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Laparoscopic drilling by diathermy or laser for ovulation induction in anovulatory polycystic ovary syndrome (Review)

Farquhar C, Brown J, Marjoribanks J



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Laparoscopic drilling by diathermy or laser for ovulation induction in anovulatory polycystic ovary syndrome (Review)
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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON	2
BACKGROUND	5
OBJECTIVES	5
METHODS	5
Figure 1.	7
Figure 2.	8
Figure 3.	9
RESULTS	10
Figure 4.	14
Figure 5.	15
Figure 6.	17
ADDITIONAL SUMMARY OF FINDINGS	18
DISCUSSION	21
AUTHORS' CONCLUSIONS	21
ACKNOWLEDGEMENTS	22
REFERENCES	22
CHARACTERISTICS OF STUDIES	25
DATA AND ANALYSES	53
ADDITIONAL TABLES	56
FEEDBACK	56
WHAT'S NEW	56
HISTORY	57
CONTRIBUTIONS OF AUTHORS	57
DECLARATIONS OF INTEREST	57
SOURCES OF SUPPORT	58
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	58
NOTES	58
INDEX TERMS	58

Laparoscopic drilling by diathermy or laser for ovulation induction in anovulatory polycystic ovary syndrome

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ABSTRACT

Background

Surgical ovarian wedge resection was the first established treatment for women with anovulatory polycystic ovary syndrome (PCOS) but was largely abandoned both due to the risk of postsurgical adhesions and the introduction of medical ovulation induction. However, women with PCOS who are treated with medical ovulation induction, with drugs such as gonadotrophins, often have an overproduction of follicles which may result in ovarian hyperstimulation syndrome and multiple pregnancies. Moreover, gonadotrophins, though effective, are costly and time-consuming and their use requires intensive monitoring. Surgical therapy with laparoscopic ovarian 'drilling' (LOD) may avoid or reduce the need for medical ovulation induction, or may facilitate its usefulness. The procedure can be done on an outpatient basis with less trauma and fewer postoperative adhesions than with traditional surgical approaches. Many uncontrolled observational studies have claimed that ovarian drilling is followed, at least temporarily, by a high rate of spontaneous ovulation and conception, or that subsequent medical ovulation induction becomes easier.

Objectives

To determine the effectiveness and safety of laparoscopic ovarian drilling compared with ovulation induction for subfertile women with clomiphene-resistant PCOS.

Search methods

We used the search strategy of the Menstrual Disorders and Subfertility Group (MDSG) to search the MDSG Trials Register, CENTRAL, MEDLINE, EMBASE, CINAHL and PsycINFO. The keywords included polycystic ovary syndrome, laparoscopic ovarian drilling, electrocautery and diathermy. Searches were conducted in September 2011, and a further search of the MDSG Trials Register was made on 14 May 2012.

Selection criteria

We included randomised controlled trials of subfertile women with clomiphene-resistant PCOS who undertook laparoscopic ovarian drilling in order to induce ovulation.

Data collection and analysis

This is an update of a previously updated review. There were nine RCTs in the previous version; an additional 16 trials were added in the current (2012) update. All trials were assessed for quality. The primary outcomes were live birth and multiple pregnancy. The secondary outcomes were rate of miscarriage, ovulation and pregnancy rates, ovarian hyperstimulation syndrome (OHSS), quality of life and cost.

Main results

Eight trials, including 1034 women, reported on the primary outcome of live birth rate per couple. Live births were reported in 34% of women in the LOD groups and 40% in other medical treatment groups. There were five different comparisons with LOD and there was no evidence of a difference in live births when compared with clomiphene citrate + tamoxifen (OR 0.81; 95% CI 0.42 to 1.53; $P = 0.51$, 1 trial, $n = 150$), gonadotrophins (OR 0.97; 95% CI 0.59 to 1.59; $P = 0.89$, $I^2 = 0\%$, 2 trials, $n = 318$) or aromatase inhibitors (OR 0.84; 95% CI 0.54 to 1.31; $P = 0.44$, $I^2 = 0\%$, 2 trials, $n = 407$). There was evidence of significantly fewer live births following LOD compared with clomiphene citrate + metformin (OR 0.44; 95% CI 0.24 to 0.82; $P = 0.01$, $I^2 = 78\%$, 2 trials, $n = 159$); the high heterogeneity in this subgroup could not be explained by population differences or differences in quality of the trials.

Twelve trials reported on multiple pregnancies ($n = 1129$ women). There were no multiple pregnancies in either group for clomiphene citrate or aromatase inhibitors compared with LOD. The rate of multiple pregnancies was significantly lower in the LOD group compared with trials using gonadotrophins (OR 0.13; 95% CI 0.03 to 0.52; $P = 0.004$, $I^2 = 0\%$, 5 trials, $n = 166$).

Authors' conclusions

There was no evidence of a significant difference in rates of clinical pregnancy, live birth or miscarriage in women with clomiphene-resistant PCOS undergoing LOD compared to other medical treatments. The reduction in multiple pregnancy rates in women undergoing LOD makes this option attractive. However, there are ongoing concerns about the long-term effects of LOD on ovarian function.

PLAIN LANGUAGE SUMMARY

Laparoscopic 'drilling' by diathermy or laser for ovulation induction in anovulatory polycystic ovary syndrome

Ovarian surgery in women with clomiphene-resistant polycystic ovarian syndrome reduces the risk of multiple pregnancy without decreasing the pregnancy rate. Women with polycystic ovary syndrome (PCOS) have trouble ovulating. Some treatment schedules with medical ovulation induction can overstimulate the ovary and cause multiple pregnancy. An alternative is a minor surgical procedure called laparoscopic ovarian drilling, where a long telescope is passed through a small cut in the umbilicus. The ovaries are then surgically treated by drilling, using either heat or laser. This review of trials found that ovarian drilling without or with ovulation induction, if necessary, was as effective as medical ovulation induction alone in inducing ovulation, but the risk of multiple pregnancies was lower in the group of women who had laparoscopic ovarian drilling. Approximately 37% of women will have a live birth and 7% will have a miscarriage with either procedure.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

LOD with and without medical ovulation compared to other treatment for anovulatory women with PCOS						
Patient or population: patients with anovulatory women with PCOS Settings: Fertility clinics Intervention: LOD with and without medical ovulation Comparison: other treatment						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Other treatment	LOD ± medical ovulation				
Live birth rate	402 per 1000	341 per 1000 (284 to 405)	OR 0.77 (0.59 to 1.01)	1034 (8studies)	⊕⊕⊕○ moderate ¹	
Pregnancy rate per woman randomised	411 per 1000	396per 1000 (352 to 443)	OR 0.94 (0.78 to 1.14)	1930 (18studies)	⊕⊕○○ low ²	
Miscarriage rate	67 per 1000	73 per 1000 (51 to 104)	OR 1.1 (0.74 to 1.61)	1592 (15 studies)	⊕⊕○○ low ³	
Multiple pregnancy rate (per ongoing pregnancy)	34 per 1000	7 per 1000 (3 to 20)	OR 0.21 (0.08 to 0.58)	1129 (12studies)	⊕⊕⊕○ moderate ⁴	
OHSS	11 per 1000	2 per 1000 (0 to 13)	OR 0.14 (0.02 to 1.19)	908 (7 studies)	⊕⊕○○ low ^{5,6}	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

- ¹ Four of the trials were open labelled and no evidence of blinding and one of the trials lacked adequate information regarding blinding
- ² There was inadequate explanation for randomisation (4 trials) and allocation concealment (9 trials) and lack of detail or no blinding in 14 trials.
- ³ There were inadequate explanations of randomisation (in 3 trials), allocation concealment (8 trials) and inadequate or no blinding reported in 8 trials
- ⁴ Six trials had an inadequate explanation of or no blinding
- ⁵ Five trials showed no evidence of blinding
- ⁶ The summary effect crossed the line of no effect and substantive benefit or harm

BACKGROUND

Description of the condition

Problems in inducing ovulation and anovulation (failure to ovulate) are well recognised in women with polycystic ovary syndrome (PCOS). Surgical ovarian wedge resection was the first established treatment for women with anovulatory PCOS (Stein 1939) but was largely abandoned because of the risk of postsurgical adhesion formation, which converted endocrinological (or hormonal) subfertility to mechanical subfertility as a result of scarring (Adashi 1981; Buttram 1975). Wedge resection was replaced by medical ovulation induction with clomiphene and gonadotrophins (Franks 1985). Ovulation induction with clomiphene citrate is not always successful, with approximately 20% of women described as 'clomiphene-resistant' (Imani 1998). Women who are clomiphene resistant can be treated with gonadotrophins or other medical ovulation induction agents but often have an overproduction of follicles and are exposed to the risks of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancy. Drugs such as gonadotrophins are an expensive, inconvenient and time-consuming form of treatment that requires intensive monitoring. An alternative to medical ovulation induction is surgical therapy using laparoscopic techniques known as laparoscopic ovarian drilling (LOD).

Description of the intervention

Laparoscopic ovarian drilling was first described by Gjonnaess in 1984 (Gjonnaess 1984). Both laparoscopic ovarian cautery and laser vaporisation using carbon dioxide (CO₂), argon or neodymium-doped yttrium aluminium garnet (Nd:YAG; Nd:Y₃Al₅O₁₂) crystal lasers have been used to create multiple perforations (approximately 10 holes per ovary) in the ovarian surface and stroma (inner area of the ovary). The procedure can be done on an outpatient basis with less trauma and fewer postoperative adhesions than with ovarian wedge resection. Many uncontrolled observational studies claim that it is followed, at least temporarily, by a high rate of spontaneous postoperative ovulation and conception (Armar 1990; Armarm 1993; Greenblatt 1987; Kovacs 1991) or that subsequent medical ovulation induction becomes easier (Farhi 1995).

How the intervention might work

The mechanism of action of LOD is thought to be similar to that of ovarian wedge resection. Both procedures may destroy ovarian androgen-producing tissue and reduce the peripheral conversion of androgens to estrogens (one of the many disturbances of endocrine physiology that occur in women with polycystic ovarian

syndrome). A fall in the serum levels of androgens and luteinising hormone (LH) and an increase in follicle-stimulating hormone (FSH) levels have been demonstrated after ovarian drilling (Armar 1990; Greenblatt 1987). The endocrine changes following the surgery are thought to convert the adverse androgen-dominant intrafollicular environment to an estrogenic one (Aakvaag 1985) and to restore the hormonal environment to normal by correcting disturbances of the ovarian-pituitary feedback mechanism (Balen 1993). Thus, both local and systemic effects are thought to promote follicular recruitment, maturation and subsequent ovulation.

Why it is important to do this review

The aim of this review was to determine the effectiveness and safety of laparoscopic ovarian drilling with ovulation induction for subfertile women with clomiphene-resistant polycystic ovarian syndrome (PCOS).

OBJECTIVES

To determine the effectiveness and safety of laparoscopic ovarian drilling compared with ovulation induction for subfertile women with clomiphene-resistant PCOS.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) of laparoscopic ovarian diathermy or a drilling procedure (with or without subsequent medical ovulation induction) in anovulatory subfertile women with clomiphene-resistant PCOS.

Types of participants

Subfertile women with anovulation and PCOS, which was diagnosed by a combination of clinical features, abnormal endocrine tests, ultrasonographic or visual appearance of the ovaries, who had been shown to be resistant to clomiphene (100 mg/day or more). Clomiphene resistance was defined as lack of proven ovulation with the use of clomiphene citrate.

Types of interventions

1. Laparoscopic ovarian drilling (with or without medical ovulation induction) versus other medical treatments
2. Laparoscopic drilling in women undergoing artificial reproductive technologies (ART) such as in vitro fertilisation (IVF)
3. Various techniques of laparoscopic ovarian drilling, for example:
 - laser versus diathermy;
 - laparoscopic ovarian drilling plus second-look laparoscopy versus drilling plus expectant management;
 - laparoscopic ovarian drilling of one ovary (unilateral) compared with laparoscopic drilling of both ovaries (bilateral).

Types of outcome measures

Primary outcomes

- Live birth rate (per couple)
- Incidence of multiple pregnancy (per ongoing pregnancy)

Secondary outcomes

- Pregnancy rate (per woman randomised), defined as a gestational sac seen on ultrasound
- Miscarriage rate (per pregnancy)
- Incidence of ovarian hyperstimulation syndrome (OHSS) (per couple)
- Ovulation rate (per couple)
- Costs
- Quality of life

Search methods for identification of studies

Electronic searches

The 2012 update of this review searched five electronic databases using searches developed by the Cochrane Menstrual Disorders and Subfertility Group. Searches were conducted in September 2011, with a further search of the MDSG Trials Register on 14 May 2012. The searches were not restricted by language. The search strings for each database can be referred to in the associated Appendix (see below).

The following databases were searched:

- Menstrual Disorders and Subfertility Group Trials Register (Appendix 1)
- MEDLINE (Appendix 2)
- EMBASE (Appendix 3)
- CINAHL: searches using CINAHL were not re-run in the update, as per MDSG protocol, but the original search string is shown (Appendix 4)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Appendix 5)
- PsycINFO (Appendix 6)

Searching other resources

Citation lists of included trials, conference abstracts and relevant review articles were also searched. Authors and other content experts were contacted.

Data collection and analysis

Selection of studies

In the original review CF and JM were responsible for the selection of studies. In the 2012 update CF and JB performed this task. Titles and abstracts were scanned and those thought to be relevant were obtained in full text. If disagreements emerged a third review author was available or the issue was resolved by consensus.

Data extraction and management

Data extraction was performed independently by two review authors (CF and JM in the original review; CF and JB in the 2012 update) using forms designed according to Cochrane guidelines. Differences of opinion were recorded and resolved by consensus.

Assessment of risk of bias in included studies

All assessments of the quality of trials ([Characteristics of included studies](#)) were performed independently by two review authors (CF and JM in the original review; CF and JB in the 2012 update). Information was obtained on method of randomisation, allocation concealment, blinding, incomplete outcome data and selection bias (refer to [Figure 1](#); [Figure 2](#)). Additional information on trial methodology and actual original trial data were sought from the authors of trials which appeared to meet the eligibility criteria but had aspects of methodology that were unclear, or where the data were in a form unsuitable for meta-analysis.

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

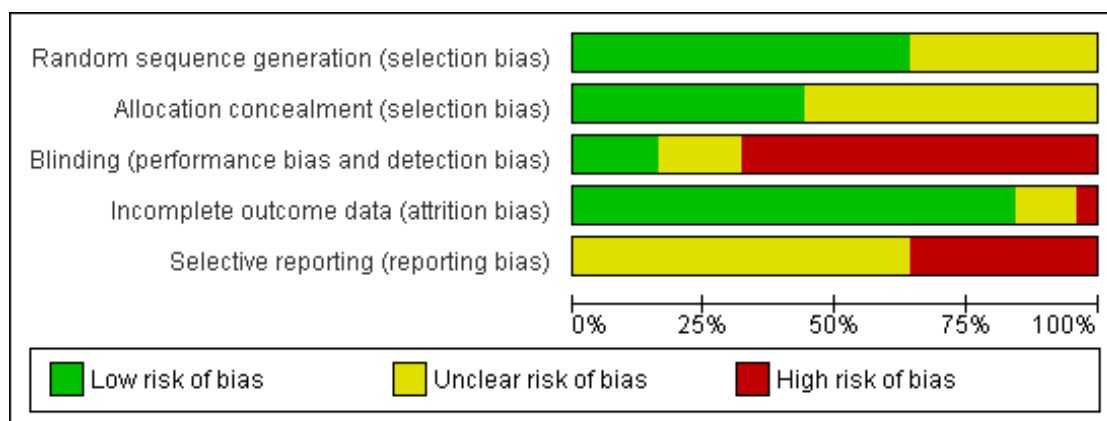


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Abdellah 2011	+	+	-	?	-
Abu Hashim 2010	+	+	+	+	-
Abu Hashim 2011	+	+	-	+	?
Al-Mizyen 2000	?	?	-	+	-
Amer 2009	+	+	-	+	-
Ashrafinia 2009	?	+	-	+	-
Balen 1994	?	?	-	+	-
Bayram 2004	+	+	-	+	?
Farquhar 2002	+	+	-	+	?
Ghafarnegad 2010	+	?	?	+	?
Gurgan 1992	+	?	-	+	?
Hamed 2010	+	+	?	+	?
Kaya 2005	+	+	-	+	?
Lazoviz 1998	?	?	-	+	-
Mamonov 2000	?	?	-	?	-
Palomba 2004	+	?	+	+	?
Palomba 2010	+	+	?	+	?
Rimington 1997	+	?	-	+	?
Roy 2009	?	?	-	+	?
Roy 2010	+	?	+	-	?
Sharma 2006	+	?	-	+	-
Vegetti 1998	?	?	-	?	?
Youssef 2007	?	+	+	+	?
Zakherah 2009	?	?	?	+	?
Zakherah 2010	+	?	-	+	?

Measures of treatment effect

Binary outcome data for each study were expressed as odds ratios (OR) with 95% confidence intervals (CI). For continuous data (for example cost), if all studies reported exactly the same outcomes we calculated mean differences (MD) between treatment groups, with 95% CI. If similar outcomes were reported on different scales we planned to calculate the standardised mean difference.

Unit of analysis issues

In some of the trials the women received multiple cycles of treatment and the authors reported data per cycle and not per woman or couple randomised. Where this occurred the primary authors were contacted for data per woman randomised. Per cycle data were not included in the meta-analyses.

Dealing with missing data

Where data were missing, the primary authors were contacted directly to provide this information. Intention-to-treat analyses were conducted on the data in this review, where possible.

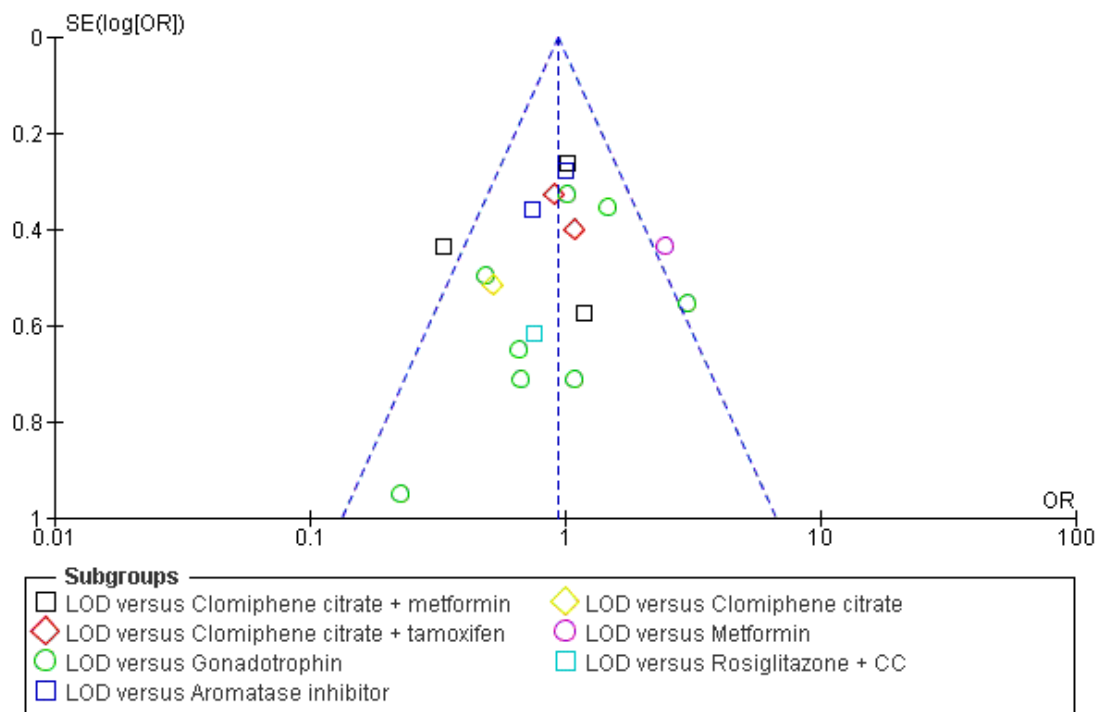
Assessment of heterogeneity

Heterogeneity between the results of different studies was examined by inspecting the scatter in the data points and the overlap in their CIs, and more formally by χ^2 tests and the I^2 statistic. If heterogeneity was detected, it was planned, a priori, to look at the possible contribution of differences in trial design.

Assessment of reporting biases

A funnel plot was produced for the outcome of pregnancy per woman randomised as there were 18 studies reporting this outcome. Refer to [Figure 3](#).

Figure 3. Funnel plot of comparison: 1 LOD \pm medical ovulation versus other treatment, outcome: 1.2 Pregnancy rate per woman randomised.



Data synthesis

The results were combined for meta-analysis using RevMan software (using the Mantel-Haenszel method) and a fixed-effect model. Comparisons were as follows.

1. Laparoscopic drilling or diathermy with or without medical ovulation induction versus other treatment

- i) Live birth rate
- ii) Multiple pregnancy rate
- iii) Pregnancy rate
- iv) Miscarriage rate
- v) OHSS
- vi) Ovulation rate
- vii) Costs
- viii) Quality of life

2. Unilateral versus bilateral drilling

- i) Live birth rate
- ii) Multiple pregnancy rate
- iii) Pregnancy rate
- iv) Miscarriage rate
- v) OHSS
- vi) Ovulation rate
- vii) Costs
- viii) Quality of life

3. Second-look laparoscopy versus expectant management

- i) Live birth rate
- ii) Multiple pregnancy rate
- iii) Pregnancy rate
- iv) Miscarriage rate
- v) OHSS
- vi) Ovulation rate
- vii) Costs
- viii) Quality of life

4. Laparoscopic diathermy or electrocautery + IVF versus IVF

- i) Live birth rate
- ii) Multiple pregnancy rate
- iii) Pregnancy rate
- iv) Miscarriage rate
- v) OHSS
- vi) Ovulation rate
- vii) Costs
- viii) Quality of life

Subgroup analysis and investigation of heterogeneity

The different medical treatments (ovulation induction) that were compared with LOD formed the subgroups in the meta-analysis:

- i) clomiphene citrate + metformin;
- ii) clomiphene citrate + tamoxifen;
- iii) gonadotrophins;
- iv) aromatase inhibitors;
- v) clomiphene citrate;

vi) metformin;

vii) rosiglitazone + clomiphene citrate.

Sensitivity analysis

There were no sensitivity analyses conducted in this review. If future updates identify high levels of heterogeneity, sensitivity analyses may be conducted based on study quality.

Updating the review

The review will be updated every two years.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of studies awaiting classification](#).

Results of the search

The original review retrieved 19 full text articles and included nine RCTs. In the 2012 update 86 potential articles were identified. Sixteen trials met the inclusion criteria ([Abdellah 2011](#); [Abu Hashim 2010](#); [Abu Hashim 2011](#); [Amer 2009](#); [Bayram 2004](#); [Ghafarnegad 2010](#); [Hamed 2010](#); [Palomba 2004](#); [Palomba 2010](#); [Rimington 1997](#); [Roy 2009](#); [Roy 2010](#); [Sharma 2006](#); [Youssef 2007](#); [Zakherah 2009](#); [Zakherah 2010](#)).

Two studies are awaiting assessment ([Lockwood 1995](#); [Malkawi 2003](#)). [Lockwood 1995](#) is a conference abstract that the review authors are trying to obtain. It was originally excluded due to lack of usable data. It has now been moved to an included study status and the review authors will enter details when these are obtained. The authors of [Malkawi 2003](#) were contacted in September 2011 with regards to the methods of group allocation to determine if trial was randomised. There has been no response to date (refer to [Characteristics of studies awaiting classification](#)).

A total of 19 studies were excluded. See study tables: [Characteristics of included studies](#); [Characteristics of excluded studies](#). In addition, one of the studies that was originally excluded ([Mamonov 2000](#)) was moved into the included studies, as it was an abstract from which no usable data could be retrieved (despite trying to contact authors),

Included studies

Study design and setting

A total of 26 trials was included in this systematic review. All studies were parallel-design randomised controlled trials (RCTs).

All of the trials recruited women with fertility problems who were attending fertility clinics. Seven were from Egypt (Abdellah 2011; Abu Hashim 2010; Abu Hashim 2011; Hamed 2010; Youssef 2007; Zakherah 2009; Zakherah 2010), four from the UK (Al-Mizyen 2000; Amer 2009; Balen 1994; Rimington 1997), one from the Netherlands (Bayram 2004), one from New Zealand (Farquhar 2002), two from Iran (Ashrafinia 2009; Ghafarnegad 2010), two from Turkey (Gurgan 1992; Kaya 2005), one from Yugoslavia (Lazoviz 1998), one from Ukraine (Mamonov 2000), three from Italy (Palomba 2004; Palomba 2010; Vegetti 1998) and three from India (Roy 2009; Roy 2010; Sharma 2006).

Participants

1.0 Laparoscopic ovarian drilling (LOD) with or without medical ovulation induction versus other treatment

There were 948 women in the LOD groups and 985 women in the control groups. All were women with subfertility. The mean reported age of the participants in the laparoscopic drilling groups was 26.8 years and in the other medical treatment groups was 26.7 years. All of the women had polycystic ovary syndrome (PCOS).

2.0 Bilateral versus unilateral drilling

There were 91 women who had undergone bilateral ovarian drilling and 90 women who had undergone unilateral ovarian drilling. The mean age of women in the bilateral group was 28 years and in the unilateral group it was 28.8 years.

3.0 Second-look laparoscopy versus expectant management

There were 20 women who had undergone second-look laparoscopy and 20 women who had expectant management. The mean age of the women was 25.2 years.

4.0 Laparoscopic electrocautery + IVF versus conventional IVF

There were 25 women who had undergone laparoscopic ovarian electrocautery (LOE) + IVF and 25 women had undergone conventional IVF. The mean age of the women in the LOE + IVF group was 31.8 years and in the conventional IVF group the mean age was 31 years.

Interventions

1.0 Interventions for LOD with or without medical ovulation versus other treatment

- 8/19 trials compared LOD with gonadotrophins (Bayram 2004; Farquhar 2002; Ghafarnegad 2010; Gurgan 1992; Kaya 2005; Lazoviz 1998; Mamonov 2000; Vegetti 1998)
- 3/19 trials compared LOD with clomiphene citrate + metformin (Abu Hashim 2011; Palomba 2004; Palomba 2010)
- 2/19 trials compared LOD with clomiphene citrate + tamoxifen (Zakherah 2009; Zakherah 2010)
- 1/19 trials compared LOD with clomiphene citrate (Amer 2009)
- 1/19 trials compared LOD with rosiglitazone + clomiphene citrate (Roy 2010)
- 2/19 trials compared LOD with aromatase inhibitors (Abdellah 2011; Abu Hashim 2010)
- 2/19 trials compared LOD with metformin (Ashrafinia 2009; Hamed 2010)

2.0 Unilateral versus bilateral ovarian drilling

- 5/5 trials compared unilateral and bilateral drilling (Al-Mizyen 2000; Balen 1994; Roy 2009; Sharma 2006; Youssef 2007)

3.0 Second-look laparoscopy versus expectant management

- 1/1 trial compared second-look laparoscopy versus expectant management (Gurgan 1992)

4.0 Laparoscopic ovarian electrocautery + IVF versus conventional IVF

- 1/1 trial compared laparoscopic ovarian electrocautery + IVF versus conventional IVF (Rimington 1997)

Outcomes

1.0 Outcomes for LOD with or without medical ovulation versus other treatment

- 8/19 reported live birth (Abdellah 2011; Abu Hashim 2010; Bayram 2004; Farquhar 2002; Ghafarnegad 2010; Palomba 2004; Palomba 2010; Zakherah 2010)
- 18/19 reported pregnancy rates (Abu Hashim 2011; Palomba 2004; Palomba 2010; Abdellah 2011; Abu Hashim 2010; Amer 2009; Bayram 2004; Farquhar 2002; Ghafarnegad 2010; Gurgan 1992; Hamed 2010; Kaya 2005; Lazoviz 1998; Mamonov 2000; Roy 2010; Vegetti 1998; Zakherah 2009; Zakherah 2010)

- 15/19 reported miscarriage (Abdellah 2011; Abu Hashim 2010; Abu Hashim 2011; Bayram 2004; Farquhar 2002; Ghafarnegad 2010; Gurgan 1992; Hamed 2010; Lazoviz 1998; Mamonov 2000; Palomba 2004; Palomba 2010; Roy 2010; Vegetti 1998; Zakherah 2010)
- 12/19 reported multiple pregnancies (Abdellah 2011; Abu Hashim 2010; Abu Hashim 2011; Amer 2009; Bayram 2004; Farquhar 2002; Kaya 2005; Lazoviz 1998; Palomba 2004; Palomba 2010; Roy 2010; Vegetti 1998)
- 6/19 reported ovulation rates (Amer 2009; Farquhar 2002; Hamed 2010; Roy 2010; Zakherah 2009; Zakherah 2010)
- 7/19 reported OHSS (Abu Hashim 2011; Abu Hashim 2010; Amer 2009; Bayram 2004; Farquhar 2002; Kaya 2005; Roy 2010)
- 4/20 reported costs (Bayram 2004; Farquhar 2002; Kaya 2005; Palomba 2010)
- 1/20 reported quality of life (Bayram 2004)

One trial was identified that met all of the inclusion criteria associated with the population and interventions but did not report on any obstetric outcomes (Ashrafinia 2009). The authors have been contacted for information but there has been no response to date.

2.0 Outcomes for unilateral versus bilateral ovarian drilling

- 1/5 reported live birth (Roy 2009)
- 5/5 reported pregnancy rate (Al-Mizyen 2000; Balen 1994; Roy 2009; Sharma 2006; Youssef 2007)
- 4/5 reported ovulation rate (Balen 1994; Roy 2009; Sharma 2006; Youssef 2007)
- 2/5 reported miscarriage (Roy 2009; Youssef 2007)

3.0 Outcomes for second look laparoscopy versus expectant management

No trial reported on live birth.

- 1/1 reported pregnancy (Gurgan 1992)
- 1/1 reported ovulation rate (Gurgan 1992)
- 1/1 reported miscarriage rate (Gurgan 1992)

4.0 Outcomes for laparoscopic ovarian electrocautery + IVF versus conventional IVF

- 1/1 reported live birth (Rimington 1997)
- 1/1 reported pregnancy rate (Rimington 1997)
- 1/1 reported miscarriage (Rimington 1997)
- 1/1 reported multiple pregnancy (Rimington 1997)
- 1/1 reported OHSS (Rimington 1997)

Excluded studies

Nineteen studies were excluded from the review, for the following reasons (refer to [Characteristics of excluded studies](#) for further details):

- 9/19 were not randomised controlled trials
- 1/19 had participants not of interest to this review
- 1/19 reported outcomes not of interest to this review
- 7/19 had comparisons not of interest to this review
- 1/19 had ovaries as the unit of randomisation

Risk of bias in included studies

The risk of bias of included studies is illustrated in [Figure 1](#); [Figure 2](#).

Allocation

Fifteen trials were at low risk of bias due to random sequence generation as they clearly explained the methods used (Abdellah 2011; Abu Hashim 2010; Abu Hashim 2011; Amer 2009; Bayram 2004; Farquhar 2002; Ghafarnegad 2010; Gurgan 1992; Hamed 2010; Kaya 2005; Palomba 2004; Palomba 2010; Rimington 1997; Roy 2010; Sharma 2006). Ten trials did not provide an adequate explanation of the randomisation process (Al-Mizyen 2000; Ashrafinia 2009; Balen 1994; Lazoviz 1998; Mamonov 2000; Roy 2009; Vegetti 1998; Youssef 2007; Zakherah 2009; Zakherah 2010).

Eleven trials were at low risk of selection bias related to allocation concealment as they used central allocation concealment or sealed opaque sequentially numbered envelopes (Abdellah 2011; Abu Hashim 2010; Abu Hashim 2011; Amer 2009; Ashrafinia 2009; Bayram 2004; Farquhar 2002; Hamed 2010; Kaya 2005; Palomba 2010; Youssef 2007). Fourteen trials did not provide adequate details to establish whether an appropriate method of allocation concealment had been used (Al-Mizyen 2000; Balen 1994; Ghafarnegad 2010; Gurgan 1992; Lazoviz 1998; Mamonov 2000; Palomba 2004; Rimington 1997; Roy 2009; Roy 2010; Sharma 2006; Vegetti 1998; Zakherah 2009; Zakherah 2010).

Blinding

Adequate blinding was reported in only four trials (Abu Hashim 2010; Palomba 2004; Roy 2010; Youssef 2007). In all five trials the outcome assessors were blinded. There was no blinding of researchers or participants. Details of blinding were unclear in five trials (Ashrafinia 2009; Ghafarnegad 2010; Hamed 2010; Palomba 2010; Zakherah 2009). For the remaining trials there was no blinding of participants, researchers or outcome assessors.

Incomplete outcome data

One trial (Roy 2010) was considered to be at high risk of bias as the attrition of women in the trials was not adequately explained and

intention-to-treat analysis was not conducted. Three other trials (Abdellah 2011; Mamonov 2000; Vegetti 1998) were considered to have an unclear risk. The remaining trials provided adequate explanations of attrition.

Selective reporting

None of the original trial protocols were viewed. The majority of the trials did report on all of the outcomes listed in the methods section of the papers. Seven trials were considered to be at high risk of bias (Abdellah 2011; Abu Hashim 2010; Al-Mizzen 2000; Amer 2009; Balen 1994; Lazoviz 1998; Mamonov 2000); the majority of these papers reported on outcomes that had not been listed in the methods section. Lazoviz 1998 was published in conference abstract form only and no full paper could be identified, and Mamonov 2000 did not list any outcomes in the methods section of the conference abstract. One trial was identified (Ashrafinia 2009) that met the inclusion criteria for the population group of women with subfertility who were clomiphene resistant investigating the intervention of laparoscopic drilling versus metformin. However there were no obstetric outcomes reported in the paper. The authors have been contacted to establish whether they have any data.

Other potential sources of bias

We identified no other potential sources of bias in the included trials.

Effects of interventions

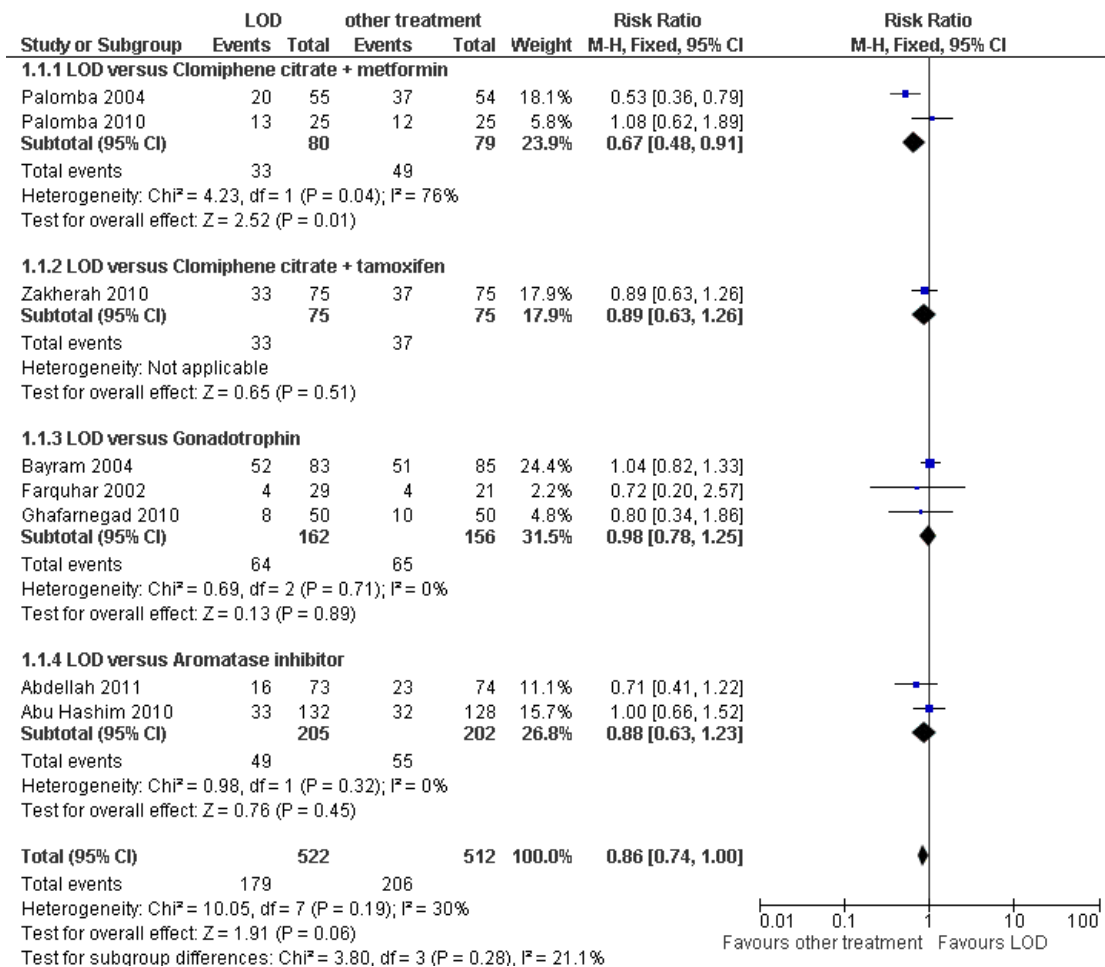
See: [Summary of findings for the main comparison](#) LOD with and without medical ovulation compared to other treatment for anovulatory women with PCOS; [Summary of findings 2](#) Unilateral ovarian drilling compared to bilateral ovarian drilling for anovulatory women with PCOS

1.0 Laparoscopic ovarian drilling with or without ovulation induction compared with ovulation induction with other treatments

1.1 Live birth rate

Eight trials including 1034 women reported live birth rate per couple (Abdellah 2011; Abu Hashim 2010; Bayram 2004; Farquhar 2002; Ghafarnegad 2010; Palomba 2004; Palomba 2010; Zakherah 2010). The proportion of live births following laparoscopic drilling ranged from 24% to 44% and following other medical treatments ranged from 27% to 62%. The overall summary effect was OR 0.77 (95% CI 0.59 to 1.01, $P = 0.18$, 8 trials, 1034 women, $I^2 = 31\%$). There were four different comparisons with LOD and there was no evidence of a significant difference in live births when compared with clomiphene citrate + tamoxifen (OR 0.81; 95% CI 0.42 to 1.53; $P = 0.51$, 1 trial, $n = 150$), gonadotrophins (OR 0.97; 95% CI 0.59 to 1.59; $P = 0.89$, $I^2 = 0\%$, 2 trials, $n = 318$) or aromatase inhibitors (OR 0.84; 95% CI 0.54 to 1.31; $P = 0.44$, $I^2 = 0\%$, 2 trials, $n = 407$). There was evidence of significantly fewer live births following LOD compared with clomiphene citrate + metformin (OR 0.44; 95% CI 0.24 to 0.82; $P = 0.01$, $I^2 = 78\%$, 2 trials, $n = 159$); the high heterogeneity in this subgroup could not be explained by population differences or differences in the quality of the trials. Refer to [Figure 2](#); [Figure 4](#).

Figure 4. Forest plot of comparison: I LOD \pm medical ovulation versus other treatment, outcome: I.I Live birth rate.



One of the trials continued longitudinal follow-up for a mean of 133.5 months (Bayram 2004) for 95% of the original sample. At this extended follow-up point 86% of couples having electrocautery and 81% of couples having recombinant FSH (rFSH) had conceived and reported a live birth ($P = 0.63$). However, electrocautery resulted in significantly reduced requirements for stimulated cycles to reach a live birth outcome (44/71 live births in the electrocautery group versus 65/69 live births in the rFSH group; RR 0.69; 95% CI 0.55 to 0.88). Significantly more women in the electrocautery group had a second live birth compared with the rFSH group (61% versus 46%; RR 1.3; 95% CI 1.01 to 1.8; $P = 0.03$). Of those women achieving a second live birth in the electrocautery group 24% required additional treatment as did 19% of those in the rFSH group who had a second live birth. At the end of follow-up there had been 134 live births in the electrocautery group and 124 in the rFSH group ($P = 0.09$). Of the 175 pregnan-

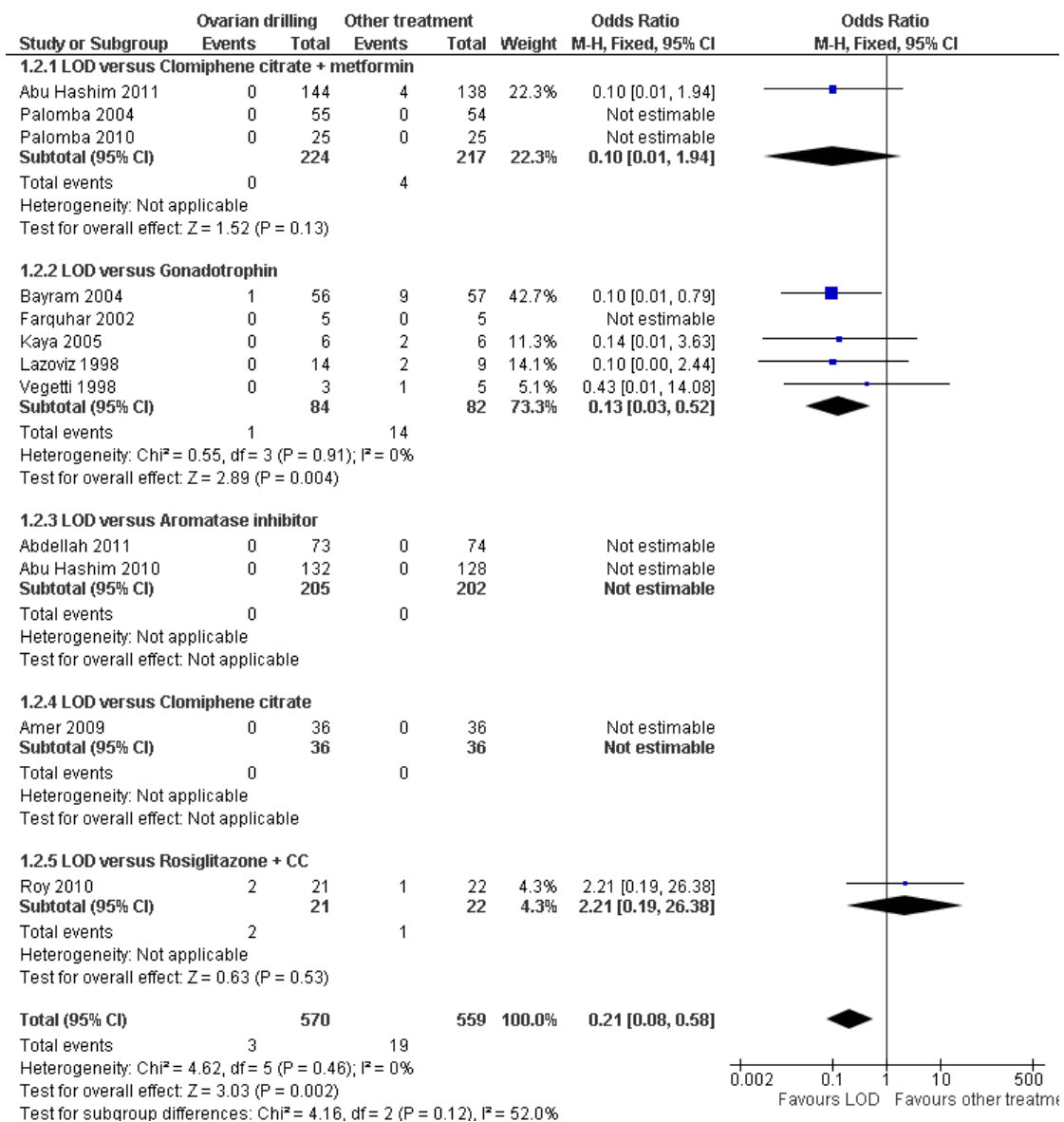
cies in the electrocautery group, 5 were ectopic pregnancies and 31 miscarriages occurred, compared with 3 ectopic pregnancies of a total of 159 pregnancies in the rFSH group (relative risk (RR) 1.5; 95% CI 0.37 to 6.2) and 23 miscarriages (RR 1.2; 95% CI 0.75 to 2.0).

1.2 Multiple pregnancy

Twelve trials including 1129 women reported on multiple pregnancies (Abdellah 2011; Abu Hashim 2010; Abu Hashim 2011; Amer 2009; Bayram 2004; Farquhar 2002; Kaya 2005; Lazoviz 1998; Palomba 2004; Palomba 2010; Roy 2010; Vegetti 1998). The proportion of women with multiple pregnancies who had undergone laparoscopic drilling ranged from 0% to 10%. The overall summary effect was OR 0.21 (95% CI 0.08 to 0.58, $P =$

0.002, 12 trials, 1129 women, $I^2=0\%$). For women who had received other medical treatments the proportion of multiple pregnancies ranged from 0% to 17%. There were no cases of multiple pregnancies in either group for clomiphene citrate or aromatase inhibitors compared with LOD. The rate of multiple pregnancies was significantly lower in the LOD group compared with using gonadotrophins (OR 0.13; 95% CI 0.03 to 0.52; $P = 0.004$, $I^2 = 0\%$, 5 trials, $n = 166$). Refer to [Figure 5](#).

Figure 5. Forest plot of comparison: 1 LOD \pm medical ovulation versus other treatment, outcome: 1.4 Multiple pregnancy rate (per ongoing pregnancy).



1.3 Pregnancy rate per woman randomised

Eighteen studies reported this outcome in 1930 women (Abdellah 2011; Abu Hashim 2010; Abu Hashim 2011; Amer 2009; Bayram 2004; Farquhar 2002; Ghafarnegad 2010; Gurgan 1992; Hamed 2010; Kaya 2005; Lazoviz 1998; Mamonov 2000; Palomba 2004; Palomba 2010; Roy 2010; Vegetti 1998; Zakherah 2009; Zakherah 2010). The proportion of women who became pregnant ranged from 25% to 51% following laparoscopic drilling and 30% to 51% following other medical treatments. The overall summary effect was OR 0.94 (95% CI 0.78 to 1.14, $P=0.53$, 18 trials, $n=1930$, $I^2=18.3\%$). There were seven different comparisons made with LOD. LOD versus metformin was the only comparison with evidence of a significant benefit in favour of LOD (OR 2.47; 95% CI 1.05 to 5.81; $P=0.04$, 1 trial, $n=110$).

There was no evidence of a significant difference in pregnancy rates when LOD was compared to clomiphene citrate + metformin (OR 0.79; 95% CI 0.53 to 1.18; $P=0.24$, $I^2=63\%$, 3 trials, $n=441$), clomiphene citrate + tamoxifen (OR 0.97; 95% CI 0.59 to 1.59; $P=0.90$, $I^2=0\%$, 2 trials, $n=250$), gonadotrophins (OR 1.01; 95% CI 0.72 to 1.32; $P=0.61$, $I^2=33\%$, 8 trials, $n=607$), aromatase inhibitors (OR 0.89, 95% CI 0.58 to 1.37, $P=0.60$, $I^2=0\%$, 2 trials, $n=407$), clomiphene citrate (OR 0.52, 95% CI 0.19 to 1.44, $P=0.21$, one trial, $n=72$) or rosiglitazone + clomiphene citrate (OR 0.75; 95% CI 0.23 to 2.50; $P=0.64$, 1 trial, $n=43$). Refer to Analysis 1.3. The funnel plot for this outcome was not suggestive of publication bias (Figure 3).

A random effects model was used for the comparison of LOD compared with clomiphene citrate + metformin, which had heterogeneity of 63% (I^2) using the fixed effects model. The heterogeneity and lack of statistical significance remained unaffected.

One trial provided the pregnancy rate per cycle rather than per woman randomised and the authors have been contacted to provide per woman data (Abu Hashim 2011). There has been no response to date.

1.4 Miscarriage

Fifteen trials of 1592 women compared ovarian drilling with or without medical ovulation induction versus other treatments for this outcome (Abdellah 2011; Abu Hashim 2010; Abu Hashim 2011; Bayram 2004; Farquhar 2002; Ghafarnegad 2010; Gurgan 1992; Hamed 2010; Lazoviz 1998; Mamonov 2000; Palomba 2004; Palomba 2010; Roy 2010; Vegetti 1998; Zakherah 2010). The proportion of women who suffered a miscarriage ranged from 4% to 9% for those who had undergone laparoscopic drilling and 3% to 12% for those who had undergone other medical treatments. Refer to Analysis 1.4. The overall summary effect was OR 1.10 (95% CI 0.74 to 1.61, $P=0.64$, 15 trials, $n=1592$, $I^2=0\%$). There were six different comparisons with LOD. There was no ev-

idence of a significant difference in the number of miscarriages between LOD and clomiphene citrate + metformin (OR 1.43; 95% CI 0.70 to 2.91; $P=0.33$, $I^2=0\%$, 3 trials, $n=441$), clomiphene citrate + tamoxifen (OR 1.71; 95% CI 0.39 to 7.45; $P=0.47$, 1 trial, $n=150$), gonadotrophins (OR 0.73; 95% CI 0.40 to 1.33; $P=0.31$, $I^2=11\%$, 7 trials, $n=441$), aromatase inhibitors (OR 1.33; 95% CI 0.45 to 3.90; $P=0.60$, $I^2=0\%$, 2 trials, $n=407$), metformin (OR 2.08; 95% CI 0.36 to 11.85; $P=0.41$, 1 trial, $n=110$) or rosiglitazone + clomiphene citrate (OR 1.05; 95% CI 0.06 to 17.95; $P=0.97$, 1 trial, $n=43$). In Farquhar 2002 one pregnancy ended with termination of pregnancy and was reported in the text as such.

1.5 Incidence of ovarian hyperstimulation syndrome (OHSS)

Seven trials reported on rates of OHSS (Abu Hashim 2010; Abu Hashim 2011; Amer 2009; Bayram 2004; Farquhar 2002; Kaya 2005; Roy 2010). There were no cases of OHSS associated with LOD in any of the seven trials. The five cases of OHSS reported in the other medical treatment groups were associated with clomiphene citrate ($n=1/36$) (Amer 2009) and gonadotrophin ($n=4/16$) (Kaya 2005). Refer to Analysis 1.5.

1.6 Ovulation rate

Ovulation rate was reported in six trials including 525 women (Amer 2009; Farquhar 2002; Hamed 2010; Roy 2010; Zakherah 2009; Zakherah 2010). There was no evidence of a significant difference in ovulation rate for any of the subgroups observed (clomiphene citrate + metformin, clomiphene citrate + tamoxifen, gonadotrophins, clomiphene citrate, metformin, or rosiglitazone + clomiphene citrate). Refer to Analysis 1.6. Only first cycle data were included in the meta-analyses from the trials reported by Palomba 2010. Abu Hashim 2010, Abu Hashim 2011, and Abdellah 2011 reported ovulation rates as per cycle data and not per woman randomised. These data could not be included in the meta-analysis. See Analysis 1.6.

1.7 Costs

Both direct and indirect cost data were collected in five papers from four studies (Bayram 2004; Farquhar 2002; Kaya 2005; Palomba 2004). Heterogeneity was $I^2=99\%$, which is probably due to the differing currencies used and the different factors taken into account when calculating costs. Only subgroups have been reported. In the Bayram 2004 study the addition of laparoscopic ovarian drilling to the diagnostic laparoscopy added 20 minutes to the procedure. The total cost of treatment for the group having ovarian drilling with medical induction therapy, if necessary, was EUR 4664 \pm 1967 and for the gonadotrophin-only group the cost

was EUR 5418 ± 3785. The difference was EUR 754 (95% CI 1666.1 to 155.1). In the discussion section of this paper it was estimated that the cost per term pregnancy would be EUR 14,489 for gonadotrophin and EUR 11,301 for ovarian drilling followed by medical induction therapy, if necessary (22% lower). The higher rates of multiple pregnancies in the gonadotrophin group were considered to be responsible for the increased costs. The long-term costs at 10 years follow-up were reported in a 2011 economic analysis of the study by [Bayram 2004](#). The costs were significantly lower for the treatment strategy starting with electrocautery when compared to the gonadotrophin strategy (mean difference EUR 2235; 95% CI 80 to 3790). Refer to Analysis 1.7.

The costs associated with [Farquhar 2002](#) were reported in a 2004 publication. The authors reported that the costs of a live birth were one third lower in the group that underwent laparoscopic ovarian diathermy compared to those women who received gonadotrophins (NZD 19,640 and NZD 29,836, respectively). The costs were based on hospital and clinic direct and indirect costs. No estimates of a standard deviation were reported so these data have not been included in the analysis. Refer to [Table 1](#).

[Kaya 2005](#) reported that the costs of LOD were almost half that of treatment with gonadotrophins (\$1081 ± 234 versus \$2214 ± 356).

[Palomba 2004](#) reported that LOD was significantly ($P < 0.05$) more expensive than metformin treatment in a six-month treatment programme (EUR 1050 versus EUR 50 respectively). Refer to [Table 1](#).

1.8 Quality of life

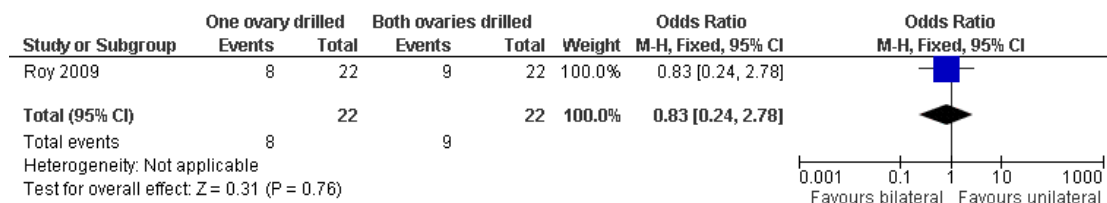
Only [Bayram 2004](#) reported on health-related quality of life, using the SF-36, Rotterdam Symptom Checklist (RS CL) and depression scales (CES-D). The intention-to-treat analysis comparing electrocautery and rFSH showed no statistically significant treatment effect on any of the SF-36 subscales. The intention-to-treat analysis comparing electrocautery and recombinant FSH showed no statistically significant treatment or time effects for physical symptoms, psychological measures or overall quality of life on the RSCL checklist. The intention-to-treat analysis comparing electrocautery and recombinant FSH showed no statistically significant treatment or time effects on the depression scales (CES-D). See Analysis 1.8; Analysis 1.9; Analysis 1.10; Analysis 1.11.

2.0 Laparoscopic ovarian drilling of one ovary (unilateral) compared with both ovaries (bilateral)

2.1 Live birth

Live birth was reported in one trial ([Roy 2009](#)). Live birth was reported in 36% of women having undergone unilateral drilling and 40% in those who had undergone bilateral drilling. The difference was not significant (OR 0.83; 95% CI 0.24 to 2.78; $P = 0.76$, 1 trial, $n = 44$). See [Figure 6](#).

Figure 6. Forest plot of comparison: 2 Unilateral versus bilateral ovarian drilling, outcome: 2.1 Live birth.



2.3 Ovulation rate

2.2 Pregnancy rate

Pregnancy rate was reported in five trials ([Al-Mizyzen 2000](#); [Balén 1994](#); [Roy 2009](#); [Sharma 2006](#); [Youssef 2007](#)). Pregnancy was reported in 52% of women having undergone unilateral drilling and 51% of women who had undergone unilateral drilling. The difference was not significant (OR 1.00; 95% CI 0.55 to 1.83; $P = 0.99$, $I^2 = 0\%$, 5 trials, $n = 182$). Refer to Analysis 2.2.

Ovulation rate was reported in four trials ([Balén 1994](#); [Roy 2009](#); [Sharma 2006](#); [Youssef 2007](#)). Ovulation was successfully achieved in 76% of women who had undergone unilateral drilling and 71% of women who had undergone bilateral drilling. The difference was not significant (OR 1.20; 95% CI 0.59 to 2.46; $P = 0.61$, $I^2 = 0\%$, 4 trials, $n = 161$). Refer to Analysis 2.3.

2.4 Miscarriage

Two trials reported on miscarriage rates per woman randomised (Roy 2009; Youssef 2007). The rates of miscarriage were 9.2% for women who had undergone unilateral drilling and 9% for women who had undergone bilateral drilling. The difference was not significant (OR 1.02; 95% CI 0.31 to 3.33; $P = 0.98$, $I^2 = 0\%$, $n = 131$, 2 trials). Refer to Analysis 2.4.

3.0 Laparoscopic ovarian drilling compared with laparoscopic ovarian drilling and second-look laparoscopy

3.1 Ongoing pregnancy rate

There was no evidence of a significant difference between the ongoing pregnancy rates following ovarian drilling by laser or diathermy and second-look laparoscopy adhesiolysis three to four weeks later compared with expectant management (no second-look laparoscopy) (OR 0.66; 95% CI 0.18 to 2.35) (Gurgan 1992). In a group with anticipated ongoing pregnancy for 40% of women, laparoscopic ovarian drilling would be expected to result in ongoing pregnancy for between 11% and 61% of women. See Analysis 3.1.

3.2 Ovulation rate

One trial reported on the ovulation rate (Gurgan 1992), which was achieved in 95% of women in the second-look group and 75% in the expectant management group. This difference was not however significant (OR 6.33; 95% CI 0.67 to 60.16; $P = 0.11$, 1 trial, $n = 40$). See Analysis 3.2.

3.3 Miscarriage rate

There was no evidence of a significant difference in ongoing pregnancy rates following ovarian drilling by laser or diathermy and second-look laparoscopy and adhesiolysis three to four weeks later compared with no second-look laparoscopy (OR 1.00; 95% CI 0.13 to 7.89) (Gurgan 1992). For a group with anticipated miscarriage in 10% of pregnancies, laparoscopic ovarian drilling would

be expected to result in miscarriage in between 1% and 47% of pregnancies. See Analysis 3.3.

4.0 Laparoscopic ovarian electrocautery (LOE) + IVF compared with conventional IVF

One trial of 50 women was identified that compared LOE + IVF with conventional IVF (Rimington 1997).

4.1 Live birth

There was no evidence of a significant difference in live birth rate with the addition of LOE to IVF compared with conventional IVF (OR 1.26; 95% CI 0.33 to 4.84; $P = 0.73$). See Analysis 4.1.

4.2 Multiple pregnancy

There was no evidence of a significant difference in multiple pregnancy rate with the addition of LOE to IVF compared with conventional IVF (OR 1.00; 95% CI 0.06 to 16.93, $P = 1.00$). See Analysis 4.2.

4.3 Pregnancy rate:

There was no evidence of a significant difference in pregnancy rate with the addition of LOE to IVF compared with conventional IVF (OR 1.20; 95% CI 0.37 to 3.86; $P = 0.77$). See Analysis 4.3.

4.4 Miscarriage

There was no evidence of a significant difference in miscarriage rate with the addition of LOE to IVF compared with conventional IVF (OR 1.00; 95% CI 0.18 to 5.51; $P = 1.00$). See Analysis 4.4.

4.5 OHSS

There was no evidence of a significant difference in OHSS rate with the addition of LOE to IVF compared with conventional IVF (OR 0.22; 95% CI 0.02 to 2.11; $P = 0.19$). See Analysis 4.5.

ADDITIONAL SUMMARY OF FINDINGS [\[Explanation\]](#)

Unilateral ovarian drilling compared to bilateral ovarian drilling for anovulatory women with PCOS

Patient or population: patients with anovulatory women with PCOS

Settings: Fertility clinics

Intervention: Unilateral ovarian drilling

Comparison: bilateral ovarian drilling

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Bilateral ovarian drilling	Unilateral drilling				
Live birth	409 per 1000	365 per 1000 (142 to 658)	OR 0.83 (0.24 to 2.78)	44 (1 study)	⊕○○○ very low ^{1,2,3}	
Pregnancy rate (per patient)	505 per 1000	505 per 1000 (360 to 652)	OR 1 (0.55 to 1.83)	182 (5 studies)	⊕⊕○○ low ⁴	
Miscarriage	91 per 1000	93 per 1000 (30 to 250)	OR 1.02 (0.31 to 3.33)	131 (2 studies)	⊕⊕⊕○ moderate ⁵	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ The trial lack an adequate explanation of randomisation and allocation concealment and there was no blinding

² The summary effect crossed the line of no effect and substantive benefit and harm

- ³ Evidence is based on a single trial
- ⁴ Only one trial provided an adequate explanation of randomisation, only one trial provided an adequate explanation of allocation concealment and blinded outcome assessors
- ⁵ Randomisation was not clearly reported by either trial, allocation concealment was only reported by one trial and blinding was only conducted by one trial

DISCUSSION

Summary of main results

There was no evidence of a significant difference between LOD with and without medical ovulation induction compared with other medical treatments on the outcomes of live birth, pregnancy, miscarriage or OHSS. Multiple pregnancy rates appeared to be significantly reduced following treatment with LOD. Costs also appeared to be lower for LOD treatment. There was no evidence of a significant difference in rates of live birth, pregnancy, ovulation or miscarriage when unilateral was compared with bilateral drilling.

Overall completeness and applicability of evidence

Although the number of studies for each drug comparison was limited, the evidence does appear to encompass all available treatments for anovulatory women with PCOS seeking a fertility outcome.

Quality of the evidence

Randomisation was adequately explained in 16/25 of the included trials and allocation concealment was adequately explained in 11/25 trials. None of the included trials blinded participants. Outcome assessors were blinded in only four of the trials; the remainder of trials were either unclear about blinding or did not conduct blinding at all.

Potential biases in the review process

The authors of this systematic review believe a rigorous search of the evidence has been conducted. The evidence includes published and unpublished data and there was no restriction by language.

Agreements and disagreements with other studies or reviews

As there was no evidence of a difference for ongoing pregnancy for either treatment option, laparoscopic ovarian drilling may be the treatment of choice since the avoidance of unnecessary gonadotrophins may reduce the risk of multiple pregnancies and ovarian hyperstimulation syndrome. There were no multiple pregnancies in either arm in [Farquhar 2002](#), which may be due to the monitoring and high cancellation rate. On the other hand, although surgically-related complications associated with ovarian drilling seem rare, a case of pelvic infection following laparoscopic ovarian drilling highlights the need for caution in offering this treatment over gonadotrophin therapy ([Deans 1997](#)). There are also the associated risks and morbidity of laparoscopy under

general anaesthetic, postoperative adhesion formation ([Greenblatt 1993](#)), and the as yet theoretical long-term risk of premature ovarian failure to be considered.

Although ovarian drilling is successful in inducing ovulation in a proportion of women and in improving the responsiveness of the ovary to ovulation induction agents, it is unknown how long it has an effect on the ovary. Repeated spontaneous ovulations and further pregnancies after the first pregnancy or miscarriage were reported by [Farquhar 2002](#), which is an additional benefit of surgery. The need for monitoring in ovarian induction with gonadotrophins also makes surgery an attractive option. In addition, consumer preference and cost implications may favour this form of treatment for women with anovulatory PCOS wishing to conceive in the future. There is no evidence to support surgical treatment for other clinical symptoms of PCOS such as hirsutism.

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence of a difference between laparoscopic ovarian drilling (with or without medical ovulation induction) compared to ovulation induction with gonadotrophins for women with polycystic ovarian syndrome and clomiphene resistance for the outcomes of pregnancy and ovulation after 12 months follow-up. Multiple pregnancy rates are reduced with ovarian drilling compared with other medical treatments. However, with the exception of multiple pregnancies, the few randomised studies thus far cannot rule out differences in outcomes. With regard to adhesion formation, there is insufficient evidence to favour any one surgical technique over another. Therefore, until more data become available, the clinical decision as to which treatment to recommend could be made on other considerations such as local facilities, adverse effects, cost and consumer preference.

Implications for research

Further RCTs should consider the role of laparoscopic ovarian drilling in association with medical ovulation induction. Studies should not just evaluate the outcomes of live birth and pregnancy rates but should also include outcomes such as ease of medical ovulation induction, adverse effects (such as overstimulation, ovarian hyperstimulation syndrome, multiple pregnancy, miscarriage and surgical complications), cost benefit analyses and consumer satisfaction. The long-term benefits (spontaneous resumption of ovulation and menstruation) and potential risks of laparoscopic ovarian drilling (such as premature ovarian failure) also need to be addressed. Further trials on the techniques of ovarian drilling (including the number of holes) could also be considered.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Abdellah 2011

Methods	Randomised trial conducted in Egypt	
Participants	156 women assessed for eligibility in fertility clinics and 147 randomised. mean age of women in the letrozole group was 23.9±3.2 years and in the LOD group was 23.6±3.2 years Inclusion: Women with clomiphene-resistant PCOS, primary or secondary infertility because of anovulation and clomiphene resistance for at least 1 year, normal sperm analysis from partner, patent tubes as seen by hysterosalpingography or diagnostic laparoscopy Exclusion: Age < 20 or > 35 years, hormonal treatment within 3 months prior to study, hyperprolactinaemia, any other endocrine, hepatic or renal disorder, presence of an organic pelvic mass, history of abdominal surgery that might have caused pelvic factor infertility	
Interventions	Letrozole 5mg/day for 5 days starting on day 3 of menses for a maximum of 6 cycles (n=74) versus LOD - each ovary was punctured 4 to 6 times depending on the size of the ovary (n=73)	
Outcomes	Endometrial thickness, biochemical pregnancy, clinical pregnancy, spontaneous abortion, ovulation rate	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“computer generated random numbers table”
Allocation concealment (selection bias)	Low risk	“achieved using serially numbered opaque envelopes that were only opened once the interventions were assigned”
Blinding (performance bias and detection bias) All outcomes	High risk	There were no details of blinding in the paper. Blinding was unlikely to have occurred as the interventions were oral medication versus surgery. There are no details of outcome assessors being blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	147 randomised; 4 in the letrozole group and 3 in the LOD dropped out of the trial, all for non-compliance. However, ITT analysis was not conducted

Selective reporting (reporting bias)	High risk	The original protocol was not viewed but live birth rate was reported in the results section and was not listed as an outcome in the methods section of the paper. Adverse effects on the mother and congenital malformations were also discussed in the discussion section of the paper but had not been reported in the results section
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Abu Hashim 2010

Methods	Prospective randomised trial conducted in Egypt
Participants	260 women attending fertility clinics. Mean age of women in letrozole group was 27.3±2.6 years and in the LOD group was 26.4±2.4 years Inclusion: Clomiphene resistant PCOS, patent fallopian tubes assessed by hysterosalpingography, normal semen analysis from partner, normal serum prolactin, thyroid stimulating hormone and 17-hydroxyprogesterone Exclusion: Other causes of fertility, age > 40 years, BMI>35, contraindications to anaesthesia, previous history of LOD, and having received metformin, gonadotrophin, other hormonal drugs or OCP in preceding 6 months. Women intending to start a diet or a specific programme of physical activity were also excluded
Interventions	Letrozole - 2.5mg orally daily from day 3 of the menses for 5 days for 6 cycles (n = 128) versus LOD - each ovary was cauterised at 4 points and women were followed up for 6 months (n = 132)
Outcomes	Biochemical pregnancy, clinical pregnancy, ovulation, miscarriage, live birth rates, endometrial thickness
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"...computer-generated random numeric table." "prepared by an independent statistician" Acceptable method
Allocation concealment (selection bias)	Low risk	"...use of sealed opaque envelopes that were given to a third party (nurse).."
Blinding (performance bias and detection bias) All outcomes	Low risk	"Once allocated, the treatment was revealed to both the investigator and the patient. However, the radiologist who performed transvaginal ultrasound follow-up assessment was blinded to the treatment

		groups". Some attempt was made to provided blinding of outcome assessors. Patients could not be blinded as the comparison was an oral medication versus a surgical procedure
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no reported losses throughout the trial and all of the women who were randomised were analysed
Selective reporting (reporting bias)	High risk	The original protocol was not viewed but all the a priori outcomes listed in the methods section of the paper were reported on in the results section. Multiple pregnancies and OHSS were reported in the results section but were not listed as outcomes in the methods section of the paper

Abu Hashim 2011

Methods	Randomised prospective trial conducted in Egypt	
Participants	282 women attending fertility clinics in Egypt. Mean age of women in the metformin group was 27.2±2.5 years and in the LOD group was 26.5±2.3 years Inclusion: Clomiphene resistant PCOS, patent fallopian tubes assessed by hysterosalpingography, normal semen analysis from partner, normal serum prolactin, thyroid stimulating hormone and 17-hydroxyprogesterone Exclusion: Other causes of fertility, age > 40 years, contraindications to anaesthesia and having received metformin, gonadotrophin or OCP in preceding 6 months	
Interventions	Metformin 500mg three times a day for 6 to 8 weeks; followed by 100 mg of clomiphene citrate for 5 days starting on day 3 of spontaneous or induced menstruation. Dosage increased by 50mg at next cycle if still anovulatory. treated for 6 cycles. (n= 138) versus LOD - each ovary was cauterised at 4 points and women were followed up for 6 months (n=144)	
Outcomes	Pregnancy, miscarriage, ovulation rate, endometrial thickness	
Notes	Author contacted in Sept 2011 for details on pregnancy rates per woman rather than per cycle	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"...computer-generated random numeric table." Acceptable method

Allocation concealment (selection bias)	Low risk	"Opaque envelopes that were numbered and sealed" "...give to a third party (a nurse)
Blinding (performance bias and detection bias) All outcomes	High risk	There are no details of blinding but blinding is unlikely to have occurred as one intervention is oral medication and the other is surgical. There are no details of blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was no attrition recorded in the trial and all women randomised were analysed
Selective reporting (reporting bias)	Unclear risk	The original protocol was not viewed but all the a priori outcomes listed in the methods section of the paper were reported on in the results section

Al-Mizyen 2000

Methods	Randomised controlled trial conducted in UK	
Participants	21 patients randomised (this may be a typographical error in the abstract) Included: women with clomiphene-resistant PCOS (150 mg clomiphene) with chronic anovulation and 5 were resistant to FSH ovulation induction. Mean age 27 and 28 years, mean duration of infertility was 5.0 versus 4.8 years and the mean BMI was 19 versus 17 kg/m ²	
Interventions	Bilateral ovarian drilling by diathermy (n=10) versus unilateral ovarian drilling (n=10). Laparoscopic ovarian drilling was performed with a diathermy needle creating 4 punctures/ovary 12 months follow-up.	
Outcomes	Pregnancy rate (per patient).	
Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'allocated randomly' no other details in conference abstract
Allocation concealment (selection bias)	Unclear risk	No details in conference abstract.

Al-Mizyen 2000 (Continued)

Blinding (performance bias and detection bias) All outcomes	High risk	No evidence of blinding of researchers, patients or outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	10 randomised to each group and 10 reported in the analysis.
Selective reporting (reporting bias)	High risk	No live birth data

Amer 2009

Methods	Randomised trial of 72 anovulatory women with PCOS
Participants	UK study set in fertility clinic. Mean age of women in LOD group 28.1 ± 4.3 years and in CC group 29.1 ± 4.8 years Inclusion: Women with anovulatory infertility with PCOS. Aged 18 to 39 years, BMI $\leq 32\text{kg/m}^2$, duration of infertility ≥ 1 year. At least one patent fallopian tube on hysterosalpingogram and normal semen analysis Exclusion: inability to give informed consent, contra-indication to clomiphene citrate or general anaesthetic. Any ovarian induction therapy in previous 6 months
Interventions	Laparoscopic ovarian diathermy (LOD) - 4 punctures per ovary in both ovaries. clomiphene citrate was also given if there was no ovulation 6 - 8 weeks after surgery (n = 36) versus Clomiphene citrate daily dose increasing from 50mg to 150 mg on days 2 to 6 of a menstrual period or after a progestogen withdrawal bleed using Medroxyprogesterone acetate (MDPA) Treatment for 6 cycles and then offered LOD (n = 36) Follow-up for 12 months
Outcomes	Ovulation, pregnancy (biochemical, cumulative), multiple pregnancies, live birth rate
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'...block randomisation method using a random number table ..'
Allocation concealment (selection bias)	Low risk	Appears to be central allocation 'held centrally by a trial administrator'
Blinding (performance bias and detection bias) All outcomes	High risk	There was no blinding, once randomised the allocation was revealed to the investiga-

		tor and the patient
Incomplete outcome data (attrition bias) All outcomes	Low risk	LOD - 3 conceived before LOD, 1 discontinued and 1 postponed. 33 /36 were analysed CC- 3 conceived before CC and 1 postponed treatment. 32 were analysed
Selective reporting (reporting bias)	High risk	Original protocol not viewed. Adverse events were reported in the results but not listed as primary or secondary outcomes in the methods

Ashrafinia 2009

Methods	Iranian study. Prospective randomised trial	
Participants	126 Women attending a fertility clinic between the ages of 15 to 45 years with a history of infertility for at least one year and 3 treatment cycles of clomiphene citrate treatment with no response. mean age of women in LOD group was 26.54± 4.72 years and in the metformin group was 25.13 ± 3.47 years Inclusion: Irregular menstruation, clinical and biochemical signs of hyperandrogenism, polycystic ovaries Exclusion: Diseases that would disturb clinical and hormonal responses, pregnancy during follow-up, body mass index above 30 or below 17	
Interventions	LOD performed 4 times in each ovary (n=63) versus Metformin 1500g daily for 6 months (n=63).	
Outcomes	Menstrual regularity, hormonal levels, Ferriman-Gallwey score	
Notes	Authors have been contacted with regards to obstetric outcomes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details in paper
Allocation concealment (selection bias)	Low risk	'serially numbered opaque envelopes'
Blinding (performance bias and detection bias) All outcomes	High risk	There was no evidence that patients or researchers or outcome assessors were blinded

Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients appear to have been followed through the study and all those randomised were analysed
Selective reporting (reporting bias)	High risk	The original protocol was not viewed. However, this study includes only infertile women but does not report on any pregnancy outcomes. Authors have been contacted

Balen 1994

Methods	Prospective randomised controlled trial conducted in UK	
Participants	10 patients randomised Refractory PCO patients (see definitions). Mean age (range) of the patients was 29.5 (27 to 33) years and mean (range) duration of infertility was 5.6 years (4 to -8). Infertility work up consisted of tubal patency testing by laparoscopy, semen analysis, endocrinology. In one case the tubes were blocked, 2 had pelvic adhesions, 3 had severe oligospermia or azoospermia and underwent donor insemination. Mean BMI 23 kg/m2. The trial was carried out at the Middlesex Hospital, London, UK. Duration and timing not stated	
Interventions	Bilateral ovarian drilling by diathermy versus unilateral ovarian drilling. Laparoscopic ovarian drilling was performed with a diathermy needle creating 4 punctures/ovary, cooled with normal saline 3 months follow-up.	
Outcomes	Pregnancy rate (per patient) Ovulation rate (per patient)	
Notes	Definitions PCO: not defined. Refractory PCO: failure to ovulate on 100 mg/day (duration not specified); some had also been treated previously with tamoxifen or gonadotrophins. Pregnancy: not defined. Ovulation: not defined.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details in paper

Balen 1994 (Continued)

Allocation concealment (selection bias)	Unclear risk	No details in paper
Blinding (performance bias and detection bias) All outcomes	High risk	No evidence of blinding of researchers, patients or outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data reported from all 10 women.
Selective reporting (reporting bias)	High risk	No live birth

Bayram 2004

Methods	Randomised controlled trial. Method of randomisation: computer generated block randomisation, stratified by centre. Allocation: by phone call to central trial office. Time of randomisation: during diagnostic laparoscopy, after determining eligibility. Invited to participate: 213 consecutive women. 45 excluded (27 refused, 3 too obese for surgery, 1 had language barrier, 5 became pregnant while awaiting laparoscopy, 9 excluded during diagnostic laparoscopy due to endometriosis (1), adhesions (5), tubal occlusion (2) or infeasibility of electrocautery (1)). Randomised: 168 women.
Participants	Included: women with clomiphene-resistant PCOS (150 mg clomiphene) with chronic anovulation. Mean age 29 years, mean duration of infertility was 2.8 years and the mean BMI was 27 kg/m ² . Infertility was primary in 76% of women. Excluded: women with tubal obstruction, other causes of infertility including severe male factor infertility, > 40 years
Interventions	Laparoscopic electrocautery of the ovaries strategy: each ovary was punctured 5 to 10 times depending on its size. If the woman ovulated in 6 subsequent cycles, no further treatment was given. If ovulatory cycles were not established 8 weeks after surgery or the woman became anovulatory again then clomiphene citrate was given in increasing doses. If the woman still remained anovulatory, rFSH was given in increasing doses starting at 75 IU daily (n=83) versus 6 cycles of rFSH. Women were treated until 6 subsequent cycles were achieved within 6 months (n=85)
Outcomes	Primary: ongoing pregnancy rate within 12 months, defined as a viable pregnancy of at least 12 weeks Secondary: live birth miscarriage multiple pregnancy cost related quality of life Followed up to 1 year

Bayram 2004 (Continued)

Notes	Analyses on an intention-to-treat basis. Powered to detect a 10% difference in ongoing pregnancy rate	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated block randomisation, stratified by centre
Allocation concealment (selection bias)	Low risk	Telephone call to central office
Blinding (performance bias and detection bias) All outcomes	High risk	There was no evidence of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women randomised were analysed in the primary study.
Selective reporting (reporting bias)	Unclear risk	The original protocol was not viewed but all outcomes listed in the methods were reported in the results

Farquhar 2002

Methods	Randomised trial. Method of randomisation: computer generated, opaque envelopes. Time of randomisation: in clinic. 50 patients randomised, 3 cycles/patient.
Participants	Included: women aged 20 to 38 years with clomiphene-resistant PCOS (150 mg clomiphene for 5 days), BMI less than 32 (for European women) and less than 34 (for Polynesian women). Excluded: other known causes of infertility, including male factor infertility. Mean age 30 years. Mean BMI 28 kg/m ² . Mean length of infertility: 36 months in the LOD group and 29 months in the gonadotrophin group. Study centre: Fertility Plus, National Women's Hospital, New Zealand
Interventions	Bilateral ovarian drilling by diathermy versus 3 cycles of gonadotrophins (HMG or rFSH). Laparoscopic ovarian drilling was performed with a diathermy needle creating 10 punctures/ovary, cooled with normal saline

Outcomes	Pregnancy rate 6 months after drilling or after 3 cycles of gonadotrophins (per patient) Live birth Ovulation rate (per patient) Costs	
Notes	Analyses on an intention-to-treat basis. Powered to detect a 10% difference in ongoing pregnancy rate. Definitions PCO: clinical (oligo- or amenorrhoea) + + ovarian appearance on ultrasound (criteria by Adams et al, BMJ 1986;293:355-9). Refractory PCO: failure to conceive after 3 cycles of ovulation induction with clomiphene citrate (150 mg/day). Pregnancy: positive HCG and fetal heart on ultrasound. Ovulation: disappearance of a leading follicle or appearance of a corpus luteum on ultrasound OR mid luteal phase serum progesterone greater than 20 mmol/l	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'computer generated sequences..'
Allocation concealment (selection bias)	Low risk	'sealed numbered opaque envelopes'
Blinding (performance bias and detection bias) All outcomes	High risk	There was no evidence that researchers, patients or outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up.
Selective reporting (reporting bias)	Unclear risk	Original protocol not viewed but all outcomes listed in methods were reported in the results

Ghafarnegad 2010

Methods	Randomised trial of 100 patients
Participants	Iranian study. <i>Awaiting full translation of paper.</i> 100 infertile, clomiphene-resistant women with PCOS.
Interventions	Gonadotrophin (n=50) versus Laparoscopic ovarian electrocautery (n=50)

Outcomes	Pregnancy, live birth	
Notes	Awaiting full translation of paper	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'randomised'. Awaiting further details in translation but numbers are equal in both groups so probably satisfactory
Allocation concealment (selection bias)	Unclear risk	Awaiting translation
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Awaiting translation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women accounted for at trial end and intention-to-treat data reported
Selective reporting (reporting bias)	Unclear risk	Awaiting translation

Gurgan 1992

Methods	Randomised trial conducted in Turkey Method of randomisation: table of random numbers. Time of randomisation: after initial laparoscopic ovarian drilling. 40 patients randomised, 6 months follow-up.
Participants	Clomiphene-resistant PCOS patients (see definitions). Mean age (range) of the patients was 25.2 years (21 to 31) and mean duration of infertility was 4.4 years. 33 patients had primary and 7 had secondary infertility. Infertility work up consisted of semen analysis (normal in 36 patients and mildly oligo/asthenospermia in 4) and normal HSG. All women were anovulatory There were no clear inclusion or exclusion criteria specified. The trial was done at the University of Hecettepi, Ankara, Turkey. Timing and duration not stated
Interventions	2nd look laparoscopic adhesiolysis following ovarian laser drilling versus ovarian laser drilling only. Ovarian laser drilling consisted of creating 20 to 25 holes/ovary using beam power of 50 W with the Nd:YAG laser followed by pelvic irrigation with Ringer lactate. Laparoscopic adhesiolysis with sharp or blunt dissection was done 3 to 4 weeks later

Gurgan 1992 (Continued)

Outcomes	Pregnancy rate (per patient) Ovulation rate (per patient) Miscarriage rate (per pregnancy) Multiple pregnancy rate (per pregnancy)
Notes	Definitions PCO: clinical (oligomenorrhoea, hirsutism, obesity) + LH/FSH ratio > 2 + elevated testosterone and/or androstenedione (not specified). Clomiphene resistant: failure to ovulate on 200 mg/day for 5 days (duration not stated). Pregnancy: ultrasound (not specified). Ovulation: biphasic BBT + luteal serum progesterone > 3 ng/ml

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"table of random numbers"
Allocation concealment (selection bias)	Unclear risk	No details in paper
Blinding (performance bias and detection bias) All outcomes	High risk	No details in paper but blinding unlikely to have occurred
Incomplete outcome data (attrition bias) All outcomes	Low risk	40 women randomised, one refused second look laparoscopy
Selective reporting (reporting bias)	Unclear risk	Original protocol not viewed. A priori outcomes in methods section of paper were reported in results section

Hamed 2010

Methods	Randomised trial of 110 patients
Participants	Egyptian trial. The mean age of the women in the metformin group were 23.6 ± 2.6 years and in the LOD group were 24.3 ± 4.5 years Inclusion: Women with diagnosis of PCOS attending infertility clinic. Clomiphene resistance. Age 20 to 35 years. Patent fallopian tubes shown by hysterosalpingography. Insulin resistance. Normal semen analysis Exclusion: women under 20 years and over 35 years, received gonadotrophins or hormonal contraception in previous 3 months. having hyperprolactinaemia, or other endocrine, hepatic, or renal disorders. having organic pelvic mass, or previous abdominal surgery suggesting pelvic factor infertility

Hamed 2010 (Continued)

Interventions	850mg metformin orally twice daily (n=55) versus LOD using 4 to 8 punctures (n=55). Followed up for 6 cycles/ 30 weeks
Outcomes	BMI, ovulation, pregnancy (biochemical, clinical), miscarriage, resuming regular cycles, glucose/insulin ratio
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'..computer generated random numbers tables'. Satisfactory method
Allocation concealment (selection bias)	Low risk	'..using serially numbered opaque envelopes'. Satisfactory method
Blinding (performance bias and detection bias) All outcomes	Unclear risk	There were no details in the paper on blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 55 women allocated to each group and there were no losses to follow-up or discontinuation of medication. All women were analysed
Selective reporting (reporting bias)	Unclear risk	Report on adverse effects of treatment that were not pre-specified as outcomes in the methods section of the paper, the original protocol was not viewed

Kaya 2005

Methods	Randomised prospective trial conducted in Turkey
Participants	Clomiphene-resistant PCOS patients (see definitions). Mean age of LOMNT group was 26.3 ± 4.3 years and for gonadotrophin group 25.6 ± 4.08 years All women had anovulatory infertility for greater than 1 year Exclusions: History of abdominopelvic surgery, systemic disease, proven or suspected pelvic inflammatory disease or ectopic pregnancy
Interventions	Bilateral ovarian drilling by diathermy (n=17) versus 3 cycles of gonadotrophins (step up protocol) plus IUI (n = 18) Laparoscopic ovarian drilling was performed with a specially designed instrument which was then applied across the ovary and then squeezed

	All women followed up for 6 months	
Outcomes	Pregnancy rate per patient Multiple pregnancy rate and ovarian hyperstimulation rate Costs per treatment 8 patients of the 17 who underwent ovarian drilling had second look laparoscopy for adhesion formation	
Notes	Definitions PCO: clinical (oligomenorrhoea, hirsutism, obesity) + LH/FSH ratio > 2 + elevated testosterone and/or androstenedione (not specified). Clomiphene resistant: failure to ovulate on 200 mg/day for 5 days (duration not stated) . Pregnancy: ultrasound (not specified). Ovulation: biphasic BBT + luteal serum progesterone > 3 ng/ml	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“computer generated random sequence”
Allocation concealment (selection bias)	Low risk	“opaque envelope”
Blinding (performance bias and detection bias) All outcomes	High risk	No details of blinding which is unlikely to have occurred. No reference to outcome assessors being blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	One woman in the LOMNI group and two women in the gonadotrophin group were lost to follow-up, however their data were included in the analysis
Selective reporting (reporting bias)	Unclear risk	Original protocol not viewed but a priori outcomes stated in the methods section of the paper were reported in the results section

Lazoviz 1998

Methods	Randomised trial, cross-over design, data available prior to cross-over. Study conducted in Yugoslavia Method of randomisation: not stated. Time of randomisation: not stated. 56 patients randomised, 6 cycles/patient.
Participants	Clomiphene-resistant PCOS patients (high LH). Mean age not stated. Duration of infertility not stated. Infertility work up not stated. Mean BMI not stated. The trial was carried out at the Institute for Obstetrics and Gynaecology, University of Belgrade, Belgrade, Yugoslavia. Timing and duration of trial not stated.
Interventions	Ovarian drilling with diathermy or laser vaporisation with CO ₂ (n=28) versus gonadotrophins (FSH or hMG) for ovulation induction for 6 cycles. Number of drill holes per ovary is not stated. (n = 28)
Outcomes	Pregnancy rate (per patient) Miscarriage rate (per pregnancy) Multiple pregnancy rate (per pregnancy)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details in paper
Allocation concealment (selection bias)	Unclear risk	No details in paper
Blinding (performance bias and detection bias) All outcomes	High risk	No details of blinding but unlikely to have occurred.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All subjects appear to be included in the analysis.
Selective reporting (reporting bias)	High risk	This is a conference abstract only. No full paper was identified

Mamonov 2000

Methods	Prospective randomised trial conducted in the Ukraine
Participants	128 women with clomiphene resistant PCOS. 84% were obese.
Interventions	Metrodin HP for up to 6 cycles (n=62) versus Laparoscopic electrocoagulation of the ovarian surface (n=66) Followed up for one and half years
Outcomes	Pregnancy, miscarriage
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'..were randomized..' no other details in abstract
Allocation concealment (selection bias)	Unclear risk	No details in abstract
Blinding (performance bias and detection bias) All outcomes	High risk	No evidence of blinding of researchers, patients or outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear details
Selective reporting (reporting bias)	High risk	No outcomes were listed in the methods section.

Palomba 2004

Methods	Randomised double blind study, Italian participants
Participants	120 women; mean age of metformin group were 26.8±2.2 and in LOD group 27.5±2.4 years Inclusion: Overweight (BMI 25 - 30 kg/m ²) women with PCOS, clomiphene resistant. Exclusion: Age < 22 or > 34 years; hypothyroidism, hyperprolactinaemia, Cushings syndrome, nonclassical congenital adrenal hyperplasia, and current or previous (within 6 months) use of oral contraceptives, glucocorticoids, antiandrogens, ovulation induction agents, antidiabetic or antiobesity drugs, or other hormonal drugs; neoplasms, metabolic, hepatic, or cardiovascular disorder or other concurrent medical illness; women who were intending to start a diet or a specific programme of physical activity; having organic pelvic disease, previous pelvic surgery, suspected peritoneal factor infertility, and tubal or male infertility

Interventions	Group A (n= 60) diagnostic laparoscopy followed by metformin cloridrate 850mg twice daily. If anovulatory at 6 months clomiphene citrate 150mg daily from Day 3 -7 versus Group B (n=60) LOD (3 to 6 punctures in each ovary depending on size of ovary) followed by multi-vitamins twice daily. If anovulatory at 6 months clomiphene citrate 150mg daily from Day 3 -7 Treated for 6 cycles	
Outcomes	Live birth, adverse events, menstrual cycle characteristics, ovulation rate, pregnancy, miscarriage, costs	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'The randomisation was carried out using online software to generate a random allocation sequence in double block as method of restriction'
Allocation concealment (selection bias)	Unclear risk	'The random allocation sequence was concealed until the interventions were assigned' there were no further details in the paper
Blinding (performance bias and detection bias) All outcomes	Low risk	Outcome assessors were blinded, patients were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Six women in metformin group and 5 in the LOD group. Reasons given were evidence of minimal endometriosis via laparoscopy (four in Group A and 2 from Group B) and non-compliance (one from each group). One woman from Group A and two from group B were excluded for weight loss observed in the first 3 months of the study
Selective reporting (reporting bias)	Unclear risk	Original protocol not observed but all outcomes cited in the methods section were reported on

Palomba 2010

Methods	Randomised trial Method of randomisation - computer generated Allocation concealment - sealed dark envelopes 50 patients, anovulatory, clomiphene citrate resistant women with PCOS 6 cycles	
Participants	Inclusion: Anovulatory, clomiphene-resistant, with PCOS, seeking pregnancy Exclusion: < 18 or > 35 years, BMI > 35kg/m ² , neoplastic, metabolic, endocrine, hepatic, renal , and cardiovascular disorders, or other concurrent medical illnesses; and current or previous use of any drug that affected hormone levels, metabolism or appetite. Organic or pelvic diseases, previous pelvic surgery, suspected peritoneal factor infertility/ subfertility, and tubal or male factor infertility or subfertility that was excluded by hysterosalpingogram and semen analysis. Wanting to start a diet or a specific program of physical activity, cigarette smokers or alcoholic beverage abusers	
Interventions	N = 25 LOD followed by 6 cycles of observation N = 25 Clomiphene citrate (incremental dose) plus metformin (850mg increasing to 1700g daily) for 6 cycles Followed up for 15 months	
Outcomes	Live birth, pregnancy rates, multiple pregnancy, miscarriage, ovulation rate, adverse events, compliance, cost	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'achieved using online software (www.randomization.it)
Allocation concealment (selection bias)	Low risk	Concealed in sealed dark envelopes until the interventions were assigned
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No discussion of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 women were lost to follow-up because they missed a follow-up visit 1 in the LOD group and 2 in the CC + metformin group)
Selective reporting (reporting bias)	Unclear risk	A priori outcomes reported but original protocol not viewed by review authors

Rimington 1997

Methods	Randomised prospective study conducted in Wales, UK Fertility clinic setting
Participants	50 women, mean age in conventional IVF group was 31 (95% CI 29.8 to 32.2) and for LOE + IVF the mean age was 31.8 (95%CI 30.3 to 33.2) Exclusion: >40 years, history of more than 2 miscarriages, severe male factor infertility Inclusion: Diagnosis of PCOS, requiring IVF for reasons other than anovulation, at least one previous unsuccessful ovarian stimulation cycle with gonadotrophins
Interventions	Conventional IVF (n=25) versus Ovarian electrocautery and IVF (grid of holes 10mm apart) ovarian stimulation started one week after LOE (n=25)
Outcomes	Number of abandoned cycles, OHSS, pregnancy, miscarriage
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'Blocked method of randomisation..'
Allocation concealment (selection bias)	Unclear risk	No details in paper
Blinding (performance bias and detection bias) All outcomes	High risk	There was no evidence of blinding of researchers, participants or outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women randomised appear to be analysed.
Selective reporting (reporting bias)	Unclear risk	The original protocol was not observed but all outcomes listed in the methods section were reported in the results

Roy 2009

Methods	Prospective randomised trial conducted in India
Participants	44 women with PCOS, normal hysterosalpingography, normal semen parameters in partners, women were also clomiphene resistant. Mean age of women in unilateral group was 28.2 ± 12.7 and in the bilateral group was 28.8 ± 2.9 years Exclusion: Other causes of infertility like hypothalamic amenorrhoea, Cushing syndrome, premature ovarian failure, congenital adrenal hyperplasia, androgenic ovarian tumours, endometrial tuberculosis, abnormal TSH and prolactin; had already received

Roy 2009 (Continued)

	other regimens of ovulation induction; tubal obstruction, extensive adhesions of the ovaries or fallopian tubes and endometriosis	
Interventions	Unilateral laparoscopic drilling versus Bilateral laparoscopic drilling There were five drills performed per ovary. If there was no ovulation evident within 3 months, the women were started on clomiphene citrate 50mg daily for 5 days increasing up to a maximum of 150 mg daily for 5 days for a maximum of 6 cycles All women were followed up for 1 year.	
Outcomes	Clinical and biochemical response, ovulation rate and pregnancy rate	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'..randomly allocated..' No other details provided
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding (performance bias and detection bias) All outcomes	High risk	No evidence of blinding of researchers, patient or outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women randomised appear to have been analysed.
Selective reporting (reporting bias)	Unclear risk	The original protocol was not viewed but the outcomes listed in the methods section were reported in the results

Roy 2010

Methods	Prospective randomised trial conducted in India
Participants	Women from a gynaecological clinic. Mean age of rosiglitazone group was 27.32 ± 4.25 and for LOD group was 28.42 ± 3.65 years Inclusion: Age between 20 to 40 years, having primary infertility with clomiphene resistant PCOS, documented patent tubes on hysterosalpingography and no other infertility factor, normal semen parameters in partner Exclusion: Other PCOS like syndromes such as Cushings syndrome, congenital adrenal hyperplasia, androgen producing tumours, hyperprolactinaemia and hypothyroidism

Roy 2010 (Continued)

Interventions	All patients had laparoscopy Unilateral LOD (n=25) using 5 punctures + multivitamins twice daily + CC versus Rosiglitazone 4 mg twice daily + CC (n=25). Treatment continued for 6 months after laparoscopy	
Outcomes	Ovulation, pregnancy, number of follicles, serum E2, endocrine parameters	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'using online software to generate a random number table'
Allocation concealment (selection bias)	Unclear risk	'opening sealed envelopes containing numbers from the computer generated random table' Method looks okay but unclear if envelopes were opaque and if they were opened sequentially
Blinding (performance bias and detection bias) All outcomes	Low risk	Outcome assessor was blinded to allocation group, patients were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	5 women were lost to follow up, an additional 2 women refused to participate before randomisation and therefore 43 were analysed. The reasons for loss to follow up are not described
Selective reporting (reporting bias)	Unclear risk	Original protocol not viewed but all outcomes listed in the methods section are reported in the results

Sharma 2006

Methods	Randomised prospective pilot study, conducted in India
Participants	20 women with clomiphene-resistant PCOS, patent tubes on hysterosalpingography and normal partner semen. No exclusion criteria detailed. Average age of unipolar group was 27.3 (range 21 to 32), and for the bipolar group was 25.5 (range 23 to 30) years
Interventions	Unipolar (n=10) versus Bipolar ovarian drilling (n=10)

	The average number of punctures across both groups was 14.85 per ovary Followed up for 3 months and if no evidence of ovulation then clomiphene citrate was commenced	
Outcomes	Ovulation and pregnancy rate, androgen and biochemical measurements	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'randomly assigned by using computerized random table'
Allocation concealment (selection bias)	Unclear risk	No details in paper
Blinding (performance bias and detection bias) All outcomes	High risk	No evidence of blinding of researchers, patients or outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Although not stated it appears as though all women randomised were analysed
Selective reporting (reporting bias)	High risk	The original protocol was not viewed but the outcomes listed in the methods were all reported

Vegetti 1998

Methods	Randomised trial, no method stated. Method of randomisation: not stated. Time of randomisation: not stated. 29 patients randomised, 6 cycles/patient.
Participants	Clomiphene-resistant PCO patients (high LH). Mean age not stated. Duration of infertility: 2 to 6.5 years. Infertility work up: not stated. Mean BMI not stated. The trial was carried out at the First Department of Obstetrics and Gynaecology, University of Milan and Gynaecology Unit, University of Pavia, Varese, Italy. Timing and duration of trial not stated.
Interventions	Ovarian drilling with diathermy (at least 20 drill holes per ovary) versus gonadotrophins (pure FSH) with low dose step-up protocol) for ovulation induction for

Vegetti 1998 (Continued)

	6 cycles	
Outcomes	Pregnancy rate (per patient) Miscarriage rate (per pregnancy) Multiple pregnancy rate (per pregnancy)	
Notes	Interim results only - further patients will be randomised and a later publication is expected	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Unclear risk	Not stated

Youssef 2007

Methods	Randomised trial conducted in Egypt	
Participants	87 women with PCOS. Mean age of unilateral group was 31.1±4.2, and for the bilateral group was 29.8 ± 3.7 years Inclusion: infertility secondary to anovulation, unsuccessful treatment with clomiphene citrate and gonadotrophins	
Interventions	Weight reduction and insulin sensitising drugs were tried first for 3 months Clomiphene citrate 50mg daily for 5 days from day 3 to 7. If no response then increased up to 150mg daily for 5 days. If still no response HMG used to stimulate ovulation Unilateral LOD (n=43) If both ovaries equal size the right one was drilled, if of unequal size then the larger one was treated versus Bilateral LOD (n=44). Ovaries were cauterised at four points. Followed up for 1 year	
Outcomes	Post operative pain, post operative nausea, ovulation, pregnancy, miscarriage	

Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided in paper
Allocation concealment (selection bias)	Low risk	'randomly allocated by an independent investigator blinded to the treatment group...using the closed envelope method'
Blinding (performance bias and detection bias) All outcomes	Low risk	Outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women appear to have been followed up and analysed.
Selective reporting (reporting bias)	Unclear risk	Original protocol was not viewed but all outcomes listed in the methods section were reported in the results

Zakherah 2009

Methods	Randomised clinical trial	
Participants	100 women from Egypt from a women's Health Centre, women had clomiphene resistant PCOS	
Interventions	Clomiphene citrate + tamoxifen (n=50) versus LOD (n=50).	
Outcomes	Ovulation rate, pregnancy	
Notes	Conference abstract	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details
Allocation concealment (selection bias)	Unclear risk	No details

Zakherah 2009 (Continued)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	Appear to have data on all women.
Selective reporting (reporting bias)	Unclear risk	No protocol available and this article was a conference abstract

Zakherah 2010

Methods	Randomised trial of 150 patients
Participants	Egyptian study Women with clomiphene resistant PCOS attending an infertility clinic. Mean age for clomiphene + tamoxifen group 25.6 ± 3.5 years, laparoscopic drilling group 25.6 ± 4.1 years Inclusion: Age between 18 and 38 years, at least two years of primary or secondary infertility due to anovulation, patent fallopian tubes on hysterosalpingography or diagnostic laparoscopy, no hormonal treatment in previous 3 months and normal semen values
Interventions	Clomiphene citrate (150mg) + tamoxifen (40mg) from day 3 to day 7 for a maximum of 6 consecutive cycles (n=75) versus Laparoscopic drilling performed through triple puncture laparoscopy (4 to 6 puncture points were made through the ovarian capsule of each ovary) (n=75)
Outcomes	Pregnancy (biochemical, clinical, live birth), miscarriage, endometrial thickness, ovulation rate (follicles ≥ 18mm)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'Using a computer generated random number table.'
Allocation concealment (selection bias)	Unclear risk	'sealed envelopes'. Not clear if opaque and serially numbered
Blinding (performance bias and detection bias) All outcomes	High risk	No details provided but unlikely that there was blinding.

Incomplete outcome data (attrition bias) All outcomes	Low risk	There was no loss to follow-up and all 150 women were analysed
Selective reporting (reporting bias)	Unclear risk	Original protocol not viewed but all a priori outcomes in paper were reported on

rFSH: recombinant follicle stimulating hormone

hMG: human menopausal (urinary) gonadotrophins

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Abdel Gadir 1990	Serial randomisation
Abdel Gadir 1992	Serial method of randomisation
Abu Hashim 2011b	Participants had CC failure (defined as failure to achieve pregnancy despite successful CC-induced ovulation for 6 cycles) as opposed to CC resistance
Al-Mizyen 2007	Randomisation was by cards numbered 1 to 20 even numbers allocated to one group and odd numbers to another group
Badawy 2009	Trial compared methods of drilling only
Greenblatt 1993	RCT comparing drilling by diathermy + Interceed to one ovary versus drilling only to the other ovary 1. Unit of randomisation: ovaries, not patients 2. Only outcome is adhesion formation at second-look laparoscopy
Gurgan 1991	Use of concurrent controls
Heylen 1994	Use of concurrent controls
Kamel 2004	Compared re-electrocautery with FSH
Keckstein 1990	Non-randomised controlled trial comparing Nd:YAG laser drilling versus CO2 laser drilling Different duration of follow-up between the 2 groups (8 versus 18 to 30 months)
Kocak 2006	Wrong comparisons. LOD was compared with LOD + metformin
Malkawi 2005	Not an RCT
Muenstermann 2000	Randomisation used an 'alternate' allocation method

(Continued)

Nasr 2010	Both groups underwent LOD
Rath 2006	Quasi-RCT
Saravelos 1996	RCT comparing laparoscopic drilling + Interceed to one ovary versus drilling only to the other ovary Outcome is adhesion formation at second-look laparoscopy
Tabrizi 2005	RCT comparing 5 versus 10 versus 15 points electrocautery of the ovary
Vrbikova 1998	No reproductive outcomes of interest for this review reported
Zhu 2010	This trial compared different numbers of coagulation points

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

Lockwood 1995

Methods	
Participants	
Interventions	
Outcomes	
Notes	This is a conference abstract that the review authors are trying to obtain. It was originally excluded due to lack of usable data. It has now been moved to an included study status and the review authors will enter details when these are obtained

Malkawi 2003

Methods	Participants were divided into two groups (n=64 and n=97)
Participants	161 infertile women from Jordan with clomiphene resistant PCOS
Interventions	Metformin 850mg twice daily throughout the cycle versus LOD
Outcomes	Ovulation rate, pregnancy rate, multiple pregnancies, miscarriage rate, ectopic pregnancy rate, OHSS
Notes	Authors were contacted in September 2011 with regards to the methods of group allocation to determine if trial was randomised

DATA AND ANALYSES

Comparison 1. LOD with and without medical ovulation versus other treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth rate	8	1034	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.74, 1.00]
1.1 LOD versus Clomiphene citrate + metformin	2	159	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.48, 0.91]
1.2 LOD versus Clomiphene citrate + tamoxifen	1	150	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.63, 1.26]
1.3 LOD versus Gonadotrophin	3	318	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.78, 1.25]
1.4 LOD versus Aromatase inhibitor	2	407	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.63, 1.23]
2 Multiple pregnancy rate (per ongoing pregnancy)	12	1129	Odds Ratio (M-H, Fixed, 95% CI)	0.21 [0.08, 0.58]
2.1 LOD versus Clomiphene citrate + metformin	3	441	Odds Ratio (M-H, Fixed, 95% CI)	0.10 [0.01, 1.94]
2.2 LOD versus Gonadotrophin	5	166	Odds Ratio (M-H, Fixed, 95% CI)	0.13 [0.03, 0.52]
2.3 LOD versus Aromatase inhibitor	2	407	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 LOD versus Clomiphene citrate	1	72	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.5 LOD versus Rosiglitazone + CC	1	43	Odds Ratio (M-H, Fixed, 95% CI)	2.21 [0.19, 26.38]
3 Pregnancy rate per woman randomised	18	1930	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.78, 1.14]
3.1 LOD versus Clomiphene citrate + metformin	3	441	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.53, 1.18]
3.2 LOD versus Clomiphene citrate + tamoxifen	2	250	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.59, 1.59]
3.3 LOD versus Gonadotrophin	8	607	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.72, 1.42]
3.4 LOD versus Aromatase inhibitor	2	407	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.58, 1.37]
3.5 LOD versus Clomiphene citrate	1	72	Odds Ratio (M-H, Fixed, 95% CI)	0.52 [0.19, 1.44]
3.6 LOD versus Metformin	1	110	Odds Ratio (M-H, Fixed, 95% CI)	2.47 [1.05, 5.81]
3.7 LOD versus Rosiglitazone + CC	1	43	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.23, 2.50]
4 Miscarriage rate	15	1592	Odds Ratio (M-H, Fixed, 95% CI)	1.10 [0.74, 1.61]
4.1 LOD versus Clomiphene citrate + metformin	3	441	Odds Ratio (M-H, Fixed, 95% CI)	1.43 [0.70, 2.91]
4.2 LOD versus Clomiphene citrate + tamoxifen	1	150	Odds Ratio (M-H, Fixed, 95% CI)	1.71 [0.39, 7.45]

4.3 LOD versus Gonadotrophin	7	441	Odds Ratio (M-H, Fixed, 95% CI)	0.73 [0.40, 1.33]
4.4 LOD versus Aromatase inhibitor	2	407	Odds Ratio (M-H, Fixed, 95% CI)	1.33 [0.45, 3.90]
4.5 LOD versus Metformin	1	110	Odds Ratio (M-H, Fixed, 95% CI)	2.08 [0.36, 11.85]
4.6 LOD versus Rosiglitazone + CC	1	43	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.06, 17.95]
5 OHSS	7	908	Odds Ratio (M-H, Fixed, 95% CI)	0.14 [0.02, 1.19]
5.1 LOD versus Clomiphene citrate + metformin	1	282	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 LOD versus Gonadotrophins	3	251	Odds Ratio (M-H, Fixed, 95% CI)	0.08 [0.00, 1.61]
5.3 LOD versus Aromatase inhibitor	1	260	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.4 LOD versus Clomiphene citrate	1	72	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 8.23]
5.5 LOD versus Rosiglitazone + CC	1	43	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Ovulation rate	7		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 LOD versus Clomiphene citrate + metformin	1	47	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.27, 2.93]
6.2 LOD versus Clomiphene citrate + tamoxifen	2	250	Odds Ratio (M-H, Fixed, 95% CI)	1.34 [0.68, 2.63]
6.3 LOD versus Gonadotrophins	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.66 [0.21, 2.07]
6.4 LOD versus Clomiphene citrate	1	72	Odds Ratio (M-H, Fixed, 95% CI)	0.7 [0.27, 1.83]
6.5 LOD versus Metformin	1	110	Odds Ratio (M-H, Fixed, 95% CI)	1.78 [0.80, 3.96]
6.6 LOD versus Rosiglitazone + CC	1	43	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.13, 3.44]
7 Costs	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 LOD versus Clomiphene citrate + metformin	1	50	Mean Difference (IV, Fixed, 95% CI)	3711.3 [3585.17, 3837.43]
7.2 LOD versus Gonadotrophins only (short term)	2	203	Mean Difference (IV, Fixed, 95% CI)	-1115.75 [-1309.72, -921.77]
7.3 LOD versus Gonadotrophins only (long term)	1	168	Mean Difference (IV, Fixed, 95% CI)	-2235.0 [-4433.16, -36.84]
8 Depression scales (CES-D) at 24 weeks	1	118	Mean Difference (IV, Fixed, 95% CI)	3.0 [-0.61, 6.61]
8.1 Gonadotrophins	1	118	Mean Difference (IV, Fixed, 95% CI)	3.0 [-0.61, 6.61]
9 Health related quality of life: SF-36- gonadotrophin	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 Physical functioning at 24 weeks	1	118	Mean Difference (IV, Fixed, 95% CI)	-7.0 [-12.77, -1.23]
9.2 Social functioning at 24 weeks	1	118	Mean Difference (IV, Fixed, 95% CI)	-3.0 [-10.79, 4.79]
9.3 Role limitations (physical) at 24 weeks	1	118	Mean Difference (IV, Fixed, 95% CI)	-7.0 [-20.71, 6.71]

9.4 Role limitations (emotional) at 24 weeks	1	118	Mean Difference (IV, Fixed, 95% CI)	-10.0 [-24.44, 4.44]
9.5 Mental health at 24 weeks	1	118	Mean Difference (IV, Fixed, 95% CI)	0.0 [-6.71, 6.71]
9.6 Vitality at 24 weeks	1	118	Mean Difference (IV, Fixed, 95% CI)	-3.0 [-9.51, 3.51]
9.7 Pain at 24 weeks	1	118	Mean Difference (IV, Fixed, 95% CI)	1.0 [-6.59, 8.59]
9.8 General health at 24 weeks	1	118	Mean Difference (IV, Fixed, 95% CI)	2.0 [-5.04, 9.04]
10 Depression scales (CES-D) at 24 weeks gonadotrophin	1	118	Mean Difference (IV, Fixed, 95% CI)	3.0 [-0.61, 6.61]
11 Rotterdam Symptom Checklist at 24 weeks- gonadotrophin	1	472	Mean Difference (IV, Fixed, 95% CI)	3.18 [0.63, 5.74]
11.1 Physical symptoms	1	118	Mean Difference (IV, Fixed, 95% CI)	5.0 [-0.96, 10.96]
11.2 Psychological distress	1	118	Mean Difference (IV, Fixed, 95% CI)	6.0 [-1.05, 13.05]
11.3 Activity level	1	118	Mean Difference (IV, Fixed, 95% CI)	1.0 [-2.44, 4.44]
11.4 Overall quality of life	1	118	Mean Difference (IV, Fixed, 95% CI)	7.00 [-0.04, 14.04]

Comparison 2. Unilateral versus bilateral ovarian drilling

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth	1	44	Odds Ratio (M-H, Fixed, 95% CI)	0.83 [0.24, 2.78]
2 Pregnancy rate (per patient)	5	182	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.55, 1.83]
3 Ovulation rate (per patient)	4	161	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.20 [0.59, 2.46]
4 Miscarriage	2	131	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.31, 3.33]

Comparison 3. Second-look versus expectant management

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pregnancy	1	40	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.19, 2.33]
2 Ovulation	1	40	Odds Ratio (M-H, Fixed, 95% CI)	6.33 [0.67, 60.16]
3 Miscarriage	1	40	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.13, 7.89]

Comparison 4. LOD + IVF versus IVF

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth	1	50	Odds Ratio (M-H, Fixed, 95% CI)	1.26 [0.33, 4.84]
2 Multiple pregnancy	1	50	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 16.93]
3 Pregnancy rate per woman randomised	1	50	Odds Ratio (M-H, Fixed, 95% CI)	1.20 [0.37, 3.86]

4 Miscarriage rate per woman randomised	1	50	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.18, 5.51]
5 OHSS	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.22 [0.02, 2.11]

ADDITIONAL TABLES

Table 1. Costs

Study	LOD ± CC	Other treatment	P value
Palomba 2004	EUR 1050	Metformin ± CC EUR 50	< 0.05
Farquhar 2002	Total cost per patient \$2953NZ Chance of pregnancy 28% Cost per pregnancy \$10,938NZ Chance of live birth 14% Cost per live birth \$21,095NZ	Gonadotrophin Total cost per patient \$5461NZ Chance of pregnancy 33% Cost per pregnancy \$16,549NZ Chance of live birth 19% Cost per live birth \$28,744NZ	NS NS

FEEDBACK

Query about study inclusion

Summary

The protocol states that eligible participants were subfertile women with clomiphene-resistant PCOS. Although the term 'clomiphene-resistant' is not defined in the review, it is generally accepted to mean that women have not responded with proven ovulation to the use of clomiphene. Clomiphene failure, on the other hand, means that women have ovulated on clomiphene but have failed to achieve a successful outcome. In my opinion, the meta-analysis has therefore incorrectly included the study of Abu Hashim et al (Abu Hashim et al, 2011b), as participants in his study were infertile women with clomiphene citrate failure rather than clomiphene-resistance. (Summary of comments received from Associate Professor Luk Rombauts)

Reply

The authors agree that Abu Hashim 2011b should not have been included in this review and we have now excluded this study. We have also added a definition of clomiphene resistance in the Methods section. We would like to thank Associate Professor Rombauts for his comments.

Contributors

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WHAT'S NEW

Last assessed as up-to-date: 14 May 2012.

Date	Event	Description
6 August 2012	Feedback has been incorporated	Abu Hashim 2011a excluded in response to feedback

HISTORY

Protocol first published: Issue 2, 1998

Review first published: Issue 2, 1998

Date	Event	Description
15 May 2012	New citation required but conclusions have not changed	There is insufficient evidence for the conclusions to this review to be changed
15 May 2012	New search has been performed	This review was first published in 1998. Updates were published in 2001 and 2007. Nine trials were included in the 2007 version. In the current update an additional 16 studies have been added to the meta-analysis: Abdellah 2011 ; Abu Hashim 2010 ; Abu Hashim 2011 ; Abu Hashim 2011b ; Ashrafinia 2009 ; Amer 2009 ; Ghafarnegad 2010 ; Hamed 2010 ; Palomba 2004 ; Palomba 2010 ; Rimington 1997 ; Roy 2009 ; Roy 2010 ; Sharma 2006 ; Youssef 2007 ; Zakherah 2009 ; Zakherah 2010 .
11 November 2008	Amended	Converted to new review format.
1 May 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Cindy Farquhar prepared the original review (1998) and the first update, in 2001.

Cindy Farquhar prepared the second update (2005). Jane Marjoribanks assisted with the 2005 update by checking the data and editing the text of the review.

Julie Brown was the main contributor with Cindy Farquhar to the 2012 update.

DECLARATIONS OF INTEREST

Dr (now Professor) C Farquhar was the principal investigator on one of the clinical trials, published in 2002.

SOURCES OF SUPPORT

Internal sources

- University of Auckland, New Zealand.
- Yorkshire Regional Health Authority, UK.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Types of interventions: in the original review the only comparison was with gonadotrophins alone. In the 2012 update of this review the comparison has been expanded to include other medical treatments. It also includes women undergoing ART.

NOTES

Updated 2012. Sixteen new RCTs added.

Updated August 2001. Two new RCTs added to the review (Bayram 2001; Farquhar 2001). One of the RCTs was only published as an abstract and additional details are awaited (Bayram 2001).

INDEX TERMS

Medical Subject Headings (MeSH)

Anovulation [etiology; *surgery]; Birth Rate; Diathermy [*methods]; Infertility, Female [etiology; *surgery]; Laparoscopy [methods]; Laser Therapy [methods]; Ovulation Induction [adverse effects; methods]; Polycystic Ovary Syndrome [*complications]; Pregnancy, Multiple; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy