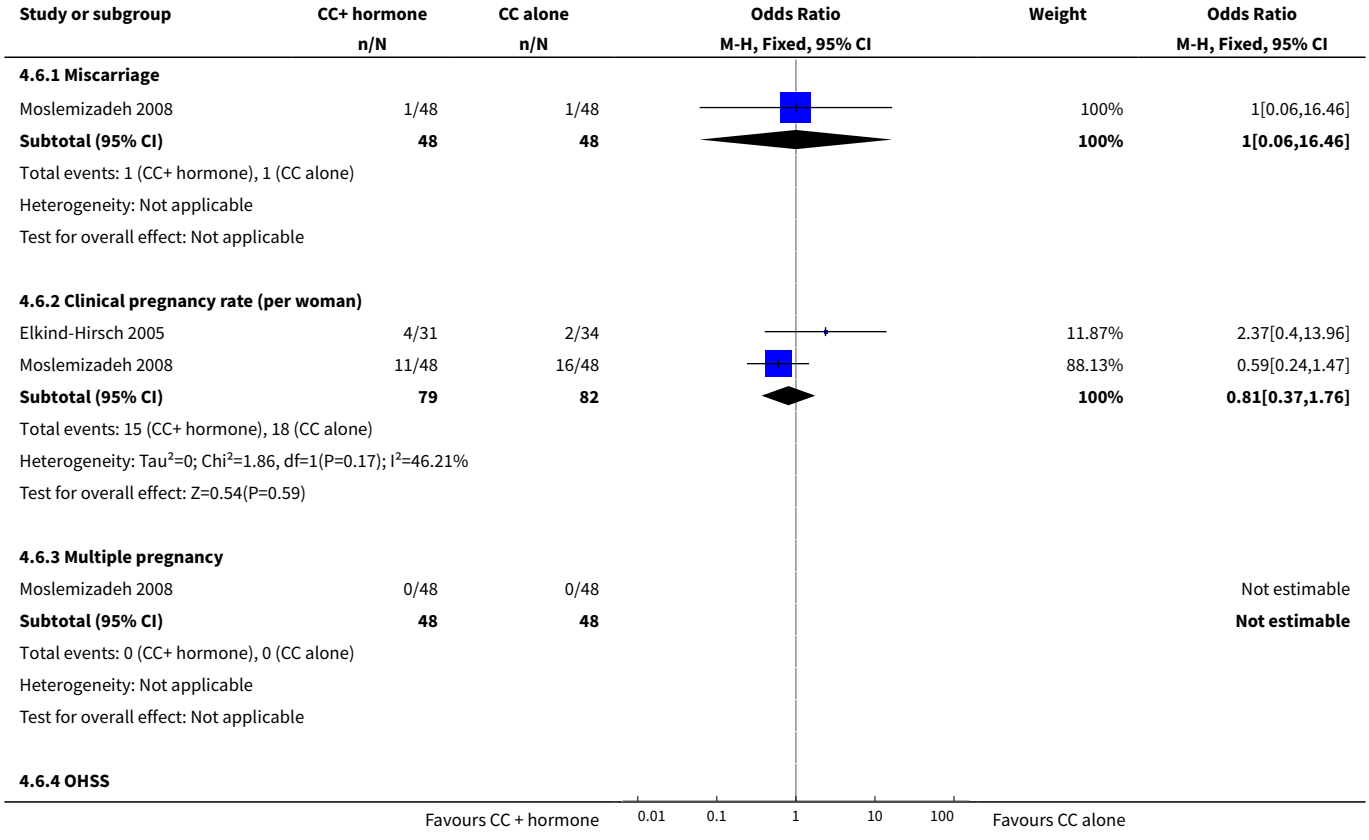


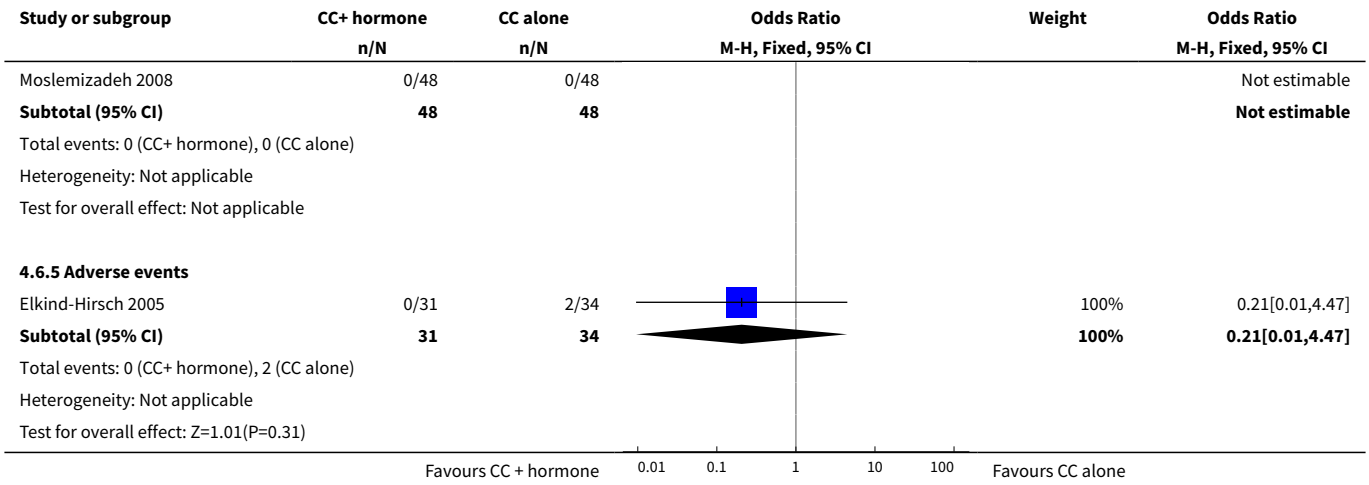
Analysis 4.5. Comparison 4 Antioestrogen plus medical adjunct versus antioestrogen alone, Outcome 5 Clomiphene citrate plus hCG versus clomiphene citrate alone.





Analysis 4.6. Comparison 4 Antioestrogen plus medical adjunct versus antioestrogen alone, Outcome 6 Clomiphene citrate plus hormone supplementation versus clomiphene citrate alone.

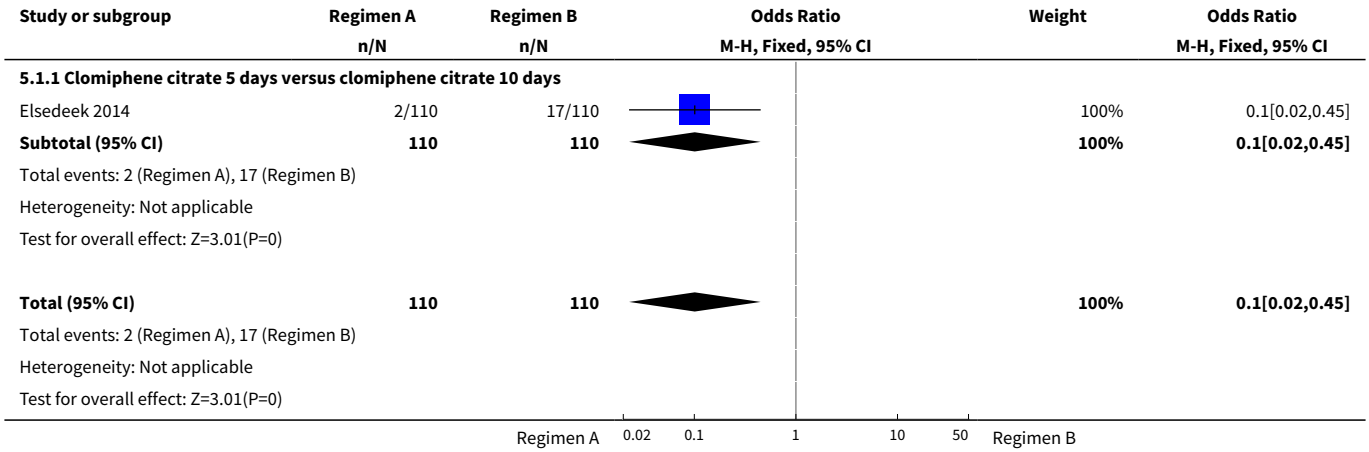




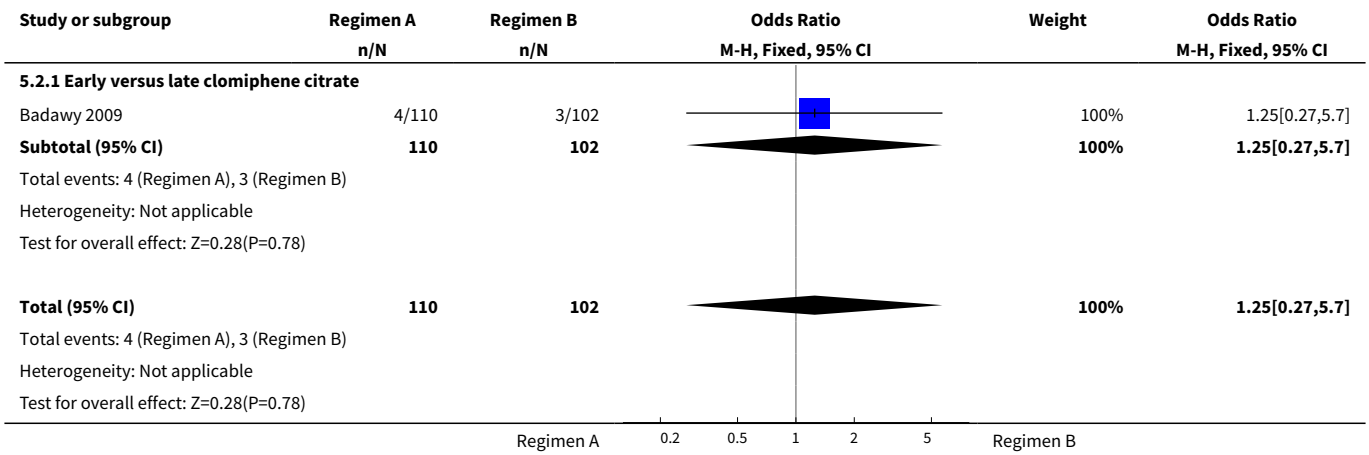
Comparison 5. Clomiphene citrate regimens

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth	1	220	Odds Ratio (M-H, Fixed, 95% CI)	0.10 [0.02, 0.45]
1.1 Clomiphene citrate 5 days versus clomiphene citrate 10 days	1	220	Odds Ratio (M-H, Fixed, 95% CI)	0.10 [0.02, 0.45]
2 Miscarriage rate	1	212	Odds Ratio (M-H, Fixed, 95% CI)	1.25 [0.27, 5.70]
2.1 Early versus late clomiphene citrate	1	212	Odds Ratio (M-H, Fixed, 95% CI)	1.25 [0.27, 5.70]
3 Clinical pregnancy	2	298	Odds Ratio (M-H, Fixed, 95% CI)	0.70 [0.37, 1.33]
3.1 Clomiphene 5 days v clomiphene 10 days	1	220	Odds Ratio (M-H, Fixed, 95% CI)	0.18 [0.06, 0.55]
3.2 Early v late clomiphene citrate	1	78	Odds Ratio (M-H, Fixed, 95% CI)	2.81 [1.02, 7.75]
4 Multiple pregnancy	1	220	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.03, 3.20]
4.1 Clomiphene 5 days v clomiphene 10 days	1	220	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.03, 3.20]

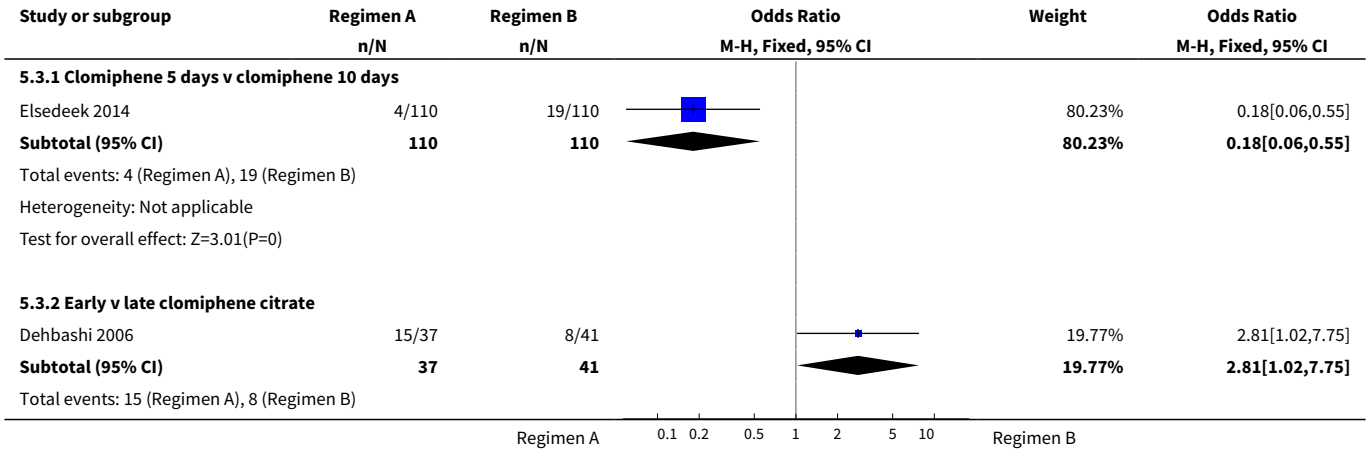
Analysis 5.1. Comparison 5 Clomiphene citrate regimens, Outcome 1 Live birth.

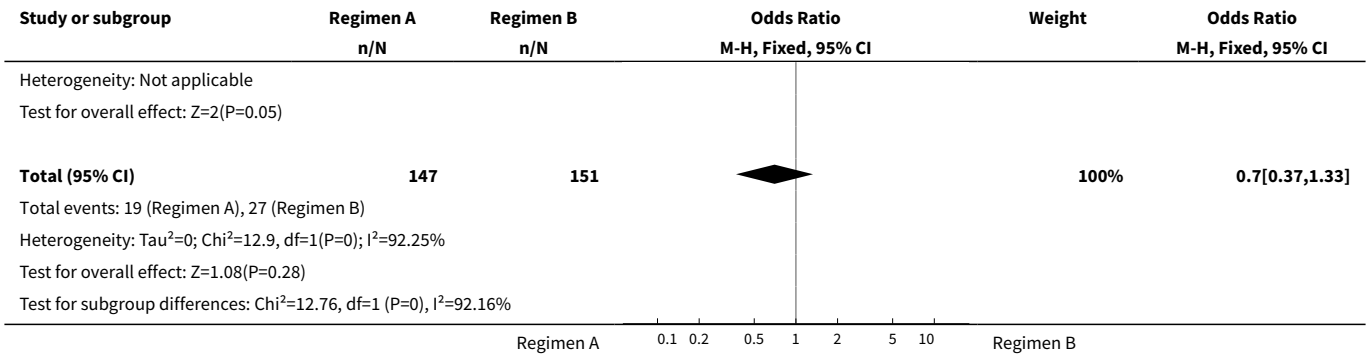


Analysis 5.2. Comparison 5 Clomiphene citrate regimens, Outcome 2 Miscarriage rate.

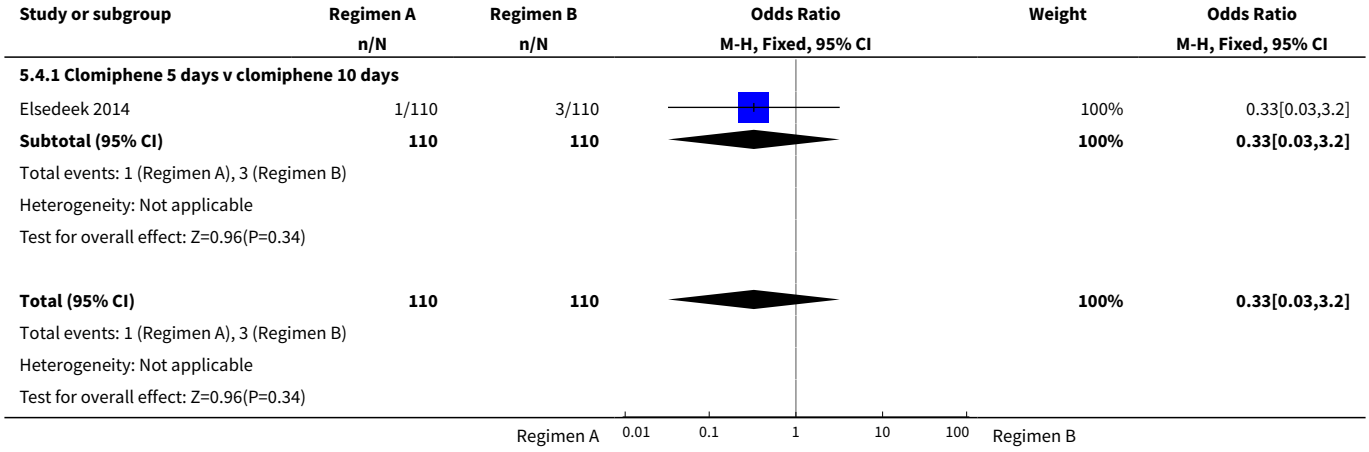


Analysis 5.3. Comparison 5 Clomiphene citrate regimens, Outcome 3 Clinical pregnancy.





Analysis 5.4. Comparison 5 Clomiphene citrate regimens, Outcome 4 Multiple pregnancy.



APPENDICES

Appendix 1. Cochrane Gynaecology and Fertility Group search strategy

Procite platform

Inception until 2 August 2016

Keywords CONTAINS "polycystic ovary morphology" or "polycystic ovary syndrome" or "PCOS" or "anovulation" or "Oligo-amenorrhea" or "oligo-ovulation" or "oligo-ovulatory" or "oligoamenorrhea" or "oligoanovulatory"or "hirsutism" or Title CONTAINS "polycystic ovary morphology" or "polycystic ovary syndrome" or "PCOS" or "anovulation" or "Oligo-amenorrhea" or "oligo-ovulation" or "oligo-ovulatory" or "oligoamenorrhea" or "oligoanovulatory"or "hirsutism"

AND

Keywords CONTAINS "anti-estrogen" or "antiestrogens" or "antioestrogens"or "Clomiphene" or "clomiphene citrate" or "clomiphene citrate resistance" or "clomiphene citrate resistant PCOS" or "clomiphene resistance" or "clomiphene resistant" or "clomiphene resistant patients" or "tamoxifen" or "tamoxifen citrate" or "*tamoxifen" or Title CONTAINS "anti-estrogen" or "antiestrogens" or "antioestrogens"or "Clomiphene" or "clomiphene citrate" or "clomiphene citrate resistance" or "clomiphene citrate resistant PCOS" or "clomiphene resistance" or "clomiphene resistant" or "clomiphene resistant patients" or "tamoxifen" or "tamoxifen citrate" or "*tamoxifen" (416 hits)

Appendix 2. CENTRAL search strategy

CRSO web platform

Inception until 2 August 2016

#1 MESH DESCRIPTOR Polycystic Ovary Syndrome EXPLODE ALL TREES (857)
#2 MESH DESCRIPTOR Anovulation EXPLODE ALL TREES (110)
#3 (Polycystic Ovar*):TI,AB,KY (1630)
#4 (PCOS or PCOD):TI,AB,KY (1251)
#5 (stein-leventhal or leventhal):TI,AB,KY (15)
#6 Anovulation:TI,AB,KY (274)
#7 (oligo ovulat* or oligoovulat*):TI,AB,KY (14)
#8 (ovar* adj3 (scelerocystic or polycystic or degeneration)):TI,AB,KY (570)
#9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 (1969)
#10 MESH DESCRIPTOR Estrogen Receptor Modulators EXPLODE ALL TREES (2386)
#11 (Estrogen Receptor Modulator*):TI,AB,KY (695)
#12 antiestrogen*:TI,AB,KY (311)
#13 (anti estrogen*):TI,AB,KY (76)
#14 (anti oestrogen*):TI,AB,KY (63)
#15 antioestrogen*:TI,AB,KY (39)
#16 MESH DESCRIPTOR Clomiphene EXPLODE ALL TREES (417)
#17 Clomiphene:TI,AB,KY (955)
#18 MESH DESCRIPTOR Tamoxifen EXPLODE ALL TREES (1816)
#19 Tamoxifen:TI,AB,KY (3618)
#20 Nolvadex:TI,AB,KY (74)
#21 Clomifene:TI,AB,KY (345)
#22 Androxal:TI,AB,KY (3)
#23 Clomid:TI,AB,KY (27)
#24 Serophene:TI,AB,KY (2)
#25 #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 (5422)
#26 #9 AND #25 (477)

Appendix 3. MEDLINE search strategy

Ovid MEDLINE(R) Epub Ahead of Print, In Process & Other Non-Indexed Citations, Ovid MEDLINE (R) Daily, and Ovid MEDLINE (R)

Ovid Platform

1946 to 2 August 2016

1 exp Polycystic Ovary Syndrome/ (11628)
2 Polycystic Ovary Syndrome.tw. (9143)
3 (PCOS or PCOD).tw. (8204)
4 (stein-leventhal or leventhal).tw. (708)
5 exp Anovulation/ (2078)
6 Anovulation.tw. (2385)
7 oligo ovulat$.tw. (77)
8 oligoovulat$.tw. (49)
9 (ovar$ adj (scelerocystic or polycystic or degeneration)).tw. (79)
10 or/1-9 (16924)
11 Estrogen Receptor Modulators/ (1932)
12 Estrogen Receptor Modulator$.tw. (2701)
13 antiestrogen$.tw. (6142)
14 antioestrogen$.tw. (491)
15 anti estrogen$.tw. (2219)
16 anti oestrogen$.tw. (787)
17 exp Clomiphene/ (4998)
18 Clomiphene.tw. (4629)
19 exp Tamoxifen/ (19471)
20 Tamoxifen.tw. (20024)
21 Nolvadex.tw. (138)
22 Clomifene.tw. (117)
23 Androxal.tw. (2)
24 Clomid.tw. (172)
25 Serophene.tw. (4)
26 or/11-25 (38622)

27 10 and 26 (1618)
28 randomized controlled trial.pt. (425556)
29 controlled clinical trial.pt. (91298)
30 randomized.ab. (364322)
31 randomised.ab. (74905)
32 placebo.tw. (181508)
33 clinical trials as topic.sh. (178394)
34 randomly.ab. (260232)
35 trial.ti. (159000)
36 (crossover or cross-over or cross over).tw. (70377)
37 or/28-36 (1106446)
38 exp animals/ not humans.sh. (4282678)
39 37 not 38 (1020128)
40 27 and 39 (426)

Appendix 4. Embase search strategy

Ovid platform

1974 to 2 August 2016

1 exp ovary polycystic disease/ (20337)
2 Polycystic ovar$ disease.tw. (883)
3 Polycystic Ovary Syndrome.tw. (12122)
4 (PCOS or PCOD).tw. (11848)
5 (stein-leventhal or leventhal).tw. (697)
6 exp anovulation/ (4438)
7 Anovulation.tw. (2905)
8 oligo ovulat$.tw. (88)
9 oligoovulat$.tw. (69)
10 (ovar$ adj (scelerocystic or polycystic or degeneration)).tw. (84)
11 or/1-10 (26127)
12 exp selective estrogen receptor modulator/ (6746)
13 Estrogen Receptor Modulator$.tw. (3523)
14 antiestrogen$.tw. (6672)
15 antioestrogen$.tw. (542)
16 anti estrogen$.tw. (2878)
17 anti oestrogen$.tw. (840)
18 exp clomifene/ (5313)
19 Clomiphene.tw. (5300)
20 Clomifene.tw. (193)
21 Androxal.tw. (18)
22 Clomid.tw. (935)
23 Serophene.tw. (189)
24 exp tamoxifen/ (52033)
25 Tamoxifen.tw. (26838)
26 Nolvadex.tw. (1369)
27 or/12-26 (72819)
28 11 and 27 (2531)
29 Clinical Trial/ (861243)
30 Randomized Controlled Trial/ (412045)
31 exp randomization/ (71505)
32 Single Blind Procedure/ (22598)
33 Double Blind Procedure/ (130362)
34 Crossover Procedure/ (48133)
35 Placebo/ (279213)
36 Randomi?ed controlled trial$.tw. (140934)
37 Rct.tw. (21143)
38 random allocation.tw. (1553)
39 randomly allocated.tw. (25331)
40 allocated randomly.tw. (2143)
41 (allocated adj2 random).tw. (761)
42 Single blind$.tw. (17780)

43 Double blind$.tw. (164421)
44 ((treble or triple) adj blind$).tw. (577)
45 placebo$.tw. (236902)
46 prospective study/ (345031)
47 or/29-46 (1600545)
48 case study/ (39626)
49 case report.tw. (311445)
50 abstract report/ or letter/ (968973)
51 or/48-50 (1312826)
52 47 not 51 (1559063)
53 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.) (5576565)
54 52 not 53 (1499261)
55 28 and 54 (863)

Appendix 5. PsycINFO search strategy

Ovid Platform

1806 to 2 August 2016

1 exp Endocrine Sexual Disorders/ (1057)
2 Polycystic Ovary Syndrome.tw. (215)
3 Polycystic Ovary disease.tw. (8)
4 (PCOS or PCOD).tw. (206)
5 (stein-leventhal or leventhal).tw. (268)
6 Anovulation.tw. (61)
7 or/1-6 (1526)
8 Estrogen Receptor Modulator$.tw. (134)
9 antiestrogen$.tw. (125)
10 antioestrogen$.tw. (2)
11 anti estrogen$.tw. (51)
12 anti oestrogen$.tw. (6)
13 Clomiphene.tw. (46)
14 Tamoxifen.tw. (453)
15 Clomifene.tw. (0)
16 Clomid.tw. (1)
17 or/8-16 (700)
18 random.tw. (47326)
19 control.tw. (366342)
20 double-blind.tw. (19967)
21 clinical trials/ (9724)
22 placebo/ (4606)
23 exp Treatment/ (657106)
24 or/18-23 (1012755)
25 7 and 17 and 24 (9)

Appendix 6. CINAHL search strategy

Ebsco platform

1982 to 2 August 2016

S36	S23 AND S35	90
S35	S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34	1,064,216
S34	TX allocat* random*	5,168
S33	(MH "Quantitative Studies")	14,720

(Continued)

S32	(MH "Placebos")	9,760
S31	TX placebo*	39,044
S30	TX random* allocat*	5,168
S29	(MH "Random Assignment")	41,345
S28	TX randomi* control* trial*	107,910
S27	TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))	843,769
S26	TX clinic* n1 trial*	187,859
S25	PT Clinical trial	79,689
S24	(MH "Clinical Trials+")	200,782
S23	S8 AND S22	174
S22	S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21	5,474
S21	TX Nolvadex	19
S20	TX Tamoxifen	3,668
S19	(MM "Tamoxifen+")	1,775
S18	TX Clomid	9
S17	TX Clomifene	18
S16	TX Clomiphene	346
S15	(MM "Clomiphene")	119
S14	TX anti oestrogen*	44
S13	TX anti estrogen*	139
S12	TX antiestrogen*	255
S11	TX antioestrogen*	18
S10	TX Estrogen Receptor Modulator*	1,314
S9	(MM "Estrogen Receptor Modulators+")	2,486
S8	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7	3,156
S7	TX oligoovulat*	6
S6	TX oligo ovulat*	3

(Continued)

S5	TX Anovulation	310
S4	(MM "Anovulation")	98
S3	TX (PCOS or PCOD)	1,620
S2	TX Polycystic Ovary Syndrome	2,145
S1	(MM "Polycystic Ovary Syndrome")	1,399

WHAT'S NEW

Date	Event	Description
12 January 2017	Review declared as stable	Further evidence is unlikely to change the conclusions of this review.

HISTORY

Protocol first published: Issue 3, 2000
Review first published: Issue 1, 2005

Date	Event	Description
13 October 2016	New search has been performed	13 new studies were included in the 2016 update (Badawy 2008; Badawy 2009; Badawy 2011; Dehbashi 2006; Elsedeek 2014; Esmaeilzadeh 2011; Ghafourzadeh 2004; Homburg 2012; Lopez 2004; Moslemizadeh 2008; Omran 2011; Seyedoshohadaei 2012; Tripathy 2013). 2 studies were added to awaiting classification (Craig 2015; Neuhausser 2011).
13 October 2016	New citation required but conclusions have not changed	The addition of 13 studies did not change the conclusions of this review.
23 June 2009	New search has been performed	9 new studies identified, review updated.
16 June 2009	Amended	Aromatase inhibitors removed from text as part of separate review.
16 June 2009	New citation required but conclusions have not changed	In June 2009 the title was changed to 'Clomiphene and antioestrogens for ovulation induction in polycystic ovarian syndrome' and new search completed. 9 additional studies identified in update.
19 February 2009	Amended	Changes made to structure of text and presentation of findings.
9 June 2008	Amended	Converted to new review format

Date	Event	Description
7 November 2004	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Julie Brown: wrote the updated version of the review, including identification of new trials, data extraction, and analysis.

Cindy Farquhar: initiated and conceptualised the protocol, commented on drafts of the original and updated review, and assisted in the identification of new trials and data extraction for the review update.

DECLARATIONS OF INTEREST

Julie Brown: None known.

Cindy Farquhar is a director/shareholder of a gynaecology clinic and undertakes private practice within those premises.

SOURCES OF SUPPORT

Internal sources

- University of Auckland, New Zealand.

  Provided salary support for Julie Brown to update this review

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the 2009 review we widened the inclusion criteria of this review from that of the original protocol (women with anovulation attributed to polycystic ovarian syndrome (PCOS)) to include all World Health Organization (WHO) group 2 causes of anovulation, but excluding hyperprolactinaemia. We included trials that were non-specific but appeared to describe PCOS-like anovulation (e.g. women with progestin-induced withdrawal bleeding). Due to the age of many of the trials, particularly for the comparison of clomiphene versus placebo, the most likely cause of anovulation was not fully described. In particular, the currently utilised diagnostic criteria for PCOS were not able to be met. These trials would have been excluded under the criteria of the protocol. We felt that their results were valid and important, and so widened the background and inclusion criteria sections of this review.

In the 2009 review we removed aromatase inhibitor comparisons from this review, as they have been addressed within a separate review (Franik 2014)

In the 2009 review we changed the title from 'Oral anti-oestrogens and medical adjuncts for subfertility associated with anovulation' to 'Clomiphene and antioestrogens for ovulation induction in polycystic ovarian syndrome'.

In the 2016 update we removed as an outcome 'ovulation rate (per woman), where ovulation was defined as evidence of serum progesterone in the luteal range for the reference laboratory or a basal body temperature rise by > 0.4 °C for 10 days or more as measured by a basal body temperature chart'.

INDEX TERMS

Medical Subject Headings (MeSH)

Anovulation [*complications] [drug therapy]; Clomiphene [adverse effects] [*therapeutic use]; Contraceptives, Oral, Combined [therapeutic use]; Dexamethasone [therapeutic use]; Drug Therapy, Combination [methods]; Estrogen Antagonists [adverse effects] [*therapeutic use]; Gonadotropins [therapeutic use]; Infertility, Female [*drug therapy] [etiology]; Live Birth; Polycystic Ovary Syndrome [complications]; Randomized Controlled Trials as Topic; Tamoxifen [therapeutic use]

MeSH check words

Female; Humans