Treatment strategies for women with WHO group II anovulation - a systematic review and network meta-analysis

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TITLE

Treatment strategies for women with WHO group II anovulation - a systematic review and network meta-analysis

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ABSTRACT

Objective: To compare the effectiveness of alternative first-line treatment options in women with WHO group II anovulation wishing to conceive.

Design: Systematic review and network meta-analysis.

Data sources: Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE.

Study selection: Randomised controlled trials (RCTs) comparing eight ovulation induction treatments in women with WHO group II anovulation: clomiphene, letrozole, metformin, combined clomiphene-metformin, tamoxifen, gonadotropins, laparoscopic ovarian drilling and placebo/no treatment. We assigned study quality utilizing the methodology and categories described in the Cochrane Collaboration Handbook. We chose pregnancy, defined preferably as clinical pregnancy, as the primary outcome. Live birth, ovulation, miscarriage and multiple pregnancy were secondary outcomes.

Results: Of the 2,631 titles and abstracts initially identified, we included 57 RCTs reporting on 8,082 women with WHO group II anovulation. All pharmacological treatments were superior to placebo or no intervention in terms of pregnancy and ovulation. Compared to clomiphene, both letrozole and the combination of clomiphene and metformin showed higher pregnancy rates (odds ratio [OR] 1.53, 95%

confidence interval [CI] 1.25 to 2.85 and OR 1.56, 95% CI 1.24 to 1.97) and ovulation rates (OR 1.99, 95% CI 1.38 to 2.87 and OR 1.55, 95% CI 1.02 to 2.36, respectively). Letrozole led to higher live birth rates than clomiphene alone (OR 1.67, 95% CI 1.11 to 2.49). Both letrozole (OR 0.46, 95% CI 0.23 to 0.92) and metformin (OR 0.22, 95% CI 0.05 to 0.92) led to lower multiple pregnancy rates than clomiphene alone.

Conclusions: In women with WHO II group anovulation, letrozole and the combination of clomiphene and metformin are superior to other treatments, including clomiphene alone, to achieve ovulation and pregnancy. Letrozole is the only drug showing a statistically significantly higher live birth rate than clomiphene alone.

Systematic review registration: PROSPERO CRD42015027579

What is already known on this topic?

- Clomiphene is the long standing first-line treatment for WHO group II anovulation.
- Existing pairwise meta-analyses are limited to comparisons of two treatments.

What this study adds?

- This is the first study to compare all the most common ovulation induction regimens with each other, using direct and indirect means.
- All pharmacological ovulation inductions are superior to placebo/no treatment in terms of pregnancy and ovulation in women with WHO group II anovulation,
- Letrozole is the most effective treatment in terms of live birth, and one of the top 3 treatments in terms of pregnancy and ovulation.
- A combination of clomiphene and metformin is the most effective treatment in terms of pregnancy, but not live birth, in comparison with clomiphene alone.
- Metformin and letrozole are associated with the lowest rates of multiple pregnancy.

INTRODUCTION

Infertility affects 1 in 7 couples and ovulation disorders account for a quarter of all cases.[1] Normogonadotrophic anovulation, also classified as World Health Organization (WHO) group II anovulation, is the most common category of anovulatory infertility and within this group polycystic ovary syndrome (PCOS) is by far the most prevalent cause.[2]

PCOS was first described in 1935 by Stein and Leventhal.[3] Previously described in a number of different ways, the diagnostic criteria for PCOS, agreed jointly by the European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM), are known as the Rotterdam criteria.[4 5] These criteria are also endorsed by the Endocrine Society[6] and are used by a wide range of medical professionals, not just obstetricians and gynaecologists. The clinical manifestations of PCOS include oligomenorrhea or amenorrhea, hirsutism, and frequently infertility.[7] When women with PCOS conceive, they and their infants are at increased risk of perinatal complications, including gestational diabetes, pre-eclampsia, preterm labor and neonatal morbidity.[8-10]

Safe and effective ovulation induction is important for women with WHO group II anovulation who wish to conceive, to avoid premature exposure to in-vitro fertilisation (IVF), which is invasive, expensive and associated with potentially higher chances of perinatal complications and congenital abnormalities.[11-14] A number of medical options are used to treat women with ovulation disorders suffering from infertility, including oestrogen receptor modulators (such as clomiphene and

tamoxifen), aromatase inhibitors (such as letrozole), insulin-sensitizing drugs (such as metformin), and direct hormonal stimulation of the ovaries (gonadotropins), with laparoscopic ovarian drilling being a surgical alternative.

Traditional pairwise meta-analysis only allows comparison of two ovulation induction interventions.[15-20] However, many of these treatment strategies have not been compared directly in previous randomised controlled trials (RCTs). Therefore, it is difficult to identify the most effective treatment based on direct evidence. Network meta-analysis, also known as multiple treatment comparison meta-analysis, allows the comparisons of multiple treatments in a single statistical model,[21-23] and a hierarchy of effectiveness of these treatments that can guide decision making.[24 25] The application of network meta-analysis is crucial in areas where multiple interventions are available, such as in WHO group II anovulation.

We therefore performed a systematic review and network meta-analysis to compare the effectiveness of different treatment options, including clomiphene, letrozole, metformin, combined clomiphene-metformin, tamoxifen, gonadotropins, laparoscopic ovarian drilling and placebo/no treatment, in women with WHO group II anovulation and to identify the best first-line treatment strategy. (Systematic review registration: PROSPERO CRD42015027579).

METHODS

Search strategy and selection criteria

We performed an extensive electronic search of the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and EMBASE for randomised controlled trials. The search strategies were based on combinations of ovulation induction and anovulation (or PCOS), using both free words and index terms (Appendix 1). We sought further trial details or protocols to establish eligibility of potential trials. We also searched previous published Cochrane systematic reviews on ovulation induction for additional studies. No language restrictions were applied. Our latest search was completed on April 11th, 2016.

We included published and unpublished RCTs comparing one or more common ovulation induction options with placebo, no treatment or other treatments: clomiphene, tamoxifen, letrozole, metformin, gonadotropins, laparoscopic ovarian drilling or the combination of clomiphene and metformin. Treatment arms were categorized according to the initial randomised allocation, although subsequent clinical management may have included further doses or an alternative treatment.

Studies were excluded if they were not RCTs, only included treatment resistant women or failed to report on clinical pregnancy, live birth or pregnancy. The population within the included studies was classified as: (1) treatment naïve women, (2) a combination of treatment naïve and treatment exposed women, and (3) women whose treatment status was unknown. Crossover trials were also included if pre-cross

over data were available. Studies were also excluded if they only compared different doses of the same treatment option or compared the effects of adding medical adjuncts such as dexamethasone. Authors were contacted for further information if necessary.

Patient involvement

There was no patient involvement in framing the research question, choosing the outcome measures or conducing the research. We plan to involve Fertility Network UK, PCOS Challenge, RESOLVE and Access Australia's National Infertility Network Ltd in the dissemination of the research results by means of short, easy to read summaries of key results, infographics and audio or video interviews that can be used by patients and caregivers.

Data extraction and assessment of risk of bias

Two reviewers (R.W. and B.V.K) independently assessed the eligibility of all identified citations, and extracted data from original trial reports using a specifically designed form capturing information on study design, trial setting, patient characteristics (inclusion criteria, age, body mass index, duration of infertility, history of ovulation induction), sample sizes, details of ovulation induction options, and outcomes. Disagreements were referred to a third reviewer (B.W.J.M) to reach consensus.

We chose pregnancy, defined preferably as clinical pregnancy, as the primary outcome. Clinical pregnancy was defined as either pregnancy visualized at ultrasonography of one or more gestational sacs.[26 27] Since the comparison of the effectiveness of a treatment based on either clinical pregnancy or live birth rate as endpoints results often in comparable conclusions,[28] we used data on live birth or pregnancy (positive hCG blood or urine test) as outcome when data on clinical pregnancy were not available. Secondary outcomes were live birth, ovulation, miscarriage and multiple pregnancy.

Study quality was assigned by two reviewers (R.W. and B.V.K) utilizing the methodology and categories described in the Cochrane Collaboration Handbook.[29] Again, in case of disagreement a third reviewer (B.W.J.M) was asked to reach consensus. Briefly, the tool for assessing risk of bias addresses seven specific domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Each domain is assigned a judgment relating to the risk of bias for that study classified as low risk, high risk or unclear. We presented risk of bias graph by Review Manager 5.3 software.[29]

Data synthesis and statistical analysis

A network meta-analysis was conducted to simultaneously compare seven ovulation induction treatment options and placebo or no treatment for each outcome.

In its simplest form, a network meta-analysis is the combination of direct and indirect estimates of relative treatment effect in a single analysis. An indirect estimate of the relative treatment effect A versus B can be formed by comparing direct trials of A versus C with trials of B versus C. Network plots were constructed to illustrate the geometry of the network.[30]

All network meta-analyses were conducted within a random effects multiple regression model using "mvmeta" package in Stata software [30 31] (Version 12.0, Stata Corp, College Station, TX). Where direct data were available, pairwise meta-analyses in random effects model were also performed in Stata and the agreement of direct and indirect evidence was assessed by constructing an inconsistency plot. Studies with 0 or 100% events in all arms were excluded from the analysis because these studies do not allow conclusions on relative effects. For studies with a 0 event in one arm only, a continuity correction of 0.5 was added to each cell. To avoid double counting of events, multi-arm trials were analyzed in their original form without the need to combine treatment arms.

We presented network meta-analysis summary treatment effects (odds ratios [ORs]) with their 95% confidence intervals (CI) as well as predictive intervals (PrI) to facilitate interpretation of the results in the light of the magnitude of heterogeneity.[30] Predictive intervals can provide an interval within which the estimate of a future study is expected to be.[30] We applied the comparison adjusted funnel plot to assess small study effects in the network. We used the surface under the cumulative ranking curve (SUCRA) to rank the treatments.[30 32] SUCRA is a percentage of the effectiveness of

every treatment relative to an imaginary treatment that is always the best without uncertainty. We then performed sensitivity analysis to explore important network inconsistency. We restricted the analysis to those trials on treatment naïve women, trials with low risk of randomization and allocation bias, and trials reporting clinical pregnancy for sensitivity analysis.

RESULTS

Characteristics of included studies

The literature search yielded a total of 2,631 publications, as is shown in the PRISMA flowchart (Figure 1). Fifty-six[33-88] publications reporting on 57 trials fulfilled the eligibility criteria, as one study[55] included two individual trials (Appendix 2). Eight studies[34 43 53 60 65 76 85 86] were reported in conference abstracts. Publication dates ranged from 1966 to 2015, with 45 trials published in the last 10 years. The studies were conducted in a variety of countries. Four studies were reported in French[45], Italian[79], Turkish[38] and Persian[68], respectively.

Out of the 57 trials, seven[53 55 57 59 63 81 87] had three comparison arms while each of the remaining 50 trials had two. Overall, 8,082 women with WHO group II anovulation were randomised to seven different treatment options including clomiphene, letrozole, metformin, combined clomiphene-metformin, tamoxifen, gonadotropins and laparoscopic ovarian drilling, and to placebo/no treatment. The

network plots are presented in figure 2 for pregnancy, live birth, ovulation, miscarriage and multiple pregnancy.

Risk of bias assessment results

There were 31 (54%) RCTs with low risk of bias on random sequence generation and 25 (44%) RCTs with low risk of bias on allocation concealment. Only 12 (21.0%) trials had low risk of bias on both blinding of participants and outcome assessment. The risk of bias assessment results are shown in Appendix 3.

Network meta-analysis results

Primary outcome – pregnancy

We performed a network meta-analysis that included 57 RCTs reporting on 8,082 women. Of these, 19 evaluated a combination of clomiphene and metformin (1,031 women). The remaining trials offered a single treatment in each arm, including clomiphene (52 trials; 3,511 women), letrozole (21 trials; 1,758 women), metformin alone (14 trials; 910 women), tamoxifen (4 trials; 327 women), FSH (2 trials; 197 women), laparoscopic ovarian drilling (1 trial; 36 women) and placebo or no treatment arm (8 trials; 312 women).

The results of network meta-analysis are shown in Figure 3 and Table 1. Compared with placebo or no intervention, all the treatment options, except for laparoscopic ovarian drilling, resulted in a significant higher chance of pregnancy.

Compared to clomiphene alone, letrozole (OR 1.58, 95% CI 1.25 to 2.00) as well as the combination of clomiphene and metformin (OR 1.81, 95% CI 1.35 to 2.42) led to significant higher pregnancy rates. Similar differences could be found when comparing these two arms to tamoxifen. The combination of clomiphene and metformin also led to a significant higher pregnancy compared to metformin alone (OR 1.71, 95% CI 1.15 to 2.53).

When considering predictive intervals in a network meta-analysis, clomiphene, letrozole, metformin, FSH and combined clomiphene-metformin still led to higher pregnancy rates compared to placebo or no intervention. However, none of the other comparisons remained statistically significant in the network meta-analysis including predictive intervals. This finding suggests that these estimates are unstable and may be influenced by future studies. For those arms compared directly, the results from pairwise meta-analysis and network meta-analysis were consistent, apart from FSH versus clomiphene (Table 1).

SUCRA probabilities were used to provide a hierarchical ranking of the different treatments. The efficacy of every intervention, expressed as a percentage was considered in relation to an imaginary intervention assumed to be the best. Higher SUCRA values therefore correspond to more effective treatments [30]. The SUCRA values for the eight ovulation induction regimens were 90%, 82%, 80%, 50%, 46%, 27%, 22% and 3%, for combined clomiphene-metformin, FSH, letrozole, metformin, clomiphene, tamoxifen, laparoscopic ovarian drilling and placebo/no treatment, respectively. (Appendix 6).

Secondary outcomes

Live birth

For the outcome live birth, 23 RCTs with 4,206 women were included in the network meta-analysis. Letrozole resulted in a significantly higher live birth rate compared with clomiphene (OR 1.67, 95% CI 1.11 to 2.49) or metformin alone (OR 1.86, 95% CI 1.02 to 3.41). The other comparisons showed no significant differences (Appendix 10).

In terms of live birth, letrozole had the highest SUCRA value (81%), followed by FSH (74%), combined clomiphene-metformin (71%), tamoxifen (48%) clomiphene (36%) and metformin (30%) while placebo/no treatment (10%) had the lowest SUCRA value (Appendix 11).

Ovulation

For the outcome ovulation per woman randomised, 40 RCTs were included in the network meta-analysis. Compared with placebo, all interventions, except for laparoscopic ovarian drilling, led to a significantly higher ovulation rate. These significances remained similar in the network meta-analysis including predictive intervals.

Letrozole (OR 1.99, 95% CI 1.38 to 2.87) and the combination of clomiphene and metformin (OR 1.55, 95% CI 1.02 to 2.36) led to a higher ovulation rate than

clomiphene alone (Appendix 15). The combination of clomiphene and metformin was superior to metformin alone (OR 2.66, 95% CI 1.54 to 4.60, 95% PrI 0.70 to 10.10), while metformin was inferior to clomiphene alone (OR 0.58, 95% CI 0.37 to 0.93). Both metformin (OR 0.29, 95% CI 0.17 to 0.52, 95% PrI 0.08 to 1.13) and tamoxifen (OR 0.37, 95% CI 0.16 to 0.81, 95% PrI 0.08 to 1.59) were inferior to letrozole.

FSH had the highest SUCRA value (88%) in terms of ovulation, followed by letrozole (86%), combined clomiphene-metformin (75%), clomiphene (51%), laparoscopic ovarian drilling (39%), tamoxifen (36%), metformin (26%) and placebo/no treatment (1%) (Appendix 16).

Miscarriage

For the outcome miscarriage, after the exclusion of trials with 0 or 100% event rates in all arms, we included 27 RCTs in the network meta-analysis. We failed to find any significant difference between each comparison in terms of miscarriage per woman randomised or miscarriage per pregnancy in the network meta-analysis (Appendix 20, 21).

Multiple pregnancy

Twenty trials assessed the outcome multiple pregnancy. When expressed per woman randomized, FSH led to higher multiple pregnancy rates than metformin (OR 16.27, 95% CI 1.59 to 166.49). This difference remained significant in network

meta-analysis including predictive intervals. FSH also led to higher multiple pregnancy rate than letrozole (OR 7.84, 95% CI 1.10 to 55.90). Both letrozole (OR 0.46, 95% CI 0.23 to 0.92) and metformin (OR 0.22, 95% CI 0.05 to 0.92) led to lower multiple pregnancy rates than clomiphene alone, but these differences were not statistically significant in network meta-analysis including predictive intervals (Appendix 26).

FSH had the highest SUCRA value (93%), followed by clomiphene (70%), placebo (50%), tamoxifen (46%), combined clomiphene-metformin (44%), letrozole (34%) and then metformin (14%) (Appendix 27).

Sensitivity analysis results

When the analyses were restricted to studies reporting clinical pregnancy (Appendix 31), the results were consistent with the main findings: letrozole and combination of clomiphene and metformin were superior to clomiphene alone. However, in studies with treatment naïve women or studies with low risk of both randomisation and allocation bias, letrozole remained superior to clomiphene (OR 1.80, 95%CI 1.20 to 2.70; OR 1.97, 95%CI 1.18 to 3.30), while the trend of the difference between combined clomiphene-metformin and clomiphene remained the same (OR 1.65, 95% CI 0.98 to 2.80; OR 1.57, 95% CI 0.96 to 2.57) (Appendix 30 and 32).

DISCUSSION

Summary of key findings

Our systematic review and network meta-analysis on ovulation induction in infertile women with WHO group II anovulation has three key findings. First, all pharmacological treatments were more effective than placebo or no intervention in terms of achieving ovulation and pregnancy. Second, the combination of clomiphene and metformin as well as letrozole on its own, were superior to clomiphene in terms of pregnancy and ovulation, and letrozole was superior to clomiphene in terms of live birth. Last, both metformin and letrozole were associated with a lower risk of multiple pregnancy than clomiphene.

Strengths and limitations

To our knowledge this is the first application of network meta-analysis in ovulation induction, analysing all the available data and providing a unique opportunity to rank ovulation induction treatments in a single pooled analysis. We reported all major reproductive outcomes in infertility trials and performed sensitivity analyses in different dimensions including study population and study quality. We made these attempts to guarantee the stability of the results. Another strength of our systematic review was the fact that we did not exclude non-English articles or trials published as abstracts only. These trials are often excluded from other meta-analyses,[19 20 89] but in our meta-analysis they contributed 21% (12/57) of the studies and 16% (1321/8082) of the women. We therefore believe that we have

included all relevant published RCTs on ovulation induction in WHO group II anovulation, thus reducing publication bias as much as possible.

Our study also has limitations. First, we only reported reproductive outcomes in our study and were unable to include other relevant outcomes such as side effects which were not reported in most of the primary publications. Metformin, for example, is known to generate gastrointestinal side effects,[15] but this could not be analyzed in our network meta-analysis as it was not systematically reported in all studies. The use of standardized outcomes in studies on ovulation induction would have improved this aspect of our systematic review.[26 27 90]

Second, we chose pregnancy, defined preferably as clinical pregnancy, as the primary outcome. While the aim of infertile couples is to have a healthy child, we did so as the overall sample size of studies reporting on pregnancy was significantly higher than the sample size of studies reporting on live birth. Studies published in early 2000s or earlier usually followed up participants till pregnancy. In order to make full use of these data and to improve the validity of the transitivity assumption of comparisons among the network, we chose pregnancy as the primary outcome. The conclusions on the effectiveness of a treatment point are often, but not always in women with PCOS,[91] in the same direction when based either on pregnancy or live birth, while conclusions based on pregnancy as endpoint are more robust as they have more statistical power.[28] Ideally, future RCTs should adhere to the Harbin consensus on outcomes reporting in infertility trials.[26 27]

Third, lifestyle intervention was not analysed in this study. Although lifestyle intervention is recommended in many countries as it leads to higher spontaneous ovulation rates[92] and natural conceptions rates[93], the role of lifestyle intervention in conjunction to drug treatment is controversial in current evidence. According to a recent Dutch study, lifestyle intervention preceding infertility treatment does not lead to better reproductive outcomes within two years in obese infertile women,[93] whist lifestyle modification with weight loss before ovulation induction improves ovulation and live birth in PCOS in a US study.[94]

Last, anovulation WHO group II is a heterogeneous condition with a variety of clinical manifestations. Women with different genetic background or metabolic conditions may respond differently on treatment options. The current systematic review only allowed general comparisons among women with WHO group II anovulation. Due to the various reporting strategies, we chose not to perform subgroup analysis, based on body mass index (BMI) and hyperandrogenaemia status in this network meta-analysis. Individual participant data (IPD) meta-analysis would allow a more personalized strategy for ovulation induction care.

Quality of evidence and interpretation of data

The overall quality of included studies was moderate in relation to the seven specific domains of the risk of bias assessment. Randomisation and allocation are fundamental requirements for a high quality RCT and therefore we integrated these domains in the network plot (Appendix 5, 9, 14, 19, 30). Although we excluded

quasi-randomised studies in the current systematic review, half of the included RCTs did not report details of randomisation, and further clarity on this eluded us even after attempts to contact the authors. Specific information about allocation concealment was also unavailable in many of the trials. In multicentre RCTs with large sample sizes [52 63 64 71], the dropout rates in different intervention arms varied from 14% to 35%. Many studies with small sample sizes have relatively low or zero dropout rates. Additionally, these studies often claim to have undertaken an intention-to-treat analysis, but it is possible that the authors may have excluded dropouts in their analysis. It is difficult to distinguish those lost to follow up due to adverse events and those for other reasons. CONSORT[95] strongly encourages to report a flow diagram of patient follow up, including reasons for dropouts, however, many included studies failed to do so.

In pairwise meta-analyses, the heterogeneity in comparisons of combined clomiphene-metformin versus clomiphene and letrozole versus clomiphene in all outcomes was low. Therefore, the results of these comparisons in network meta-analysis were robust. By contrast, there was significant heterogeneity in comparisons of clomiphene and metformin. Thus, the results of these comparisons should be interpreted with cautions.

In our network meta-analysis, predictive intervals were used to estimate the effect of a future study. When considering predictive interval in our network meta-analysis, clomiphene, letrozole, metformin, combined clomiphene- metformin, and FSH remained superior to placebo. These results indicate that in future studies,

these active treatments would remain effective in comparison with placebo/no treatment. Of note, there were significant differences between FSH and metformin/letrozole in terms of multiple pregnancy. However, the wide confidence intervals suggest significant imprecision in the effect size.

According to the rankings, combined clomiphene-metformin, letrozole, and FSH were the best interventions in terms of pregnancy, live birth and ovulation, while metformin and letrozole were the best interventions in terms of reducing multiple pregnancy rate.

Research implications

Traditionally, the effectiveness of a new treatment option comes from comparisons with placebo or current standard care. To date, there are no trials comparing letrozole and placebo in treatment naïve women. The current network meta-analysis, however, provides insight in this comparison from indirect comparisons and suggests that trials comparing letrozole to placebo are unnecessary and in our opinion even unethical. New trials evaluating ovulation induction should either compare letrozole to the combination of clomiphene and metformin, or new treatment options, including new combinations, to one of these strategies.

Current evidence showed similar miscarriage rates in women with metformin compared to women with other ovulation induction interventions during periconceptional period. Future studies on the use of metformin during pregnancy in women with WHO group II anovulation, including PCOS, can be beneficial.

IPD meta-analysis on this topic is a necessary next step to find target populations for different ovulation induction interventions and therefore to provide evidence for personally targeted infertility care.

Clinical implications and conclusion

In women with WHO group II anovulation, expectant management is not recommended, as pharmacological ovulation induction significantly improve pregnancy rate (OR 2.43 to 6.11) compared to placebo no treatment.

Letrozole can be recommended as first-line treatment due to its higher pregnancy, live birth and ovulation rate as well as lower multiple pregnancy rate, although the reluctance to adapt such new therapy is common in clinical practice.[96] The superiority of letrozole over clomiphene was stable in all sensitivity analyses including modifying the criteria of population (treatment naive), reporting strategies (reporting clinical pregnancy) and quality of included studies (low risk of randomisation and allocation bias). Combined clomiphene-metformin can also be recommended as first-line treatment, despite the lack of evidence to improve live birth rates and the instability in sensitivity analyses.[28] Clomiphene alone is not competitive in the network, in terms of effectiveness (pregnancy, live birth, and ovulation) or safety (multiple pregnancy). Gonadotropin, though an effective treatment option, had the greatest probability of leading to multiple pregnancy. It is therefore not recommended to be the first-line treatment in treatment naïve women with WHO group II anovulation.

Despite the promising results shown in this study, neither letrozole nor metformin are approved for the treatment of anovulation in many countries and continue to be used off-label.[97 98] For example, letrozole was not included in the scope of the NICE guideline in the UK.[1] The concern on congenital malformation in newborns following letrozole is the reason behind the reluctance to use letrozole.[99] Nevertheless, according to current evidence, the use of letrozole in ovarian induction or stimulation does not increase the risk of congenital anomalies.[64 100-102] These results need to be confirmed by future studies. Moreover, there is an urgent need for long-term follow-up data among the offspring of these interventions to confirm the safety of these interventions and help the subsequent guideline development.

Laparoscopic ovarian drilling was usually undertaken in clomiphene-resistant women and only one small RCT on treatment-naïve women with PCOS could be included in this network meta-analysis. According to current evidence, including data on long-term follow-up, laparoscopic ovarian drilling is recommended as an effective and economic second-line treatment for ovulation induction in women with clomiphene-resistant PCOS.[103-108]

In conclusion, in women with WHO group II anovulation, both letrozole and the combination of clomiphene and metformin are superior to other treatments, including clomiphene alone, to achieve a higher ovulation and pregnancy rate. Letrozole is the only drug showing a statistically significantly higher live birth rate than clomiphene alone.

Footnotes

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Table 1 Results from pairwise meta-analysis (where possible) and network meta-analysis for primary outcome (pregnancy).

Treatment Comparison		Pairwise meta –analysis		Network meta -analysis	
		No of Studies	OR (95% CI)	OR (95% CI)	95% PrI
PB	CC	3	0.20(0.05 to 0.74)	0.30(0.15 to 0.58)	0.11 to 0.81
LET		21	1.53(1.25 to 2.85)	1.58(1.25 to 2.00)	0.74 to 3.39
MF		9	1.10(0.62 to 1.95)	1.06(0.75 to 1.50)	0.47 to 2.37
CC+MF		19	1.56(1.24 to 1.97)	1.81(1.35 to 2.42)	0.83 to 3.95
TAM		4	0.64(0.36 to 1.12)	0.72(0.42 to 1.22)	0.29 to 1.78
FSH		2	1.57(1.04 to 2.37)	1.69(0.85 to 3.37)	0.61 to 4.65
LOD		1	0.52(0.19 to 1.44)	0.52(0.15 to 1.79)	0.12 to 2.25
LET	PB	NA	NA	5.35(2.63 to 10.87)	1.91 to 14.94
MF		5	3.58(2.06 to 6.21)	3.58(1.93 to 6.63)	1.37 to 9.37
CC+MF		NA	NA	6.11(3.02 to 12.38)	2.19 to 17.04
TAM		NA	NA	2.43(1.03 to 5.73)	0.78 to 7.60
FSH		NA	NA	5.71(2.18 to 15.00)	1.67 to 19.50
LOD		NA	NA	1.77(0.44 to 7.22)	0.35 to 8.91
MF	LET	1	0.73(0.41 to 1.32)	0.67(0.45 to 1.01)	0.29 to 1.55
CC+MF		NA	NA	1.14(0.79 to 1.65)	0.50 to 2.59
TAM		1	0.67(0.30 to 1.47)	0.45(0.26 to 0.80)	0.18 to 1.15
FSH		NA	NA	1.07(0.52 to 2.21)	0.38 to 3.03
LOD		NA	NA	0.33(0.09 to 1.16)	0.08 to 1.45
CC+MF	MF	5	1.92(0.90 to 4.06)	1.71(1.15 to 2.53)	0.74 to 3.91
TAM		NA	NA	0.68(0.36 to 1.28)	0.26 to 1.79
FSH		NA	NA	1.59(0.74 to 3.45)	0.54 to 4.67
LOD		NA	NA	0.50(0.14 to 1.78)	0.11 to 2.22
TAM	CC+MF	NA	NA	0.40(0.22 to 0.73)	0.15 to 1.03
FSH		NA	NA	0.93(0.44 to 1.97)	0.33 to 2.68
LOD		NA	NA	0.29(0.08 to 1.03)	0.07 to 1.28
FSH	TAM	NA	NA	2.35(0.99 to 5.60)	0.74 to 7.41
LOD		NA	NA	0.73(0.19 to 2.78)	0.15 to 3.45
LOD	FSH	NA	NA	0.31(0.08 to 1.27)	0.06 to 1.57

(Abbreviations: OR, odds ratio; CI, confidence interval; PrI, predictive interval; CC, clomiphene citrate; PB, placebo or no treatment; LET, letrozole; MF, metformin; TAM, tamoxifen; FSH, follicle stimulating hormone; LOD, laparoscopic ovarian drilling; NA, not available)

Figure 1 PRISMA Flow Diagram

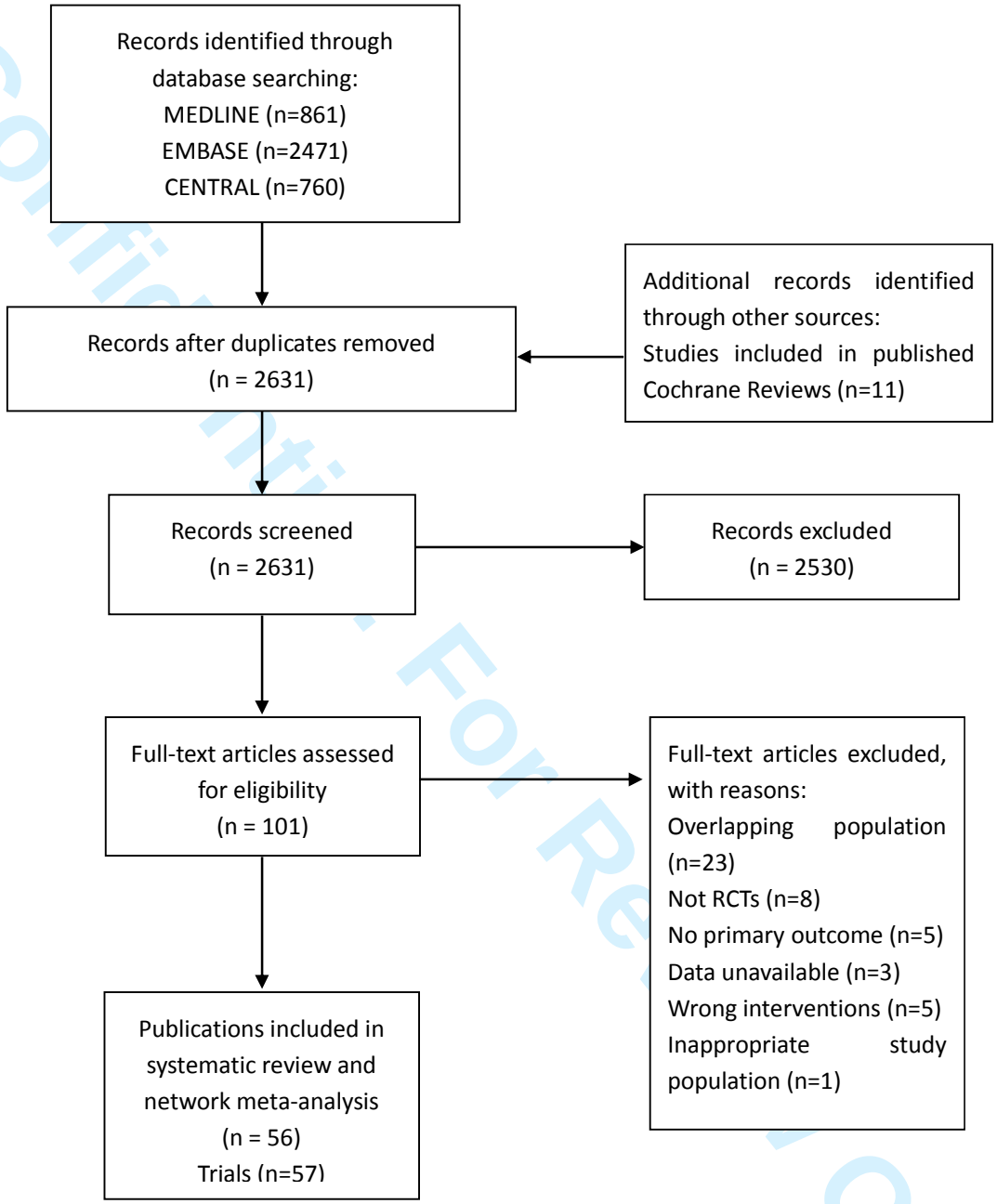
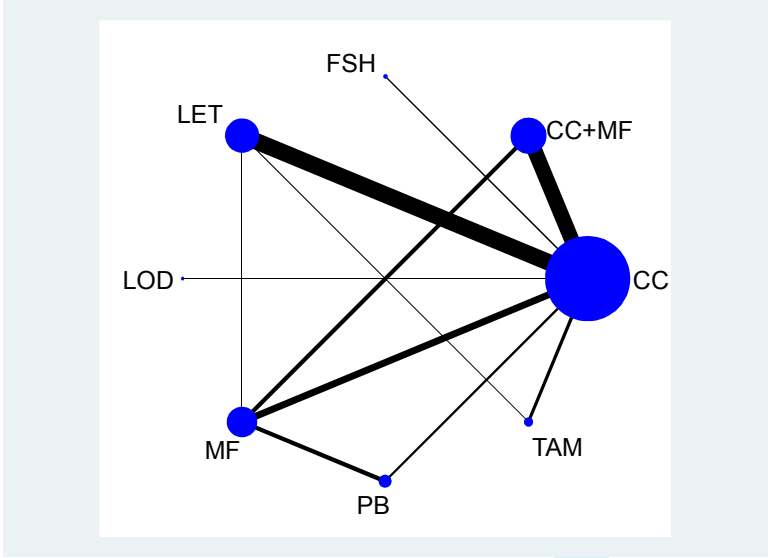


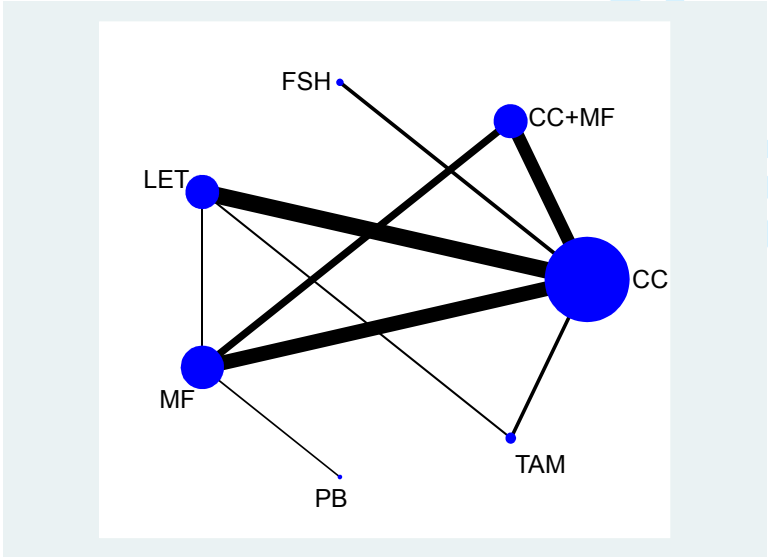
Figure 2a-e. Network plots of eligible comparisons for five outcomes: pregnancy, live birth, ovulation, miscarriage and multiple pregnancy.

The width of the lines is proportional to the number of trials comparing each pair of treatments, and the size of each node is proportional to the number of studies including the respective interventions. (Abbreviations: CC, clomiphene citrate; PB, placebo or no treatment; LET, letrozole; MF, metformin; TAM, tamoxifen; FSH, follicle stimulating hormone; LOD, laparoscopic ovarian drilling)

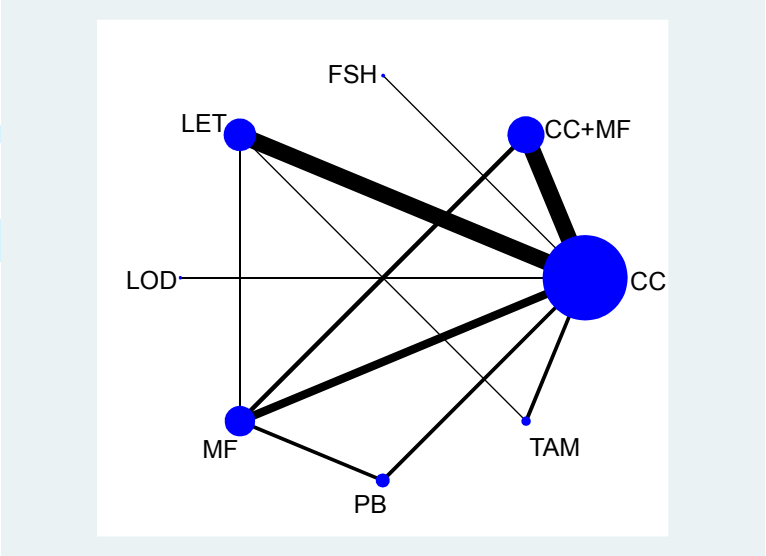
2a Pregnancy



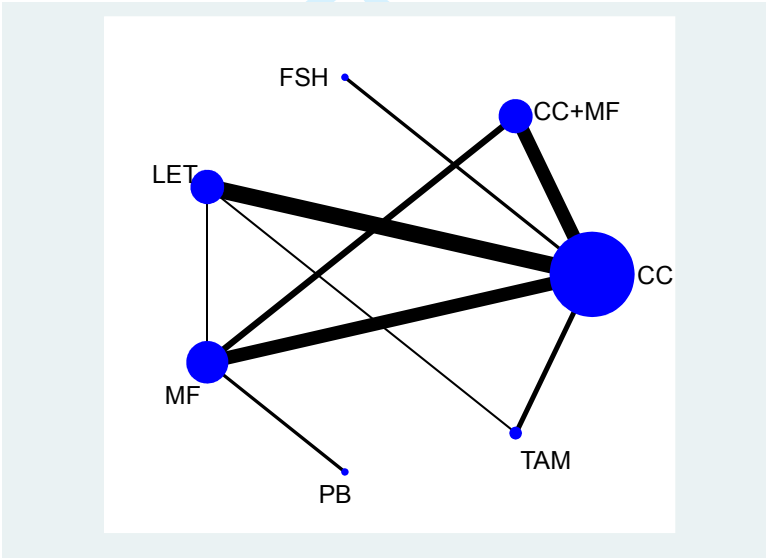
2b live birth



2c ovulation



2d miscarriage



2e multiple pregnancy

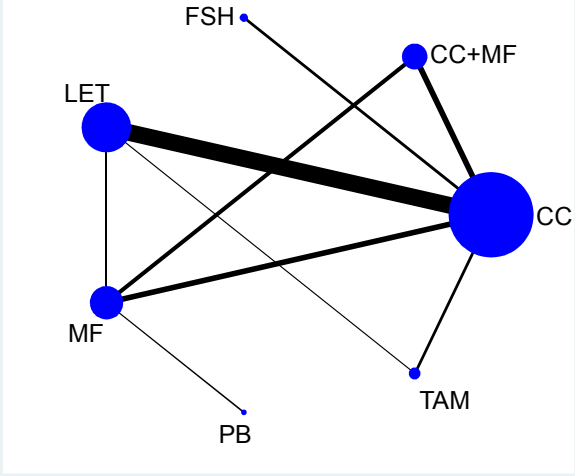
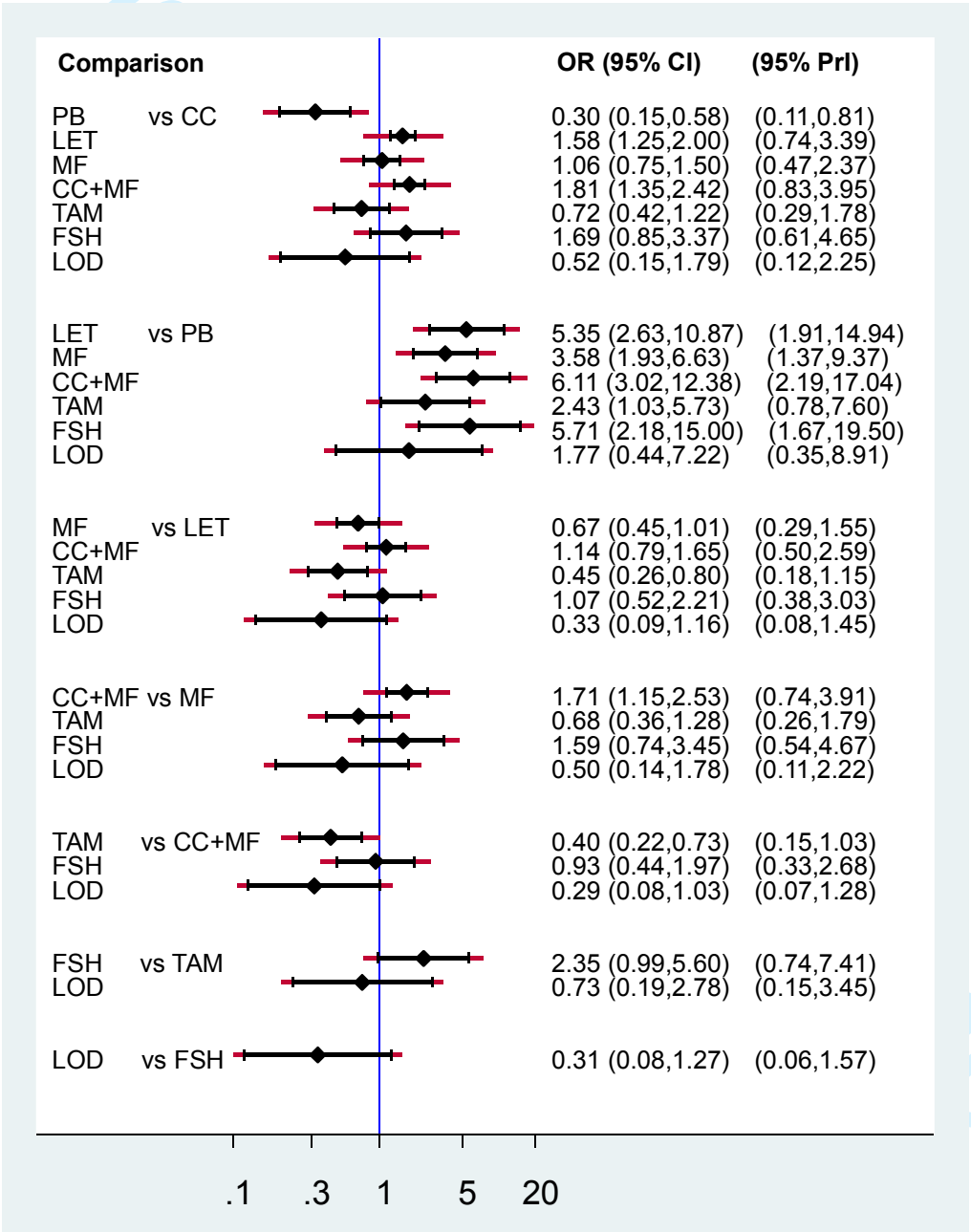


Figure 3 Network meta-analysis results for clinical pregnancy.

The diamond in each line represents the estimate summary odds ratios of each comparison. The black solid lines represent the confidence intervals for summary odds ratios for each comparison and the red dashed lines (overall length of the lines) the respective predictive intervals. The blue line is the line of no effect (odds ratio equal to 1). Right side favors the first intervention and left side favors the second. (Abbreviations: OR, odds ratio; CI, confidence interval; PrI, predictive interval; CC, clomiphene citrate; PB, placebo or no treatment; LET, letrozole; MF, metformin; TAM, tamoxifen; FSH, follicle stimulating hormone; LOD, laparoscopic ovarian drilling)



Appendices index

Appendix 1 Search strategies

1a. MEDLINE search strategy Database: Ovid MEDLINE(R)

1 exp Polycystic Ovary Syndrome/
2 Polycystic Ovar$.tw.
3 PCOS.tw.
4 PCOD.tw.
5 PCO.tw.
6 (stein-leventhal or leventhal).tw.
7 (ovar$ adj (scelerocystic or polycystic or degeneration)).tw.
8 anovulat$.ti,ab,sh,tw.
9 oligo ovulat$.ti,ab,sh,tw.
10 or/1-9
11 randomized controlled trial.pt.
12 controlled clinical trial.pt.
13 randomly.ab,ti.
14 randomized.ab,ti.
15 (crossover or cross over).tw.
16 placebo.tw.
17 RCT.tw.
18 trial.ti.
19 clinical trials as topic.sh.
20 or/11-19
21 exp animals/ not humans.sh.
22 20 not 21
23 fertil$.ti,ab,sh,tw.
24 infertil$.ti,ab,sh,tw.
25 subfertil$.ti,ab,sh,tw.
26 pregnan$.ti,ab,sh,tw.
27 exp ovulation induction/ or exp superovulation/
28 (ovulat$ adj2 induc$).tw.
29 (ovar$ adj2 stimulat$).tw.
30 superovulat$.tw.
31 or/23-30
32 10 and 22 and 31

1b. Embase search strategy Database: EMBASE.com

#1 'ovary polycystic disease'/exp OR 'stein leventhal syndrome'/exp
#2 (polycystic NEAR/2 ovar*):de,ab,ti
#3 pcos:de,ab,ti OR pcod:de,ab,ti OR pco:de,ab,ti
#4 leventhal:de,ab,ti
#5 (ovar* NEAR/2 (scelerocystic OR degeneration)):de,ab,ti
#6 'anovulation'/exp
#7 anovulat*:de,ab,ti
#8 (oligo NEAR/2 ovulat*):de,ab,ti
#9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10 'randomized controlled trial'/exp
#11 'controlled clinical trial'/exp
#12 randomized:de,ab,ti
#13 randomly:de,ab,ti
#14 trial:ti
#15 plecebo:de,ab,ti
#16 rct:de,ab,ti
#17 crossover:de,ab,ti OR (cross NEAR/1 over):de,ab,ti
#18 'clinical trial' OR 'clinical trials':de
#19 #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
#20 #19 AND [animals]/lim NOT [humans]/lim
#21 #19 NOT #20
#22'infertility'/exp OR 'fertility'/exp OR 'subfertility'/exp
#23 infertil*:de,ab,ti OR subfertil*:de,ab,ti OR feril*:de,ab,ti
#24 pregnan*:de,ab,ti
#25 'pregnancy'/exp
#26 'ovulation induction'/exp OR 'superovulation'/exp
#27 (ovulat* NEAR/2 induc*):de,ab,ti
#28 (ovar* NEAR/2 stimulat*):de,ab,ti
#29 superovulat*:de,ab,ti
#30 #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29
#31 #9 AND #21 AND #30

1c. Database: EBM Reviews - Cochrane Central Register of Controlled Trials
#1 [mh "Polycystic Ovary Syndrome"]
#2 (polycystic near ovar*):kw,ab,ti
#3 pcos:kw,ab,ti or pcod:kw,ab,ti or pco:kw,ab,ti
#4 leventhal:kw,ab,ti
#5 (ovar* near (scelerocystic or degeneration)):kw,ab,ti
#6 anovulat*:kw,ab,ti
#7 oligo near ovulat*:kw,ab,ti
#8 [mh anovulation]
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10 randomized controlled trial:pt
#11 controlled clinical trial:pt

#12 plecebo:kw,ti,ab
#13 randomly:kw,ti,ab
#14 RCT:kw,ti,ab
#15 trial:ti
#16 crossover:kw,ti,ab or (cross next over):kw,ti,ab
#17 #10 or #11 or #12 or #13 or #14 or #15 or #16
#18 [mh infertility]
#19 [mh fertility]
#20 [mh pregnancy]
#21 infertil*:kw,ti,ab
#22 fertil*:kw,ti,ab
#23 subfertil*:kw,ti,ab
#24 pregnan*:kw,ti,ab
#25 [mh "Ovulation Induction"] or [mh superovulation]
#26 ovulat* near induc*:kw,ti,ab
#27 ovar* near stimulat*:kw,ti,ab
#28 superovulat*:kw,ti,ab
#29 #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28
#30 #9 and #17 and #29

Appendix 2 Characteristics of included studies

Study	Interventions	Age (mean)	BMI (mean)	DOI (mean years)	Inclusion criteria	Sample Size	Previous Treatment	Country	Setting	Maximum of treatment cycles	IUI or TI
Abuelghar 2013[33]	CC MF+CC	28.4 27.6	28.1 28.6	2.8 3.1	Overweight and obese infertile women with PCOS (Rotterdam criteria)	66	unknown	Egypt	single-centre	1	TI
Amer 2009[34]	CC LOD	29.1 28.1	26.1 26.2	1.8 2.1	PCOS (at least 2 of the following 3 features: clinical [oligo/amenorrhoea and/or Hyperandrogenaemia], biochemical [LH≥10 IU/l, LH/FSH ratio ≥2, testosterone>2.6 nmol/l or free androgen index (FAI) >5] and/or sonographic (polycystic ovaries) features.)	72	naive	UK	single-centre	6	TI
Amer 2015[35]	CC LET	NA	NA	NA	anovulatory women with PCOS	159	naive	UK	single-centre	7	TI
Atay 2006[36]	CC LET	26.2 27.1	25.8 26.1	2.4 2.2	Women with primary infertility and PCOS(oligo- or amenorrhoea and ovaries with at least 10 subcapsular cysts 2 – 10 mm in diameter	106	unknown	Turkey	N/A	1	TI

					and hyperechogenic stroma.)						
Ayaz 2013[37]	CC MF+CC	31.3 32.0	NA[a]	NA	PCOS (the presence of two of the three following criteria:1. Polycystic ovaries [either 12 or more peripheral follicles or increased ovarian volume, > 10 cm^3]. 2. Oligo or anovulation [irregular cycles, amenorrhea]. 3. Clinical and/or biochemical signs of hyperandrogenism [Acne, hirsutism, voice changes, and Clitoromegaly].)	42	unknown	Saudi Arabia	single-centre	6	TI
Aygen 2007[38]	CC LET	23.4 26.8	27.6 26.9	4.2 5.8	Infertility and PCOS (Rotterdam criteria)	10	unknown	Turkey	single-centre	6	TI
Badawy 2009[39]	CC LET	29.3 27.1	27.1 28.1	NA	Infertile women with PCOS (Rotterdam criteria)	438	unknown	Egypt	multi-centre	>1	TI
Badawy 2011[40]	CC TAM	25.8 26.2	29.9 30.5	1.5 1.4	PCOS (Rotterdam criteria)	371	unknown	Egypt	multi-centre	1	TI
Basirat 2012[41]	CC MF+CC	25.3 24.9	25.4 26.3	2.7 2.4	Infertile PCOS (Rotterdam criteria)	334	unknown	Iran	multi-centre	3	IUI
Bayar 2006[42]	CC LET	20.6 32.2	NA	3 5	anovulatory PCOS (Rotterdam criteria)	80	naive	Turkey	single-centre	>1	TI
Beigi 2006[43]	CC MF	NA	NA	NA	PCOS based on a history of hyperandrogenism, anovulation, oligomenorrhea	70	unknown	Iran	single-centre	6	TI

					or amenorrhea, diagnostic ultrasound and laboratory findings						
Boonstanfar 2001[44]	CC TAM	26.5 26.6	30.2 30.9	3.7 3.5	anovulatory women with infertility	95	naive	USA	single-centre	>1	TI
Boudhraa 2010[45]	CC MF+CC	30.7 30.6	29.8 30.0	2.5[b]	PCOS (Rotterdam criteria) with subfertility	63	unknown	Tunis	single-centre	3-6	TI
Cudmore 1966[46]	CC PB	24.6 24.6	NA	NA	A diagnosis of secondary amenorrhea of at least 2 year's duration; persistent oligomenorrhea with no more than 4 periods in 1 year; or anovulatory infertility (infertility of more than 2 years' duration in which anovulation was the only cause found)	22	unknown	Canada	single-centre	3	TI
Dasari 2009[47]	CC MF+CC	NA[c]	NA[d]	NA	Infertile PCOS (Rotterdam criteria)	40	unknown	India	single-centre	6	TI
Dehbashi 2009[48]	CC LET	24.3 23.6	27.1 27.5	2.3 2.0	PCOS (Rotterdam criteria)	100	naive	Iran	single-centre	1	TI
El-Biely 2001[49]	CC MF+CC	25.7 26.4	27.4 28.7	4.7 4.5	Infertile obese patients with PCOS (oligomenorrhoea, ultrasound findings of ≥ 10 ovarian cysts measuring 2-8mm around a dense stroma)	90	unknown	Egypt	single-centre	6	TI

Fleming 2002[50]	MF PB	28.6 29.2	34.2 35.0	NA	Women with oligomenorrhea or amenorrhea and PCO	42	naive	UK	single-centre	4	TI
Garcia 1985[51]	CC PB	27.6[e]	NA	NA	Anovulatory infertile women	49	unknown	USA	single-centre	5	TI
Homburg 2012[52]	CC FSH	29.4 29.8	25.7 25.1	2.1 2.1	anovulatory or oligo-ovulatory infertile women with PCOS (Rotterdam criteria)	302	naive	Netherlands, UK, Malta, Belgium, Argentina Colombia	multi-centre	3	TI/IUI
Jahan 2015[53]	CC LET MF	NA	NA	NA	PCOS	460	naive	Bangladesh	single-centre	6	TI
Johnson 1966[54]	CC PB	NA	NA	NA	Anovulatory women	65	mixed	USA	single-centre	1	TI
Johnson 2010A[55]	MF PB	29.5 29.2	38.0 37.6	3.3(2.4-5.9)[f] 3.4(2-5)[f]	anovulatory or oligo-ovulatory women with PCOS (Rotterdam criteria), BMI>32 kg/m^2	65	mixed	New Zealand	multi-centre	6	TI
Johnson 2010B[55]	CC MF MF+CC	28.2 28.9 29.2	26.2 26.5 26.9	2(1-3)[f] 1(1-4)[f] 2(1.5-5)[f]	anovulatory or oligo-ovulatory women with PCOS (Rotterdam criteria), BMI≤32 kg/m^2	106	mixed	New Zealand	multi-centre	6	TI
Kar 2012[56]	CC LET	26.3 26.3	26.0 25.9	3.1 3.1	infertile PCOS (Rotterdam criteria)	103	naive	India	single-centre	1	TI/IUI
Kar 2015[57]	CC	25.8	26.5	2.8	PCOS (Rotterdam criteria),	105	naive	India	single-	6	TI

	MF MF+CC	25.2 26.6	24.5 27.2	1.7 2.5	with the primary complaints of infertility and oligomenorrhea				centre		
Karimzadeh 2007[58]	MF PB	27.2 28.6	28.8 29.5	5.6 6.2	PCOS (Rotterdam criteria)	200	unknown	Iran	single-centre	3	TI
Karimzadeh 2010[59]	CC MF MF+CC	27.5 27.3 27.3	27.2 27.2 28.0	4.1 3.9 4.6	infertile PCOS (Rotterdam criteria)	268	unknown	Iran	single-centre	6	TI
Keikha 2011[60]	CC LET	27.1 27.6	NA	2.9 3.0	infertile PCOS	116	naive	Iran	single-centre	1	TI
Khorram 2006[61]	CC MF+CC	28.0 28.4	38.8 35.3	NA	PCOS (anovulatory or oligo-ovulatory cycles, polycystic ovaries on a baseline ultrasound, hyperandrogenism) and infertility	31	naive	USA	single-centre	1	TI
Leanza 2014[62]	CC MF+CC	26-34[g]	NA	NA	PCOS (typical ultrasound situation, oligomenorrhea/amenorrhea, hyperandrogenism) with above 3 years of infertility, BMI>27.5	56	naive	Italy	single-centre	3	IUI
Legro 2007[63]	CC MF MF+CC	27.9 28.1 28.3	36.0 35.6 34.2	3.5 3.3 3.4	infertile women PCOS (oligomenorrhea and hyperandrogenemia)	626	mixed	USA	multi-centre	6	TI
Legro 2014[64]	CC	28.8	25.1	3.5	infertile women PCOS	750	mixed	USA	multi-	5	TI

	LET	28.9	35.2	3.4	(Rotterdam criteria)				centre		
Liu 2015[65]	CC LET	NA	NA	NA	PCOS patients who have conception desire	134	unknown	China	single-centre	>1	TI
López 2004[66]	CC FSH	29(23-38)[f] 30(22-39)[f]	22.3 21.9	3(1-8)[f] 3(1-8)[f]	anovulatory infertility due to PCOS (Rotterdam criteria)	76	naive	Spain	single-centre	3	TI
Lord 2006[67]	MF PB	27.8 30.6	33.7 36.4	NA	PCOS (anovulation and a raised free androgen index (FAI) >5.0)	44	unknown	UK	single-centre	3	TI
Lorzadeh 2011[68]	CC LET	26.1 28.2	25.4 24.2	NA	PCOS (based on the chronic anovulation and clinical/lab-based hyperandrogenism), age <35, No successful pregnancy after one year of weekly (2-3 times) sexual contact without contraception.	100	unknown	Iran	single-centre	>1	TI
Maged 2015[69]	CC MF+CC	26.0 25.8	27.3 27.7	2.8 2.8	PCOS (Rotterdam criteria)	80	unknown	Egypt	single-centre	3	TI
Mobusher 2014[70]	CC LET	24.3 24.3	25.9 25.9	3.1 3.2	PCOS (Rotterdam criteria) and infertility	100	naive	Pakistan	single-centre	1	TI
Moll 2006[71]	CC MF+CC	28.4 27.9	27.8 28.5	1.3 1.6	PCOS (Rotterdam criteria), all women with chronic anovulation and polycystic ovaries diagnosed by	225	naive	Netherlands	multi-centre	6	TI

					transvaginal ultrasonography						
Nazik 2012[72]	CC LET	27.8 25.6	25.9 24.7	4.4 3.4	PCOS (Rotterdam criteria)	64	naive	Turkey	single-centre	>1	TI
Palomba 2005[73]	CC MF	25.9 26.4	26.7 27.0	1.7 1.6	primary infertile anovulatory women with PCOS (NIH criteria)	100	naive	Italy	single-centre	6	TI
Raja 2005[74]	CC MF+CC	26.9 26.5	NA	4.9 4.2	Infertility and PCOS (the presence of polycystic ovaries on ultrasonography with two or more of the following criteria: Oligomenorrhoea [<6 cycles in preceding year); hirsutism; hyperandrogenism; Elevated LH or LH: FSH >2])	100	unknown	Pakistan	single-centre	6	TI
Ray 2012[75]	CC LET	29(20-35) [f] 28(19-35) [f]	28.5(24.2-33.6) [f] 28.8(23.2-34.6) [f]	2.4 2.2	Infertile PCOS (Rotterdam criteria)	147	unknown	India	single-centre	>1	TI
Robinson 2003[76]	CC MF+CC	NA	NA	NA	Women with a one-year history of infertility and diagnosed with hyperandrogenic oligoovulatory or anovulatory cycles as the sole etiology for their infertility	48	unknown	USA	single-centre	6	TI

Roy 2012[77]	CC LET	26.5 26.1	25.4 25.8	5.8 6.4	infertility and anovulatory PCOS (Rotterdam criteria), BMI<28	212	unknown	India	single-centre	3	TI
Sahin 2004[78]	CC MF+CC	24.5(19-28) [f] 27(21-31) [f]	25.7(23.1-35.7) [f] 30.4(24.6-33.9) [f]	3.5(1-8) [f] 5(2-10) [f]	Primary infertility and PCOS (on the basis of three or more of the following criteria: polycystic ovaries on pelvic ultrasound examination, oligo/amenorrhoea, hirsutism, hyperandrogenaemia (total testosterone > 80 ng/dl and/or free testosterone > 3.18 pg/ml)) and elevated serum LH:FSH ratio (LH:FSH > 2))	21	unknown	Turkey	single-centre	6	TI
Santonocito 2009[79]	CC MF	27.4 28.1	27.1 26.8	1.7 1.6	infertility and anovulatory PCOS (Rotterdam criteria), BMI< 30 kg/m^2	36	unknown	Italy	single-centre	6	TI
Selim 2012[80]	CC LET	25.1 26.0	23.8 24.4	2.6 2.9	Infertile women with PCOS (Rotterdam criteria)	220	naive	Egypt	single-centre	1	TI
Seyedoshohadaei 2012[81]	CC LET TAM	24.7 26.9 25.4	NA	3.0 4.1 3.0	non-PCOS anovulatory infertility, and ovary without evidence of polycystic ovaries	150	unknown	Iran	single-centre	6	TI
Sharief 2015[82]	CC LET	25.3 26.1	27.8 28.1	2.3 2.4	primary infertility and anovulation due to	75	unknown	Iraq	single-centre	6	TI

					PCOS (ultrasonographic polycystic ovaries plus one or more of the following: oligomenorrhoea, positive progesterone, withdrawal bleeding, hirsutism/acne, obesity, and Luteinizing hormone/Follicle-stimulating hormone (LH/FSH) ratio >2 or raised circulating androgen, normal thyroid stimulating hormone)						
Sh-El-Arab Elsedeek 2011[83]	CC LET	25.0 25.0	29.1 27.7	NA	Nulliparous PCOS (Rotterdam criteria), BMI ≤35	124	unknown	Egypt	single-centre	1	TI
Tang 2006[84]	MF PB	29.7 29.8	37.6 38.9	4.5 4.9	anovulatory PCOS (polycystic ovaries on transvaginal scan, together with either oligomenorrhoea or amenorrhoea) and a BMI of >30,	143	naive	UK	multi-centre	6	TI
Vegetti 1999[85]	CC TAM	NA	NA	NA	Infertility and normogonadotropic anovulation	95	naive	Italy	single-centre	>1	TI
Williams 2009[86]	CC MF+CC	NA	NA	NA	women with PCOS who are attempting to conceive.	55	unknown	USA	N/A	6	TI

Zain 2009[87]	CC MF MF+CC	29.6 27.8 29.3	32.9 33.9 33.0	2.9 3.1 3.3	PCOS (Rotterdam criteria)	124	naive	Malaysia	single-centre	6	TI
Zeinalzadeh 2010[88]	CC LET	23.1 23.8	NA	2.6 2.4	PCOS (based on ultrasonography finding, oligomenorrhea and an increased LH/FSH ratio (>3))	107	naive	Iran	single-centre	1	IUI

(Abbreviations: CC, clomiphene citrate; PB, placebo or no treatment; LET, letrozole; MF, metformin; TAM, tamoxifen; FSH, follicle stimulating hormone; LOD, laparoscopic ovarian drilling; NA, not available; BMI, body mass index; DOI: Duration of infertility)

a. The percentages of women with BMI>25 in CC and CC+MF group are 71.4% and 56.7%, respectively.

b. The mean duration of infertility of all the participants (including both groups).

c. The percentages of women with age >31, 26-30 and 20-25 years are 8.3%, 41.7%, 50% in CC group and 18.8%, 43.8% and 37.5% in CC+MF group.

d. The percentages of women with BMI >25 and BMI < 25 are 37.5% and 62.5%, respectively.

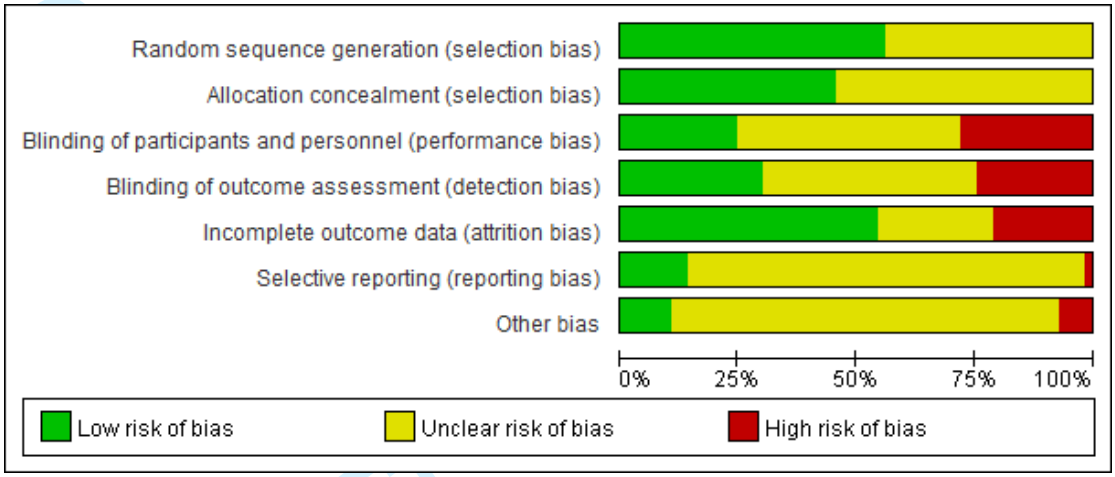
e. in treatment group only

f. median (range)

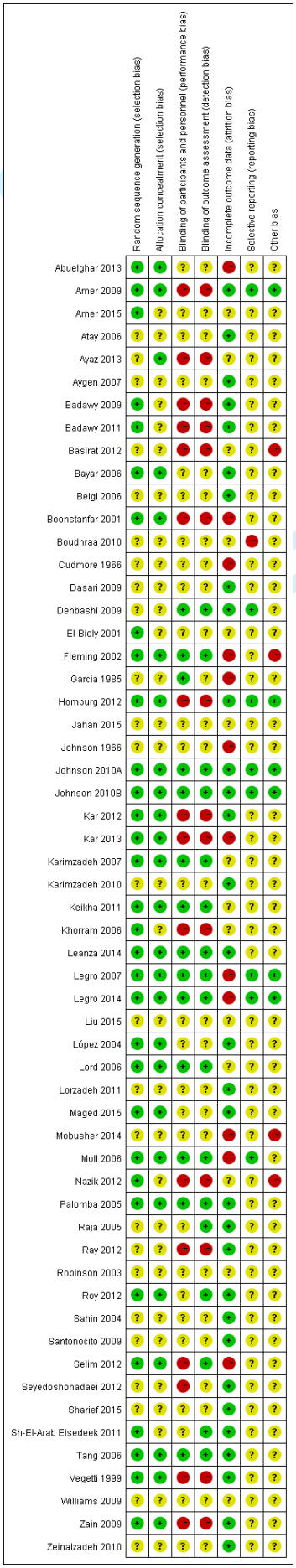
g. range

Appendix 3 Risk of bias evaluation.

3a. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.



3b. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.



Appendix 4 Pairwise meta-analysis results for direct comparisons of interventions

Comparisons		Pairwise meta-analysis odds ratio (95% CI)	No. of trials	No. of participants	Heterogeneity I^2
Pregnancy					
PB	vs CC	0.20(0.05-0.74)	3	136	0%
LET		1.52(1.26-1.85)	21	3553	24.3%
MF		1.10(0.62-1.95)	9	1335	73.1%
CC+MF		1.56(1.24-1.97)	19	2070	12.2%
TAM		0.64(0.36-1.12)	4	661	43.7%
FSH		1.57(1.04-2.37)	2	378	0%
LOD		0.52(0.19-1.44)	1	72	N/A
MF	vs PB	3.58(2.06-6.21)	5	494	0%
MF	vs LET	0.73(0.41-1.32)	1	304	N/A
TAM		0.67(0.30-1.47)	1	100	N/A
CC+MF	vs MF	1.92(0.90-4.06)	5	818	71.8%
Live Birth					
LET	vs CC	1.60(1.30-1.98)	9	1990	0%
MF		1.00(0.45-2.22)	8	1155	80.9%
CC+MF		1.14(0.81-1.61)	7	950	12.4%
TAM		0.96(0.26-3.55)	2	195	35.3%
FSH		1.50(0.98-2.29)	2	378	0%
MF	vs PB	2.87(0.51-16.02)	1	65	N/A
MF	vs LET	0.38(0.19-0.78)	1	304	N/A
TAM		0.71(0.32-1.60)	1	100	N/A
CC+MF	vs MF	2.48(1.24-4.95)	4	640	51.1%
Ovulation (per woman randomised)					
PB	vs CC	0.15(0.07-0.34)	3	136	0%
LET		1.89(1.55-2.30)	14	2568	8.8%
MF		0.62(0.32-1.22)	7	1119	82.9%
CC+MF		1.46(1.01-2.12)	14	1407	54.5%
TAM		0.61(0.43-0.86)	3	566	0%
FSH		0.11(0.76-12.79)	1	76	N/A
LOD		0.70(0.27-1.83)	1	72	N/A
MF	vs PB	3.63(0.45-29.35)	3	309	92.9%
MF	vs LET	0.14(0.09-0.24)	1	304	N/A
TAM		0.75(0.31-1.78)	1	100	N/A
CC+MF	vs MF	3.20(1.85-5.52)	4	640	44.4%
Multiple pregnancy (per woman randomised)					
LET	vs CC	0.45(0.22-0.91)	12	2460	0%
MF		0.22(0.05-0.96)	4	976	0%
CC+MF		0.57(0.19-1.74)	4	892	0%
TAM		0.48(0.06-3.76)	2	471	0%

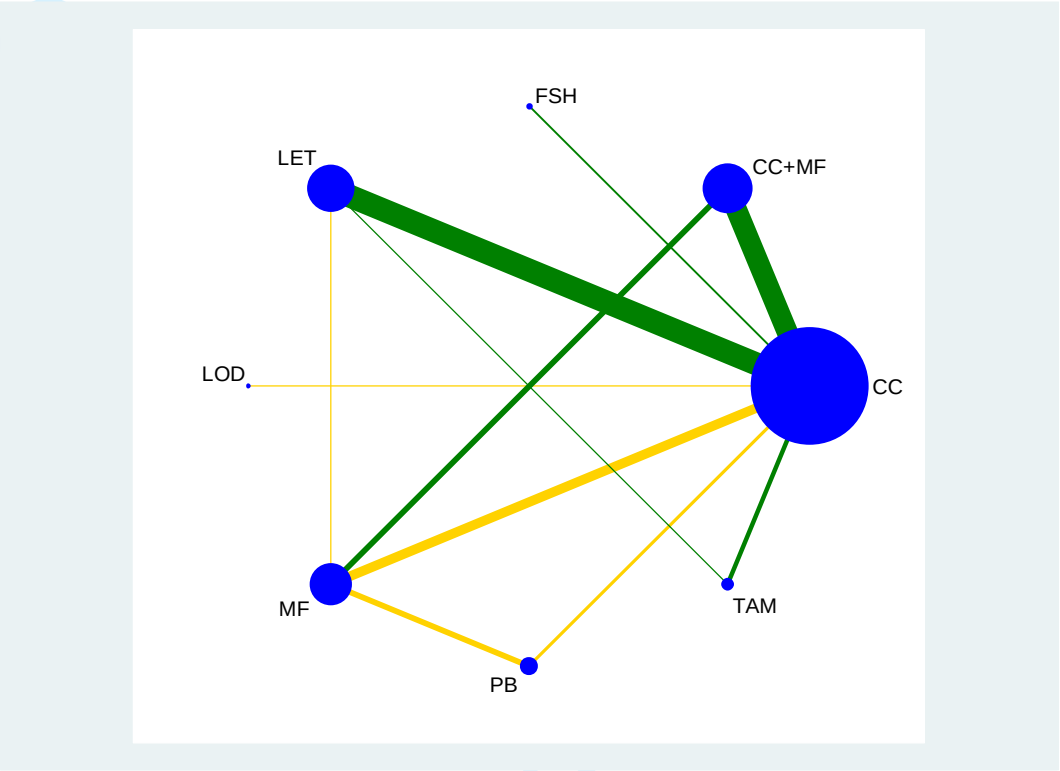
FSH		3.62(0.58-22.80)	2	378	0%
MF	vs PB	0.33(0.01-8,49)	1	65	N/A
MF	vs LET	0.20(0.01-4.15)	1	304	N/A
TAM		3.06(0.12-76.95)	1	100	N/A
CC+MF	vs MF	2.36(0.42-12.39)	4	665	0%
Miscarriage (per woman randomised)					
LET	vs CC	1.00(0.62-162)	10	2302	10.6%
MF		0.76(0.32-1.82)	8	1155	29.1%
CC+MF		1.38(0.85-2.24)	8	991	0%
TAM		0.56(0.19-1.68)	3	566	23.4%
FSH		1.44(0.57-3.63)	2	378	0%
MF	vs PB	1.02(0.28-3.73)	2	265	0%
MF	vs LET	0.33(0.13-8.20)	1	304	N/A
TAM		0.73(0.16-3.46)	1	100	N/A
CC+MF	vs MF	1.37(0.66-2.87)	4	640	10.9%
Miscarriage (per pregnant woman)					
LET	vs CC	0.79(0.52-1.21)	10	718	0%
MF		0.70(0.19-2.63)	8	277	54.9%
CC+MF		1.35(0.74-2.46)	8	384	0%
TAM		0.83(0.31-2.19)	3	123	0%
FSH		0.99(0.37-2.67)	2	164	0%
MF	vs PB	0.28(0.06-1.19)	2	63	0%
MF	vs LET	0.41(0.02-10.64)	1	55	N/A
TAM		0.93(0.18-4.72)	1	45	N/A
CC+MF	vs MF	0.67(0.27-1.66)	4	174	0%

(Abbreviations: CC, clomiphene citrate; PB, placebo or no treatment; LET, letrozole; MF, metformin; TAM, tamoxifen; FSH, follicle stimulating hormone; LOD, laparoscopic ovarian drilling)

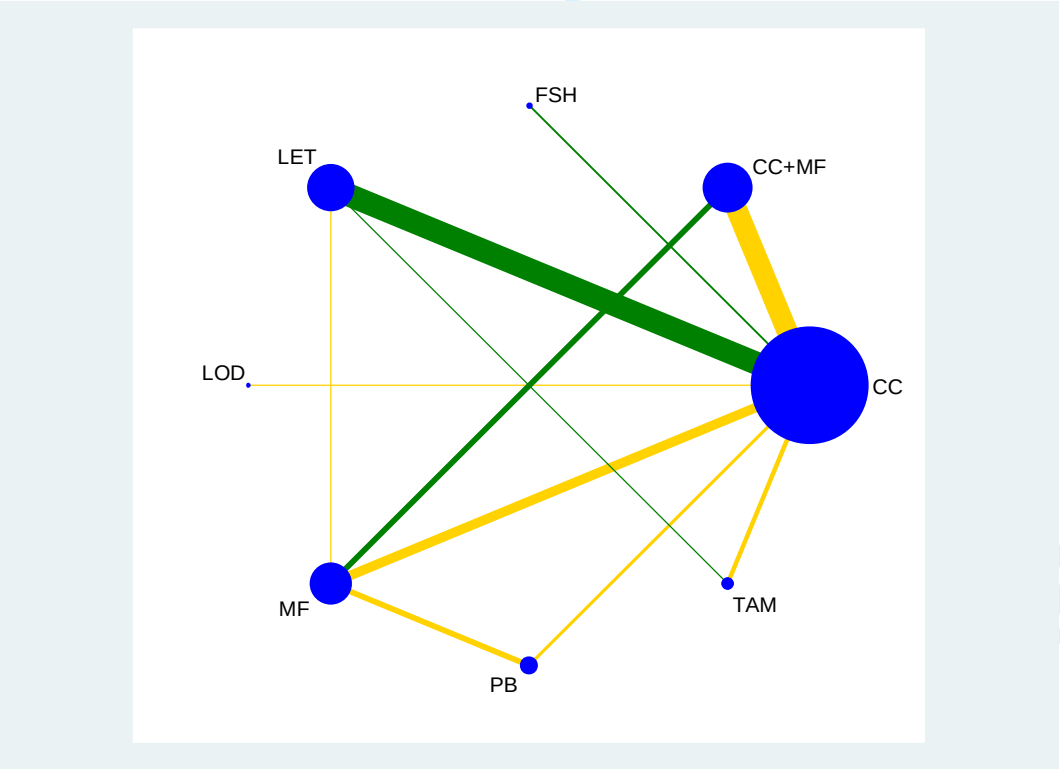
Appendix 5 Network plot for pregnancy incorporating risk of bias assessment

5.1 Risk of bias in randomisation

Colored edges are based on adequacy of randomisation in the majority of the trials in each comparison. Green, yellow and red colors represent low, unclear and high risk, respectively.

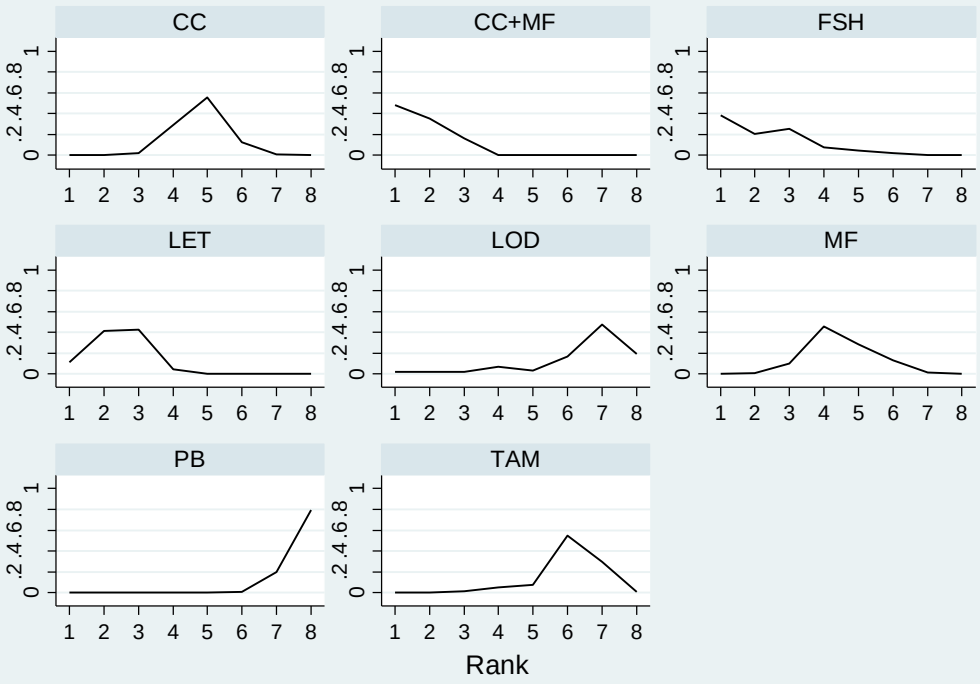


5.2 Risk of randomisation in allocation concealment



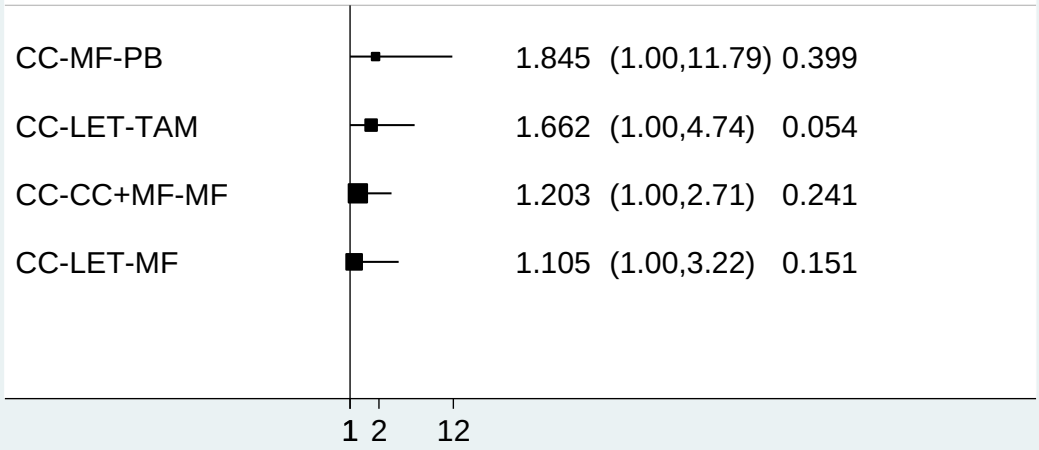
Appendix 6 Ranking of treatments for pregnancy

Rankograms below illustrate the probability per rank for each treatment in terms of pregnancy. E.g. for CC, the probabilities of being the best treatment, the second best, to the worst (eighth) are 0%, 0%, 2.4%, 29.0%, 55.5%, 12.3%, 0.8% and 0%, respectively.



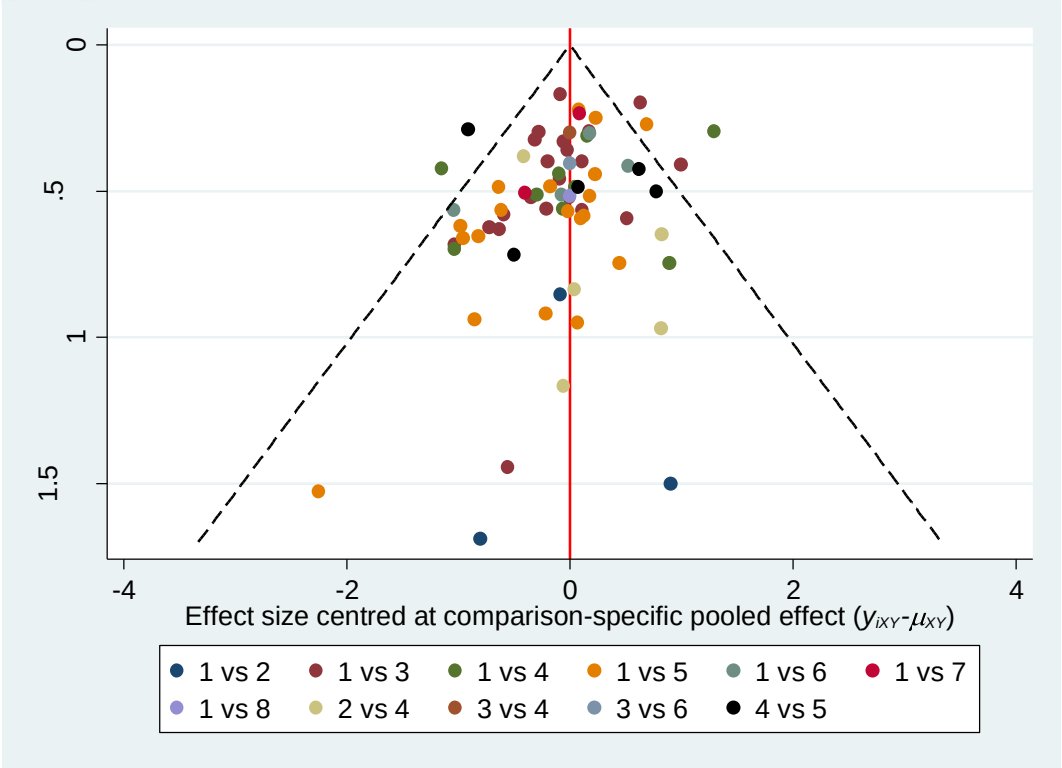
Appendix 7 Inconsistency plot for pregnancy

We estimated inconsistency as the logarithm of the ratio of two odds ratios (RoR) from direct and indirect evidence in the loop (also named inconsistency factor IF) and the corresponding 95% CI for each IF in each closed triangular or quadratic loop. RoR values is close to 1 mean that the two sources are in agreement. The inconsistency plot shows that in a total of 4 loops there is none with statistically significant inconsistency as all confidence intervals for RORs are compatible with zero inconsistency (RoR= 1).



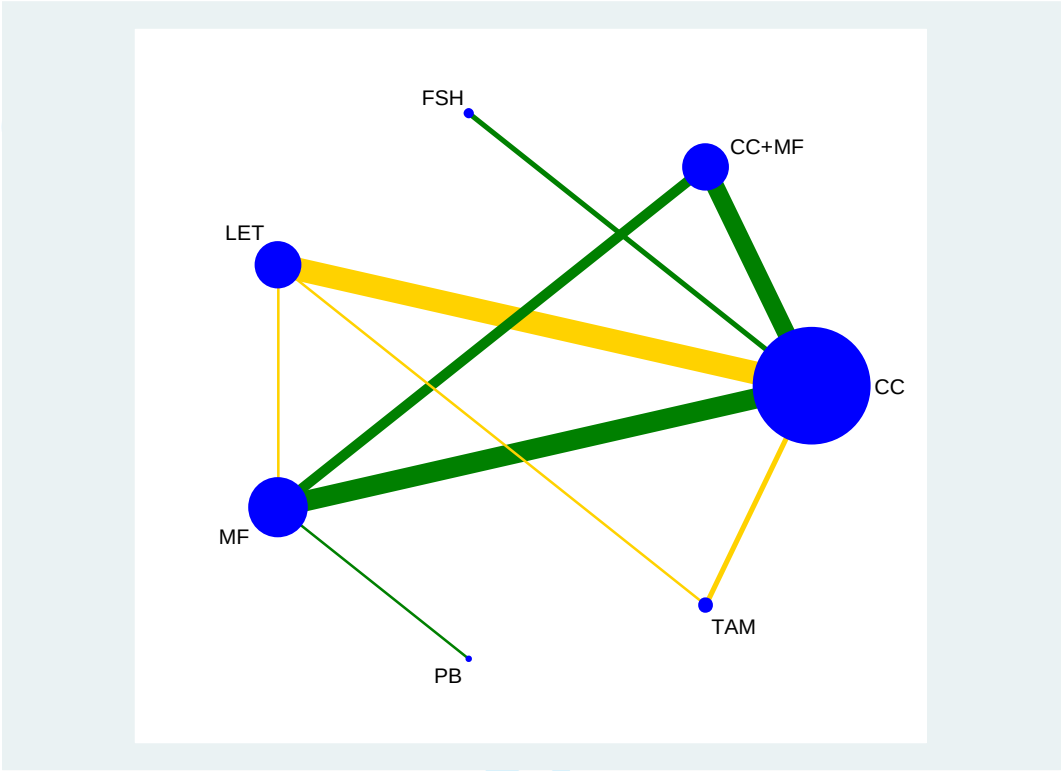
Appendix 8 Comparison-adjusted funnel plot for pregnancy

The red line represents the null hypothesis that the study-specific effect sizes do not differ from the respective comparison-specific pooled effect estimates. Different colors correspond to different comparisons. (1-clomiphene; 2-placebo/no treatment; 3-letrozole; 4-metformin; 5-clomiphene plus metformin; 6-tamoxifen; 7-FSH; 8-LOD)

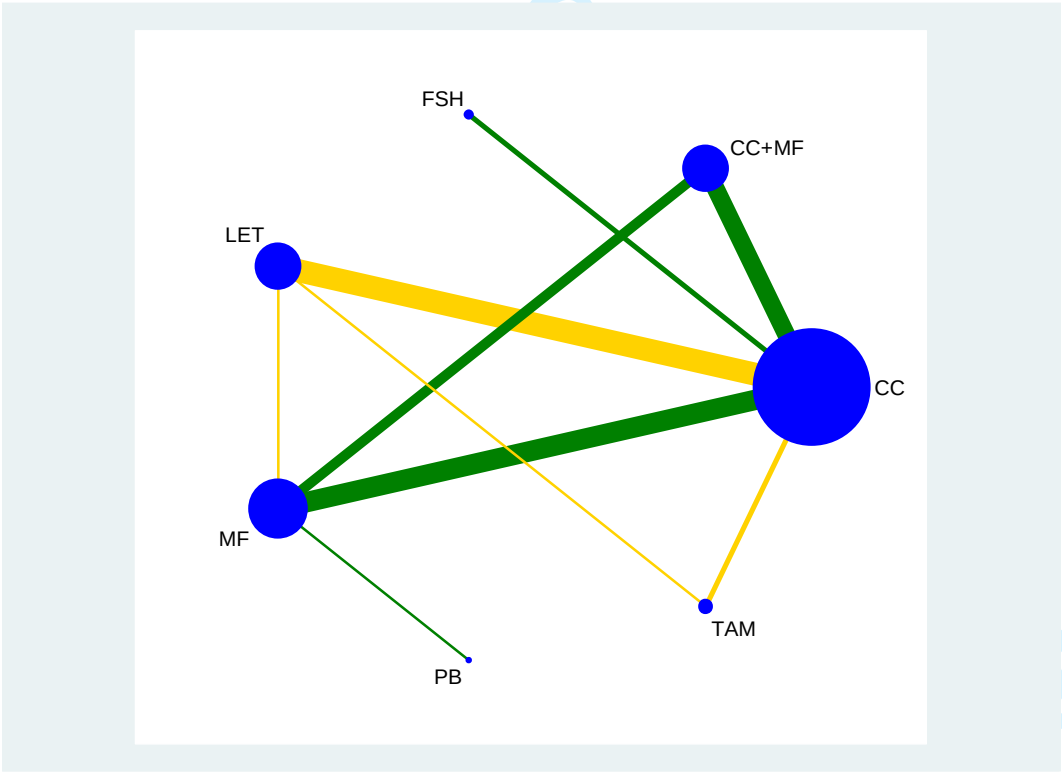


Appendix 9 Network plot for live birth incorporating risk of bias assessment

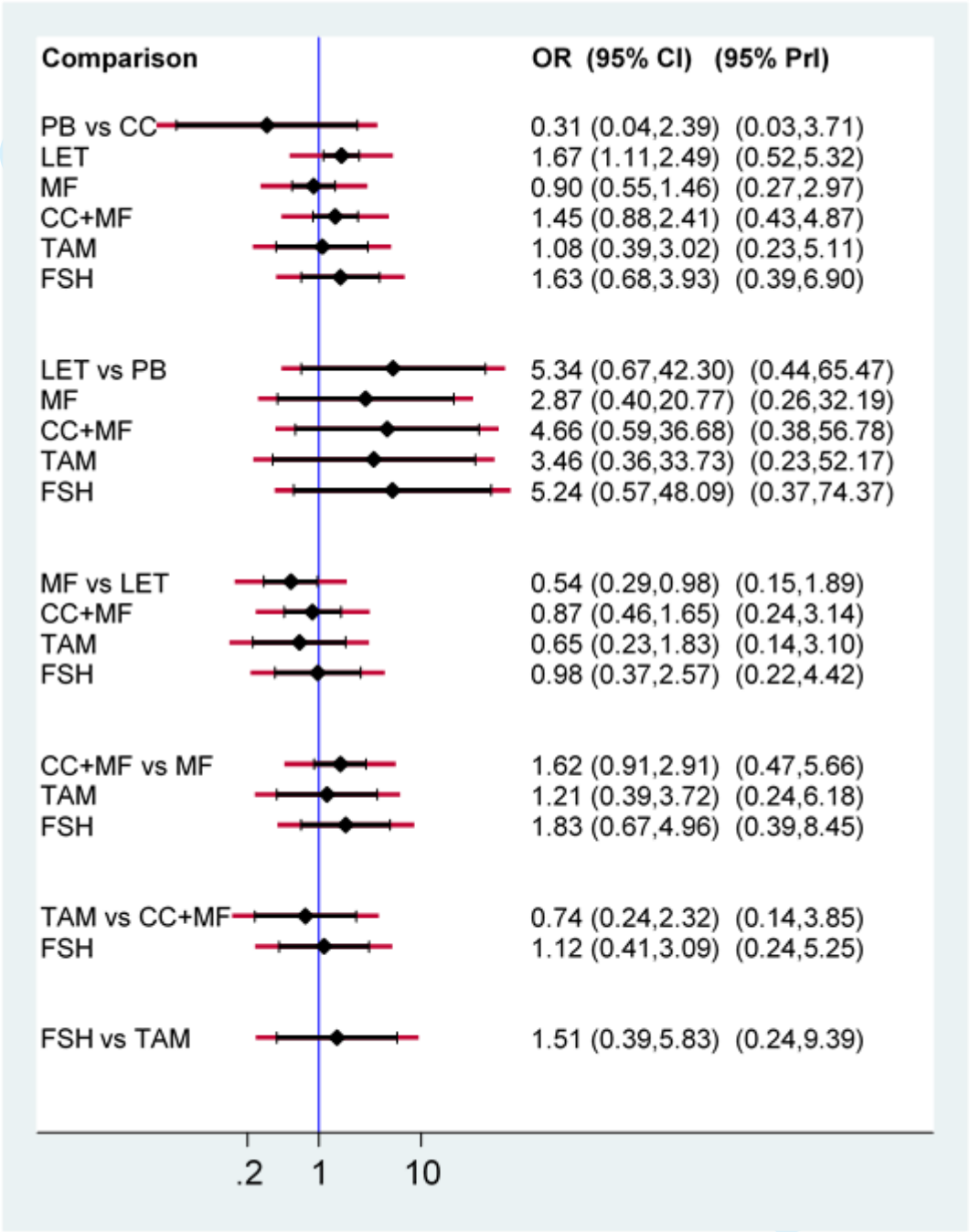
9.1 Risk of bias in randomisation



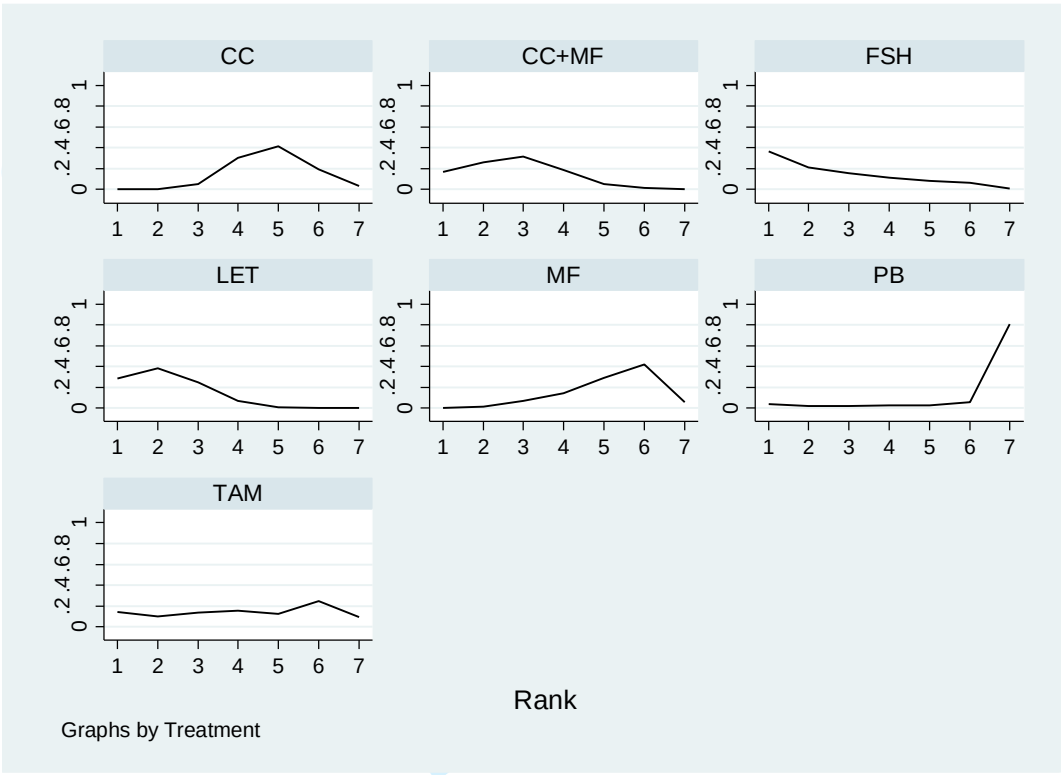
9.2 Risk of bias in allocation concealment



Appendix 10 Network meta-analysis results for live birth

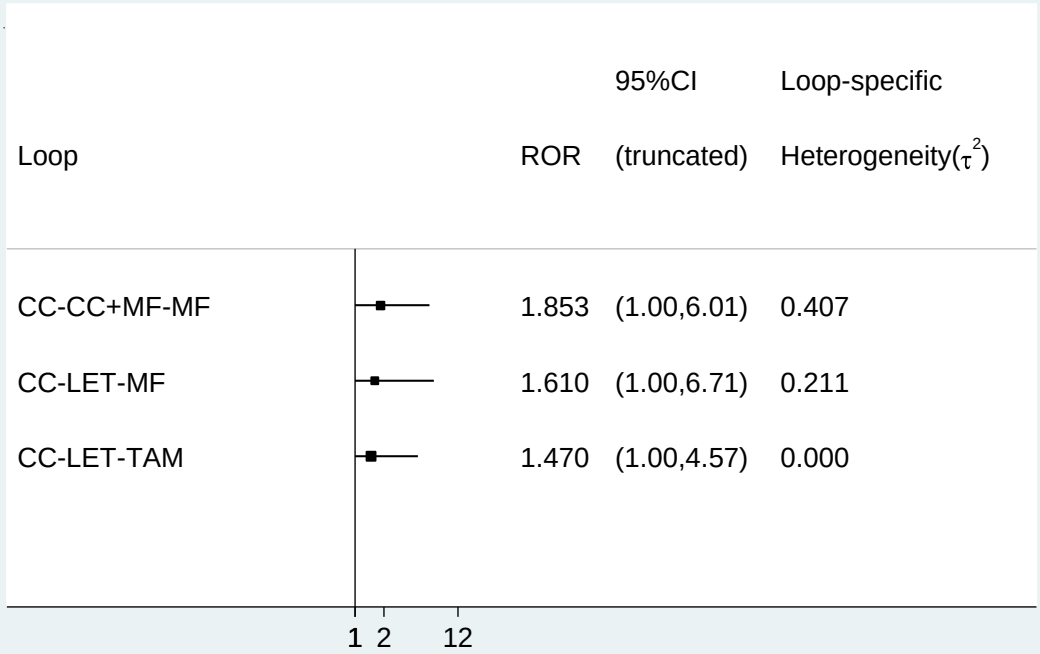


Appendix 11 Ranking of treatments for live birth

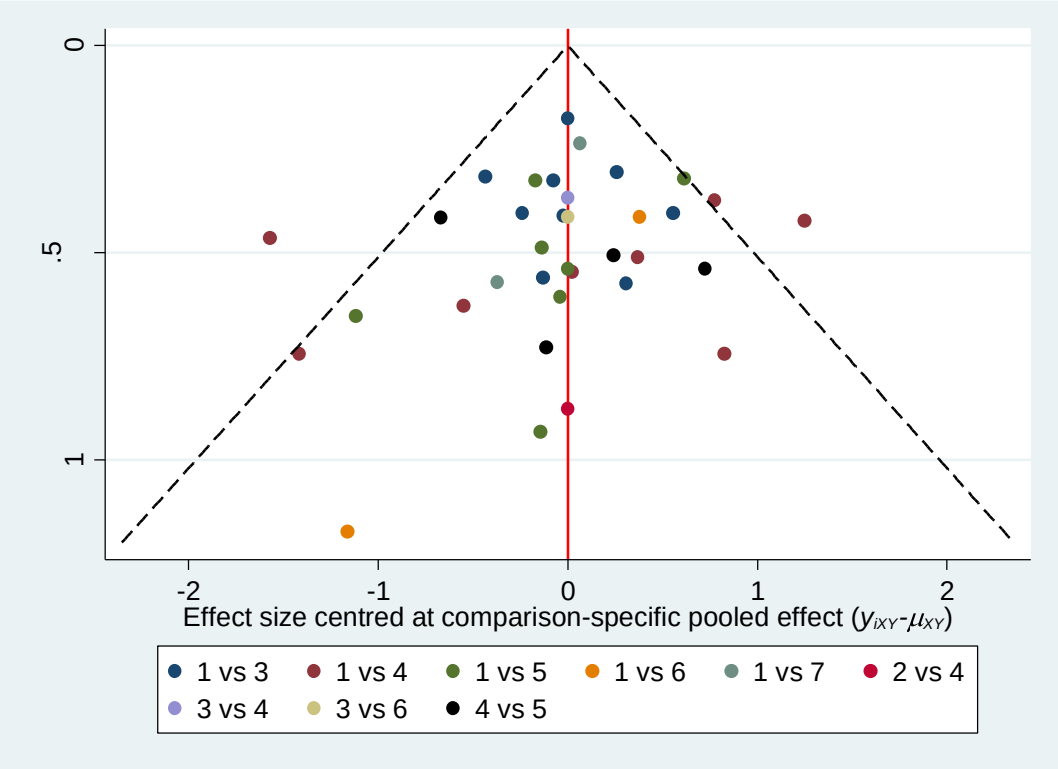


Appendix 12 Inconsistency plot for live birth.

The inconsistency plot shows that in a total of 3 loops there is none with statistically significant inconsistency as all confidence intervals for RORs are compatible with zero inconsistency (RoR= 1).



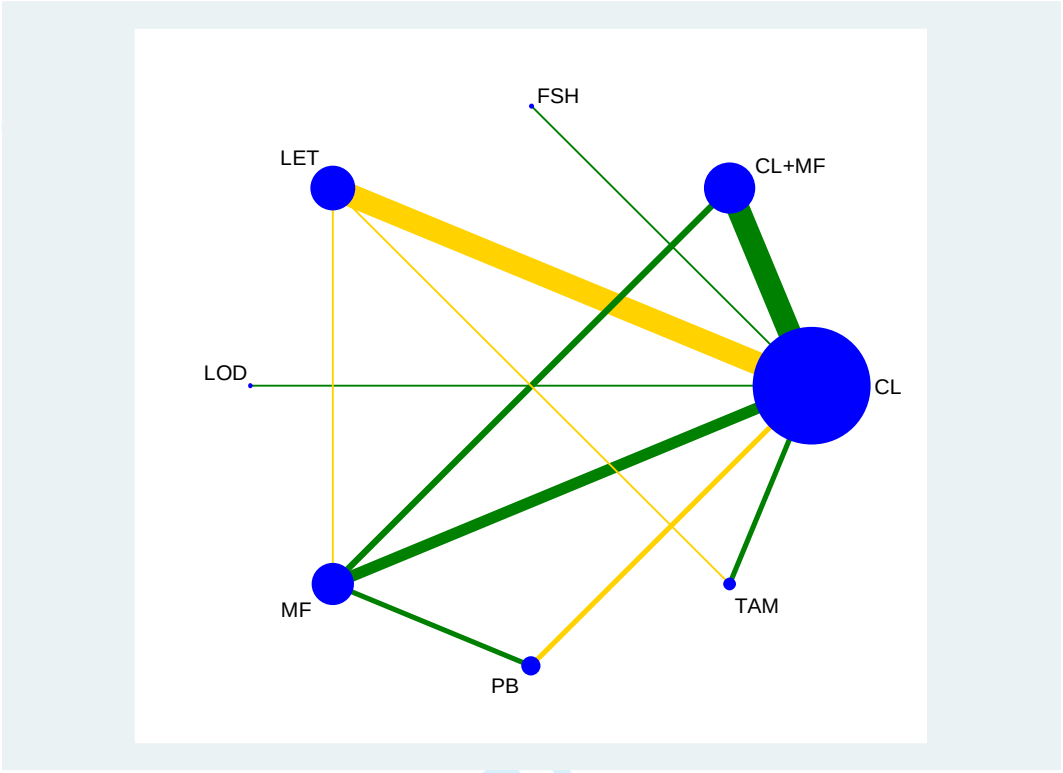
Appendix 13 Comparison-adjusted funnel plot for live birth



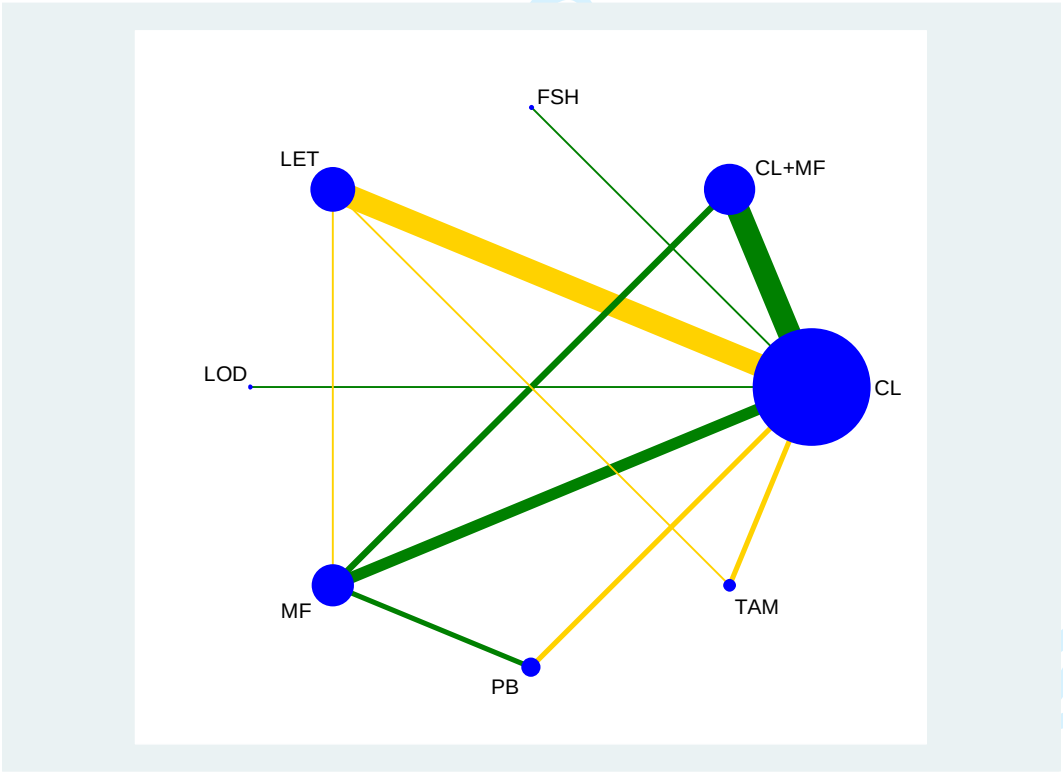
(1-clomiphene; 2-placebo/no treatment; 3-letrozole; 4-metformin; 5-clomiphene plus metformin; 6-tamoxifen; 7-FSH)

Appendix 14 Network plot for ovulation incorporating risk of bias assessment

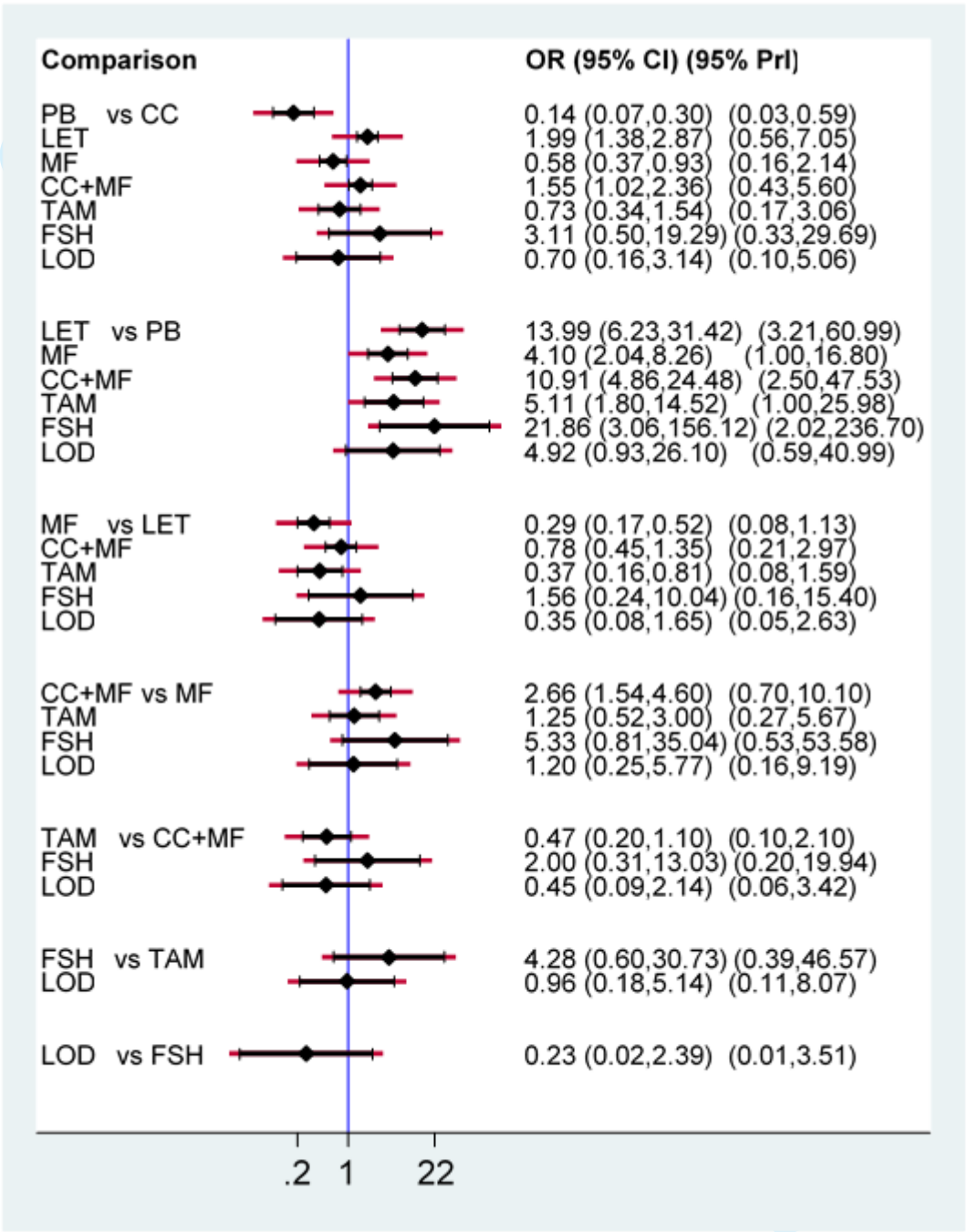
14.1 Risk of bias in randomisation



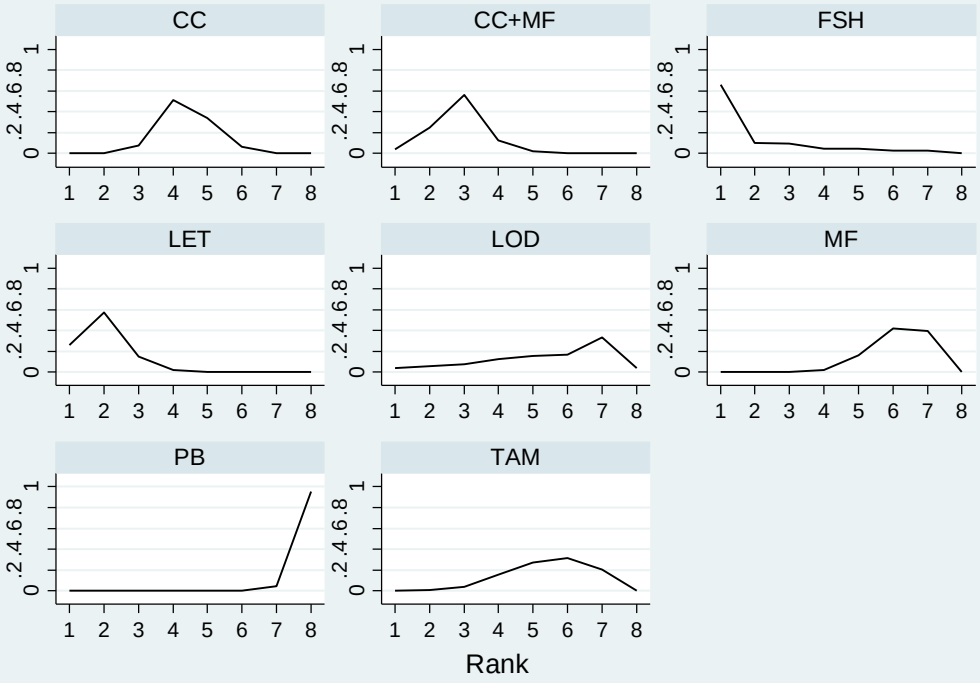
14.2 Risk of bias in allocation concealment



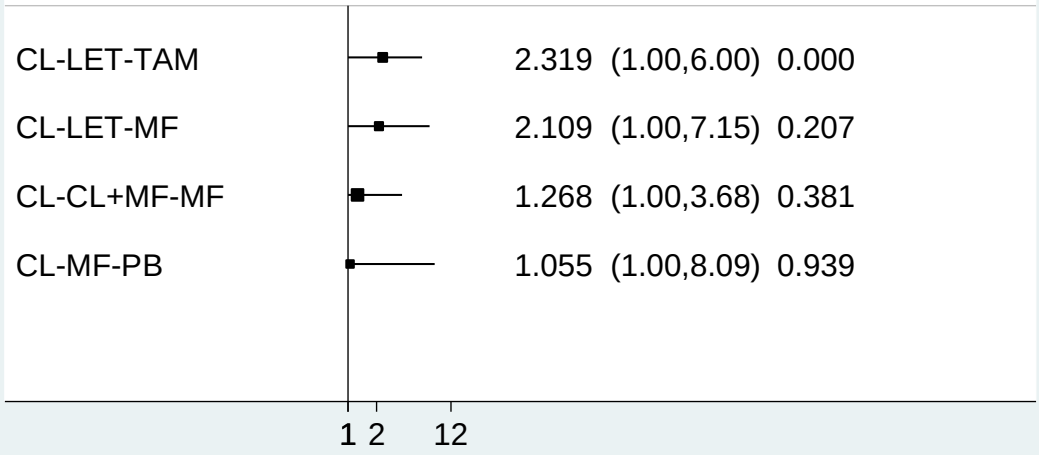
Appendix 15 Network meta-analysis results for ovulation



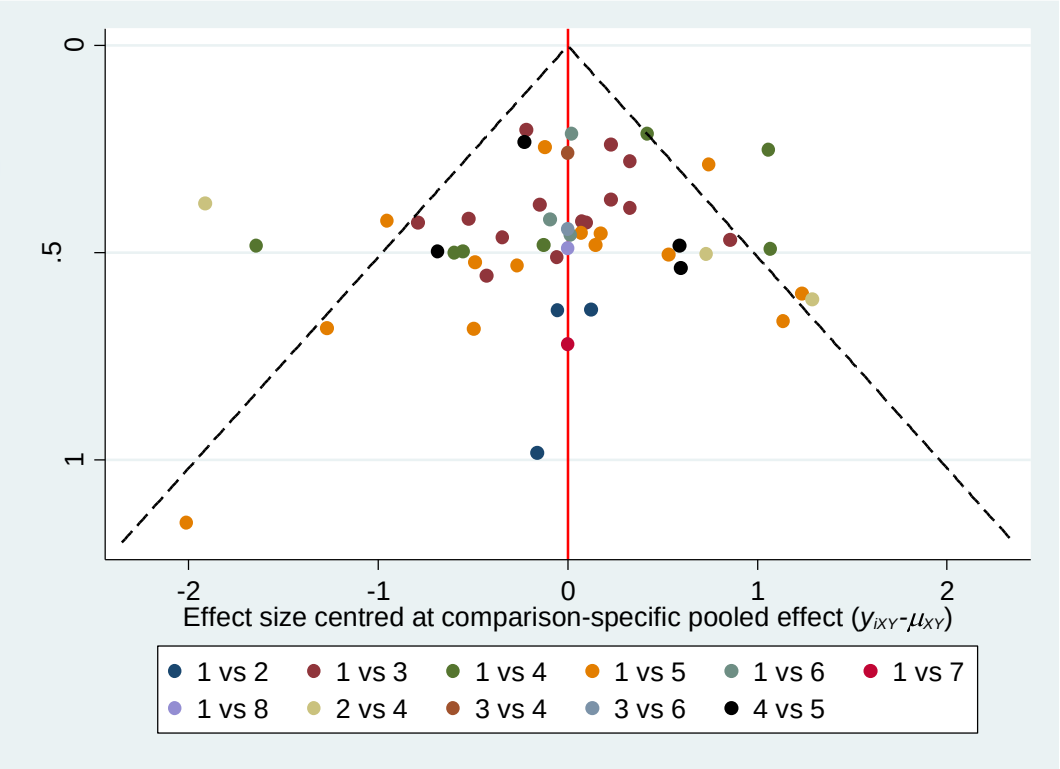
Appendix 16 Ranking of treatments for ovulation



Appendix 17 Inconsistency plot for ovulation



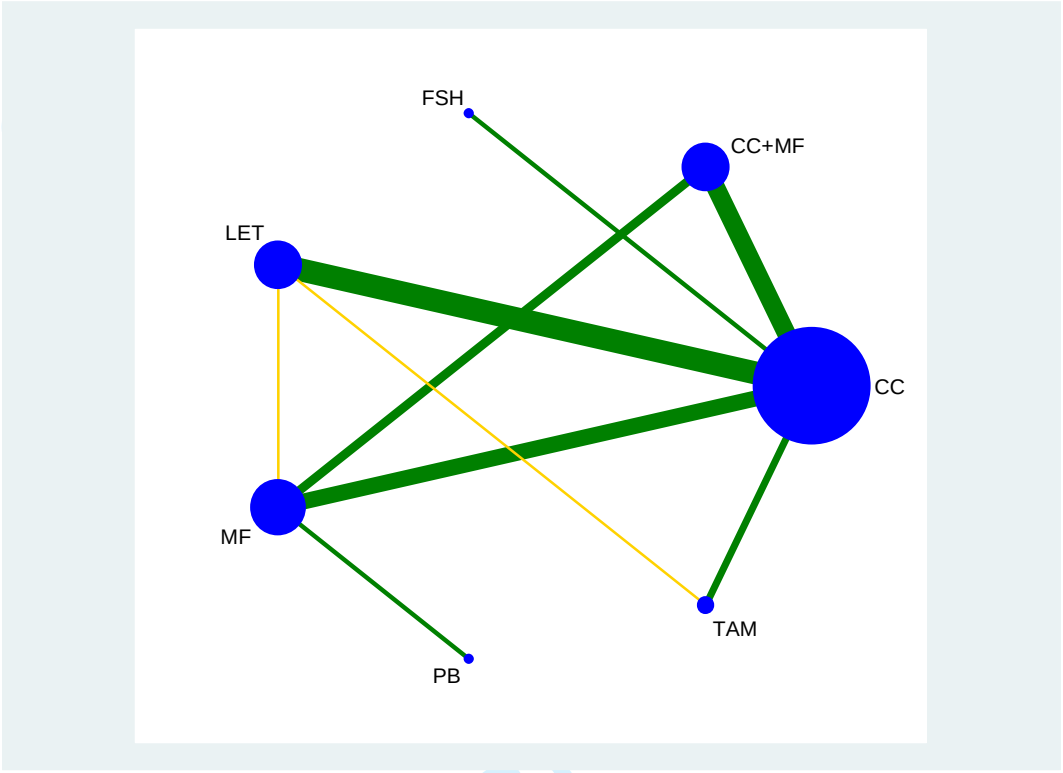
Appendix 18 Comparison-adjusted funnel plot for ovulation



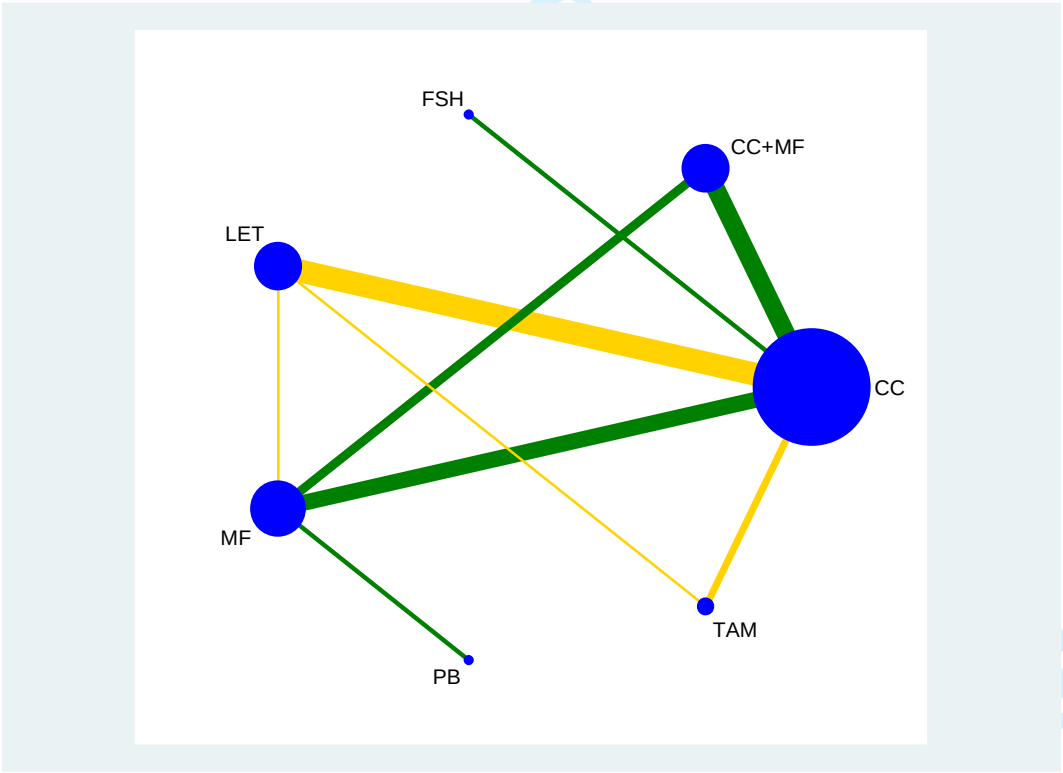
(1-clomiphene; 2-placebo/no treatment; 3-letrozole; 4-metformin; 5-clomiphene plus metformin; 6-tamoxifen; 7-FSH; 8-LOD)

Appendix 19 Network plot for miscarriage incorporating risk of bias assessment

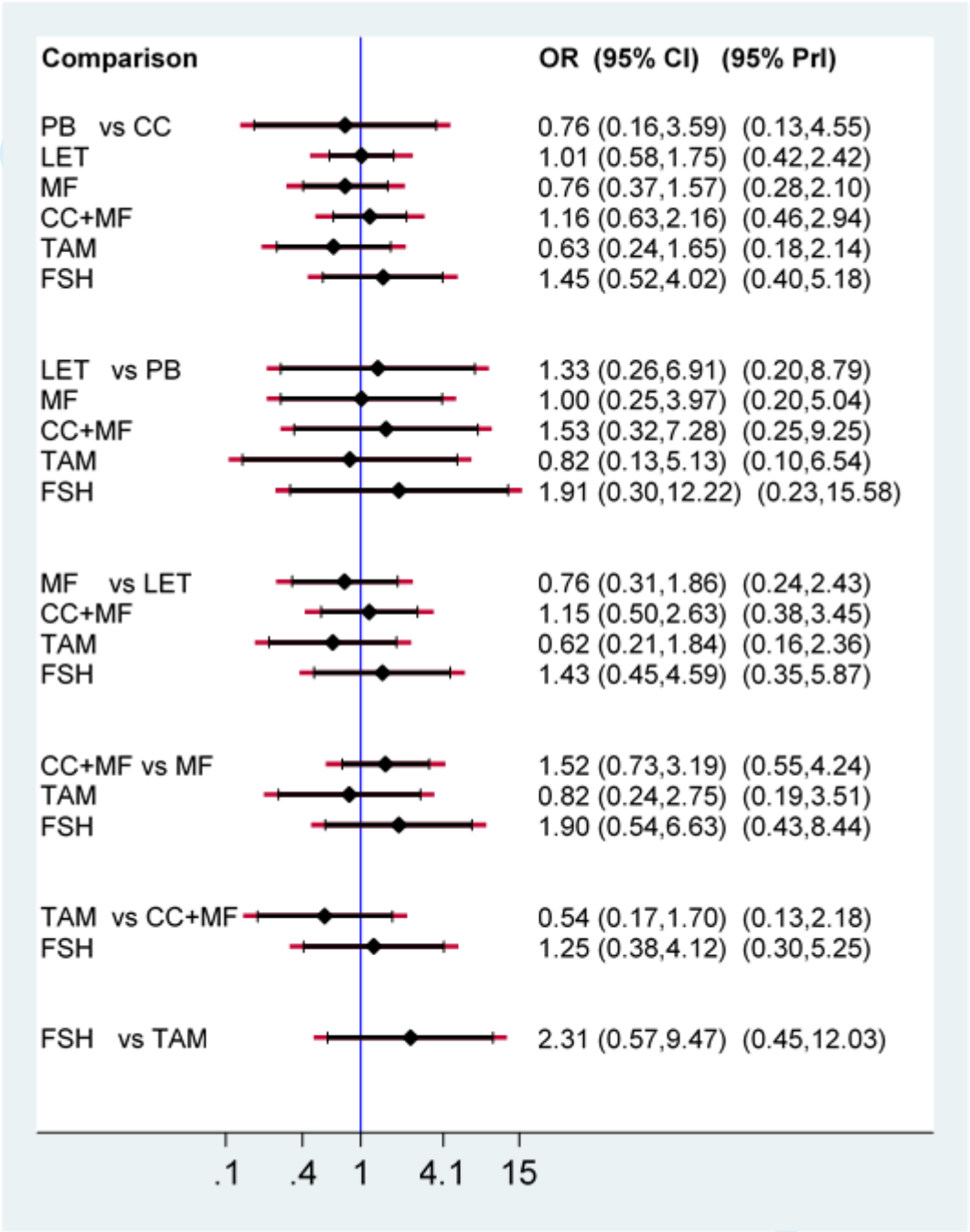
19.1 Risk of bias in randomisation



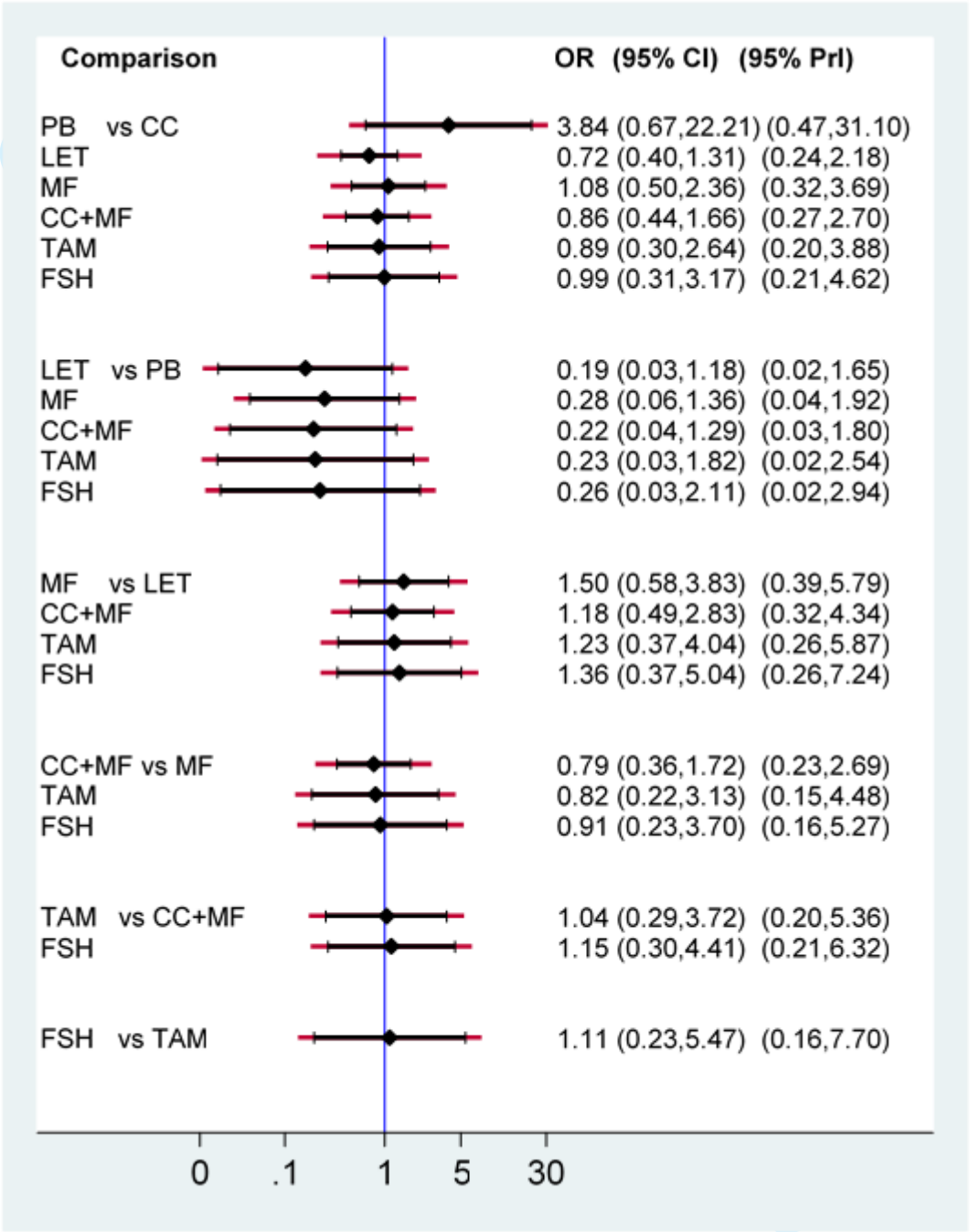
19.2 Risk of bias in allocation concealment



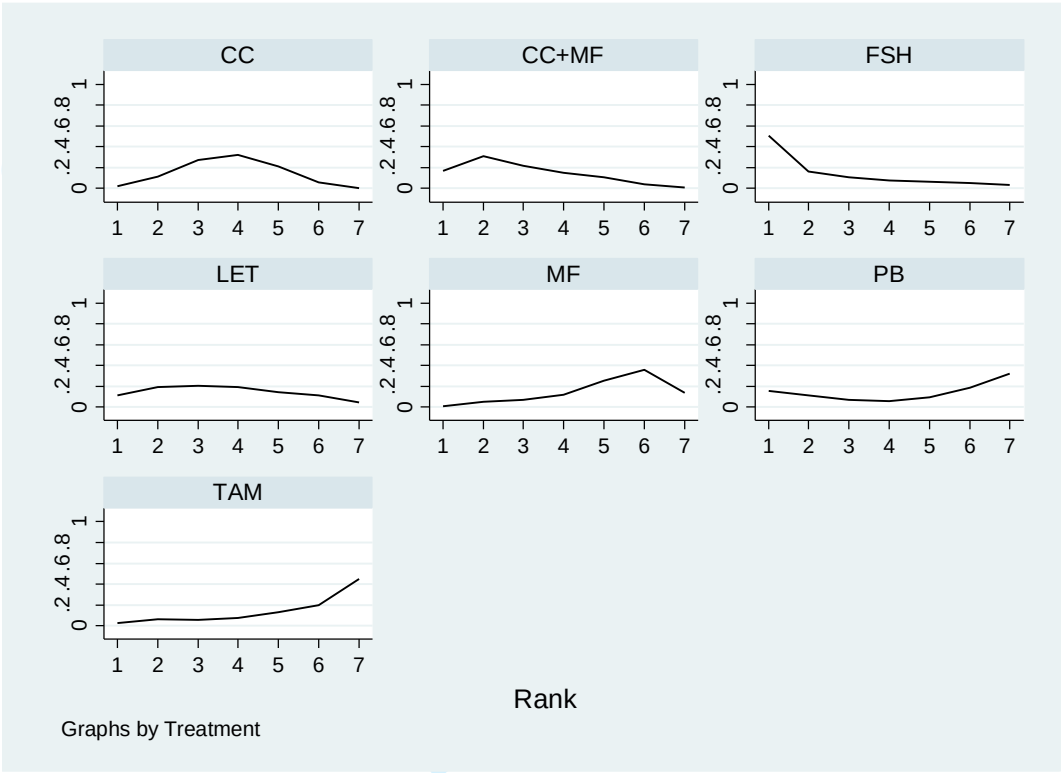
Appendix 20 Network meta-analysis results for miscarriage per woman randomised



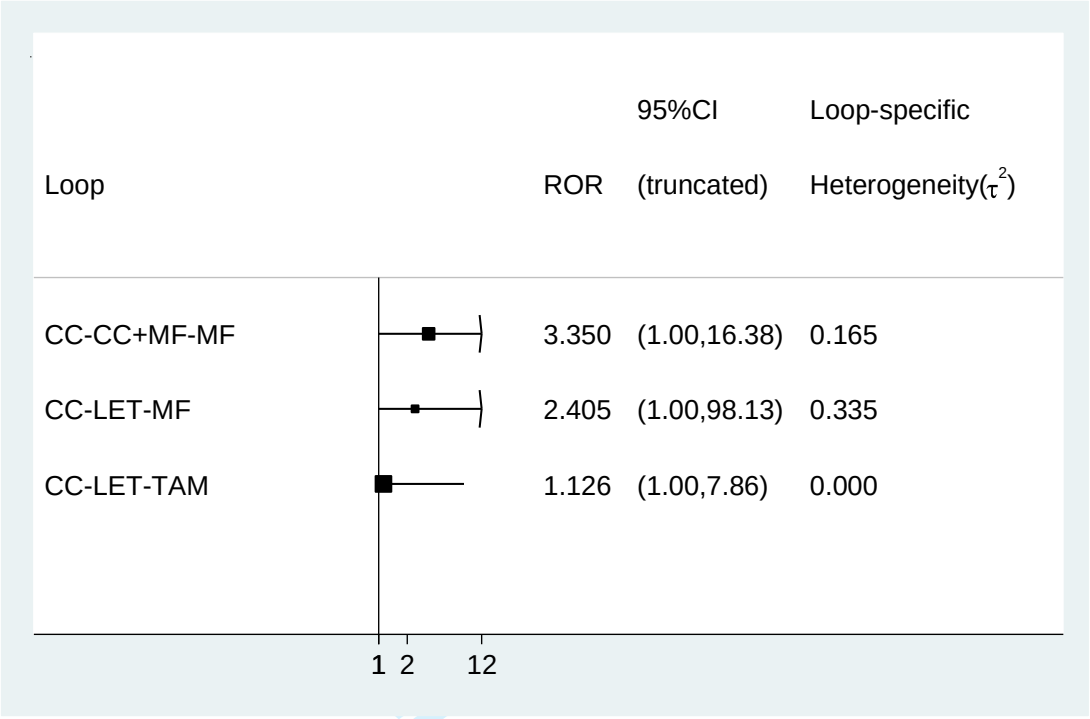
Appendix 21 Network meta-analysis results for miscarriage per pregnancy



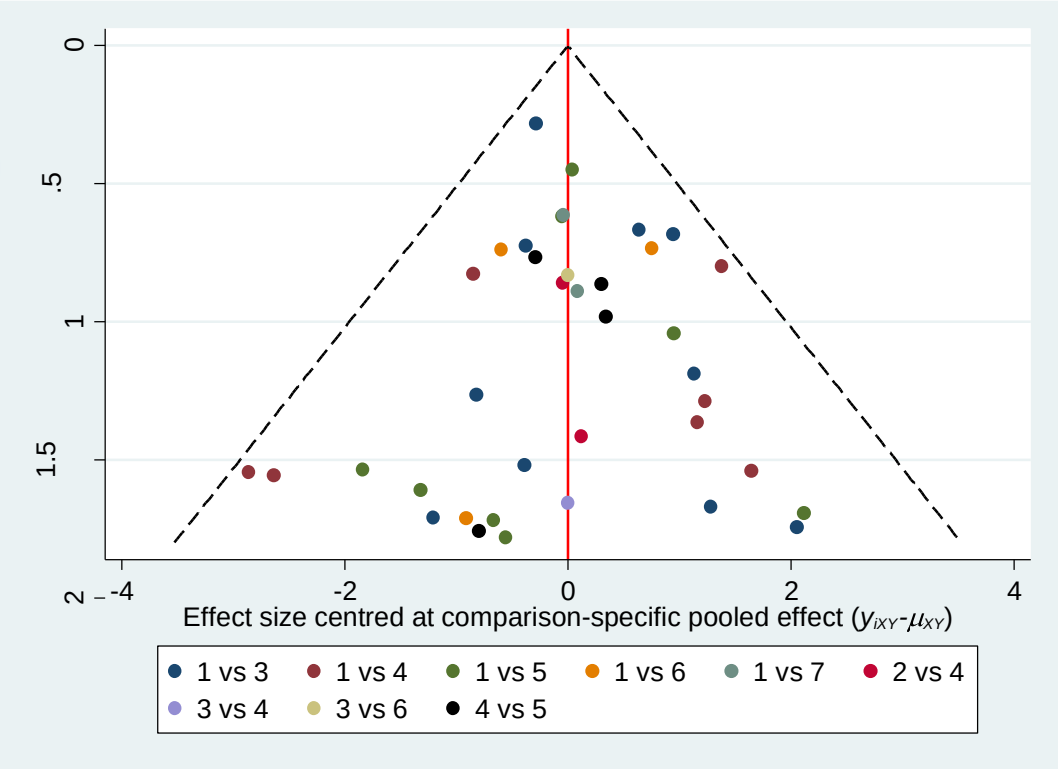
Appendix 22 Ranking of treatments for miscarriage per pregnancy



Appendix 23 Inconsistency plot for miscarriage per pregnancy



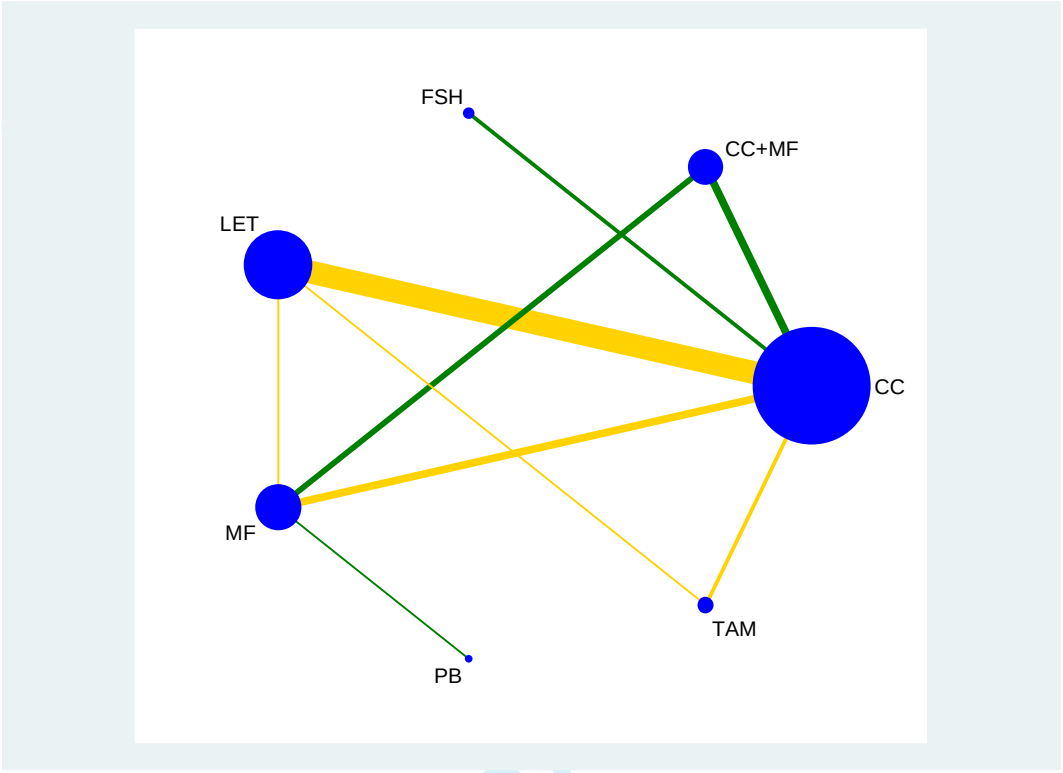
Appendix 24 Comparison-adjusted funnel plot for miscarriage per pregnancy



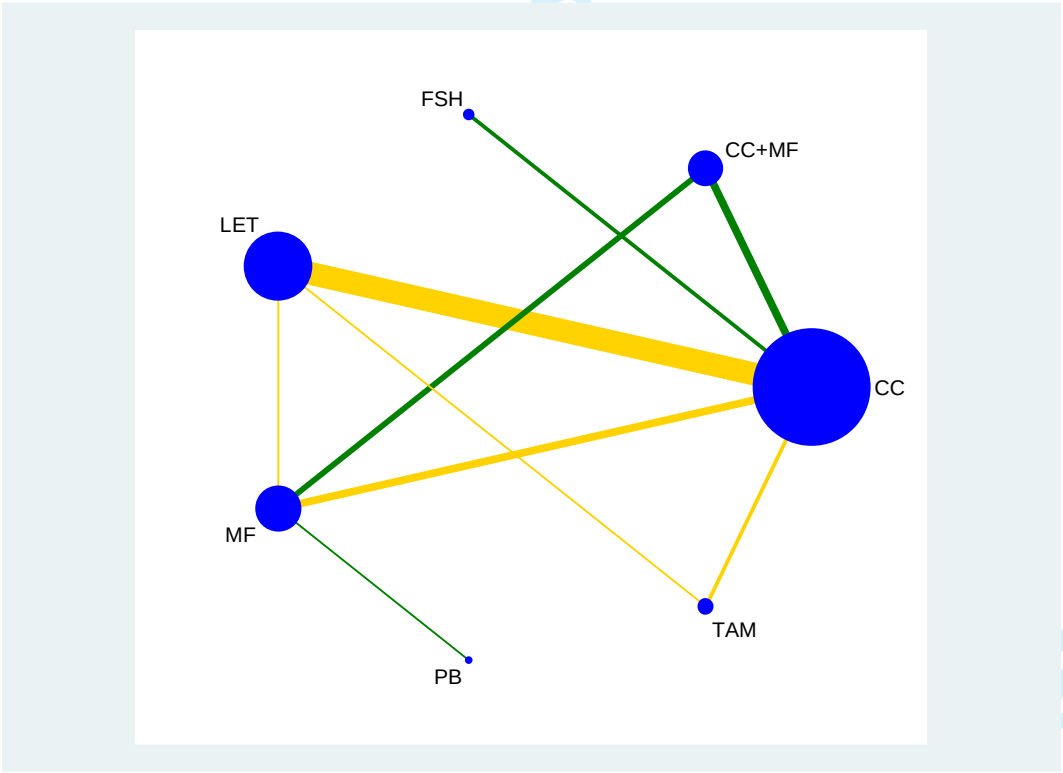
(1-clomiphene; 2-placebo/no treatment; 3-letrozole; 4-metformin; 5-clomiphene plus metformin; 6-tamoxifen; 7-FSH)

Appendix 25 Network plot for multiple pregnancy incorporating risk of bias assessment

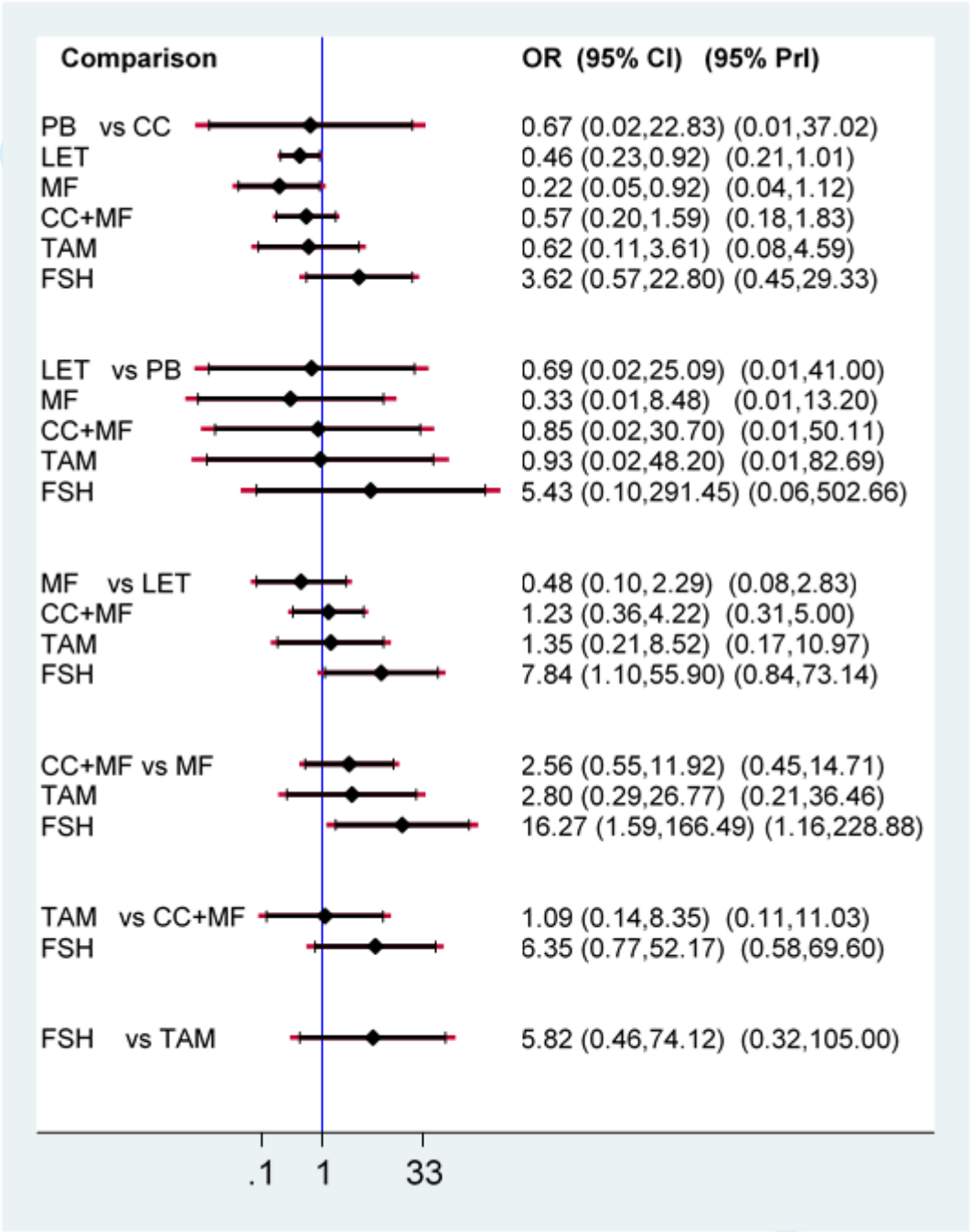
25.1 Risk of bias in randomisation



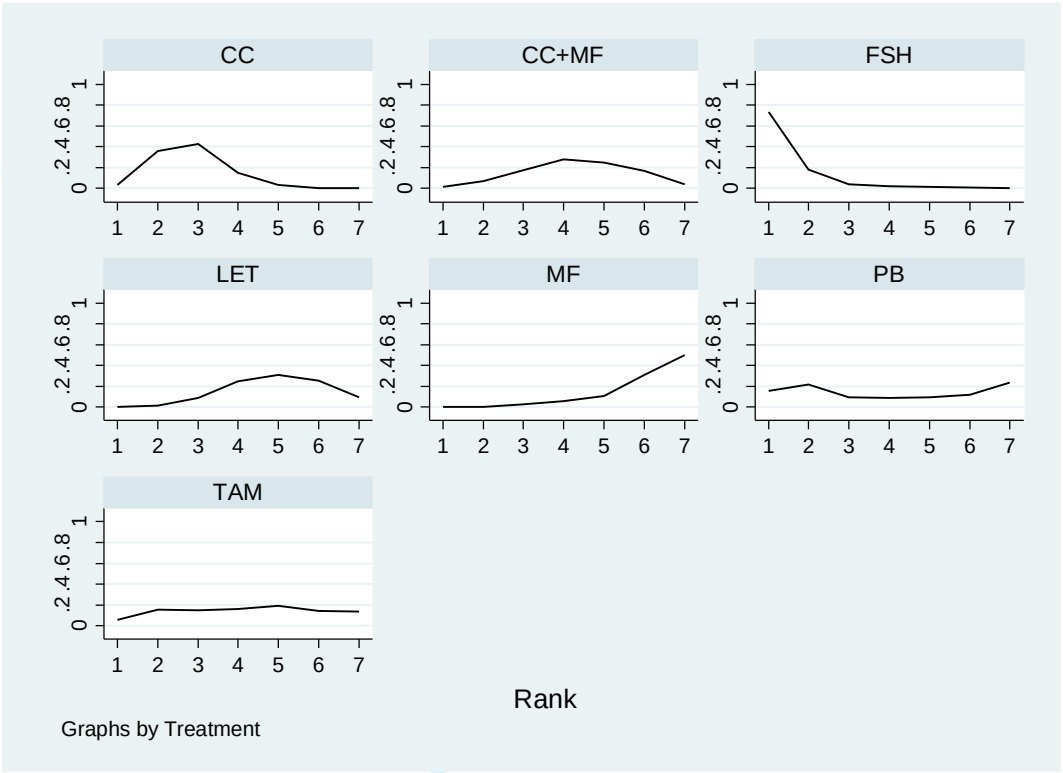
25.2 Risk of bias in allocation concealment



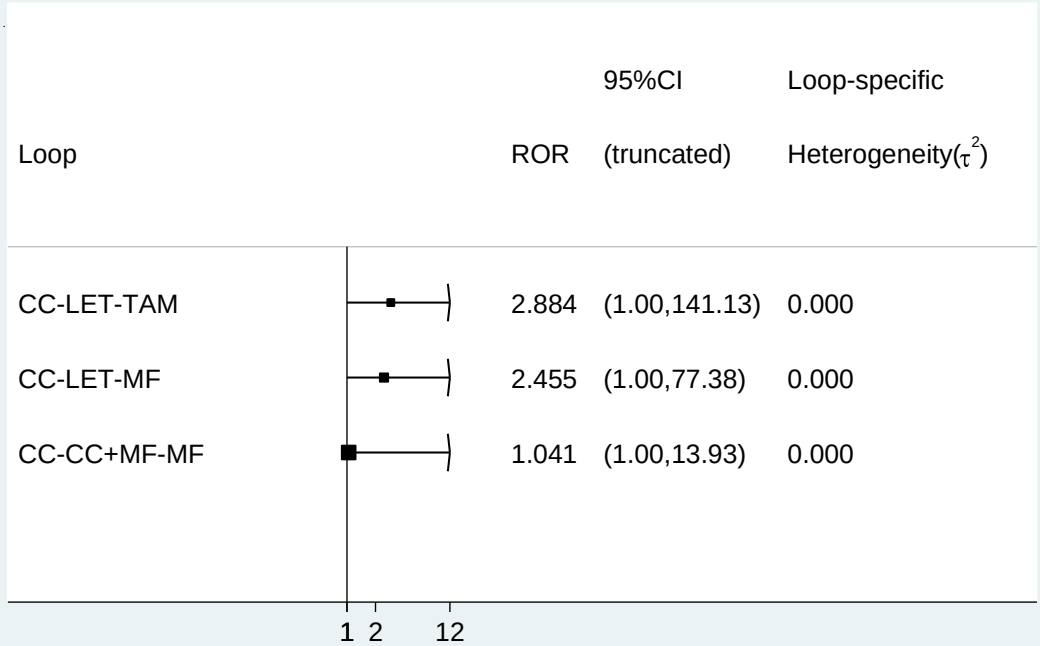
Appendix 26 Network meta-analysis results for multiple pregnancy



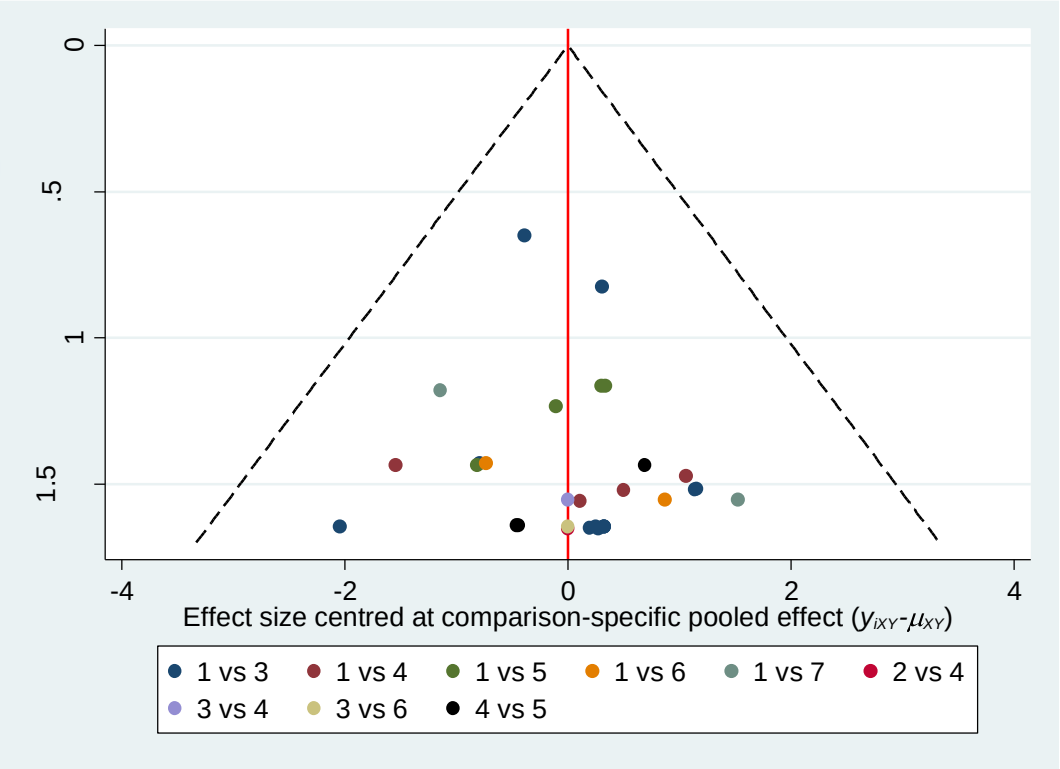
Appendix 27 Ranking of treatments for multiple pregnancy



Appendix 28 Inconsistency plot for multiple pregnancy

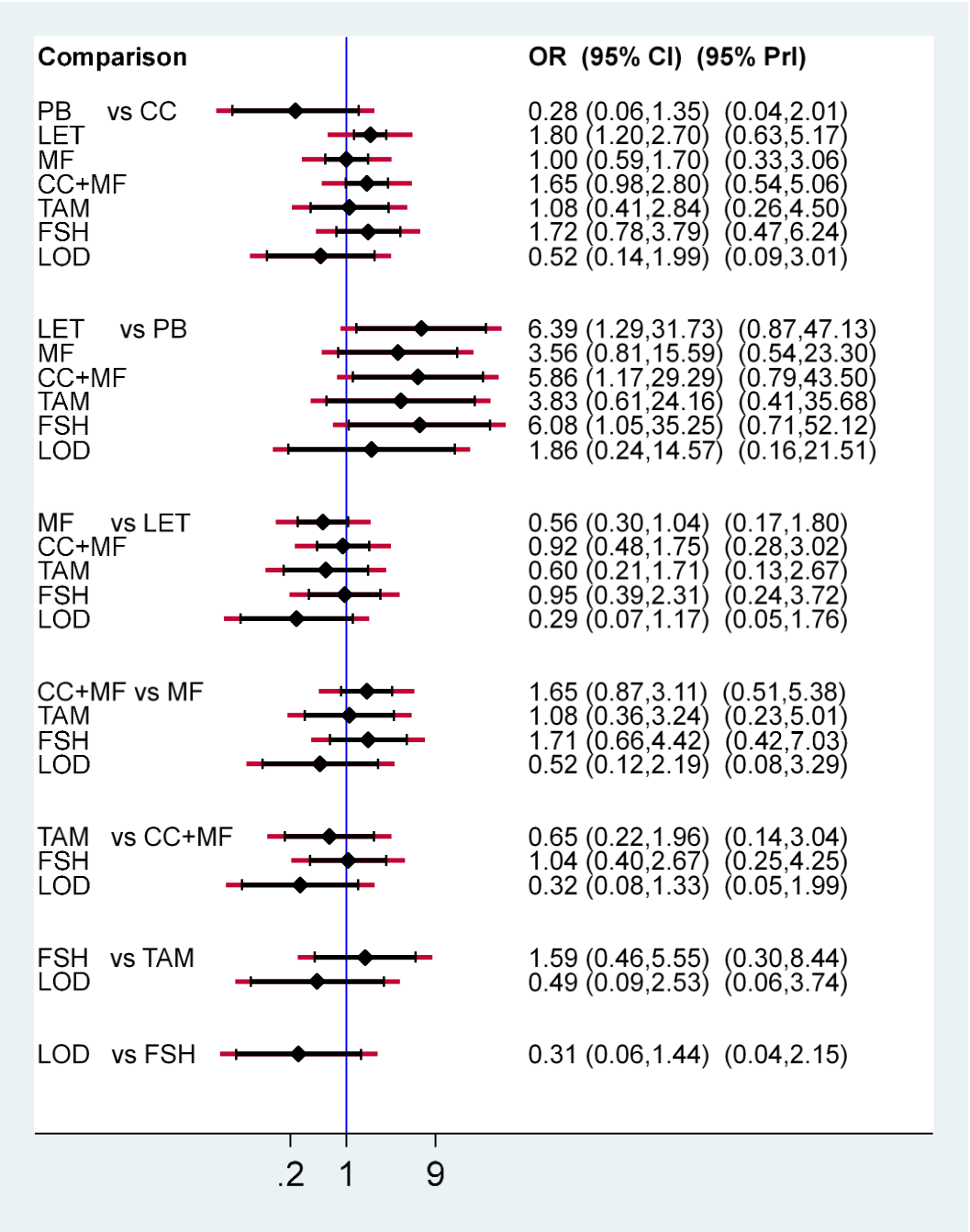


Appendix 29 Comparison-adjusted funnel plot for multiple pregnancy

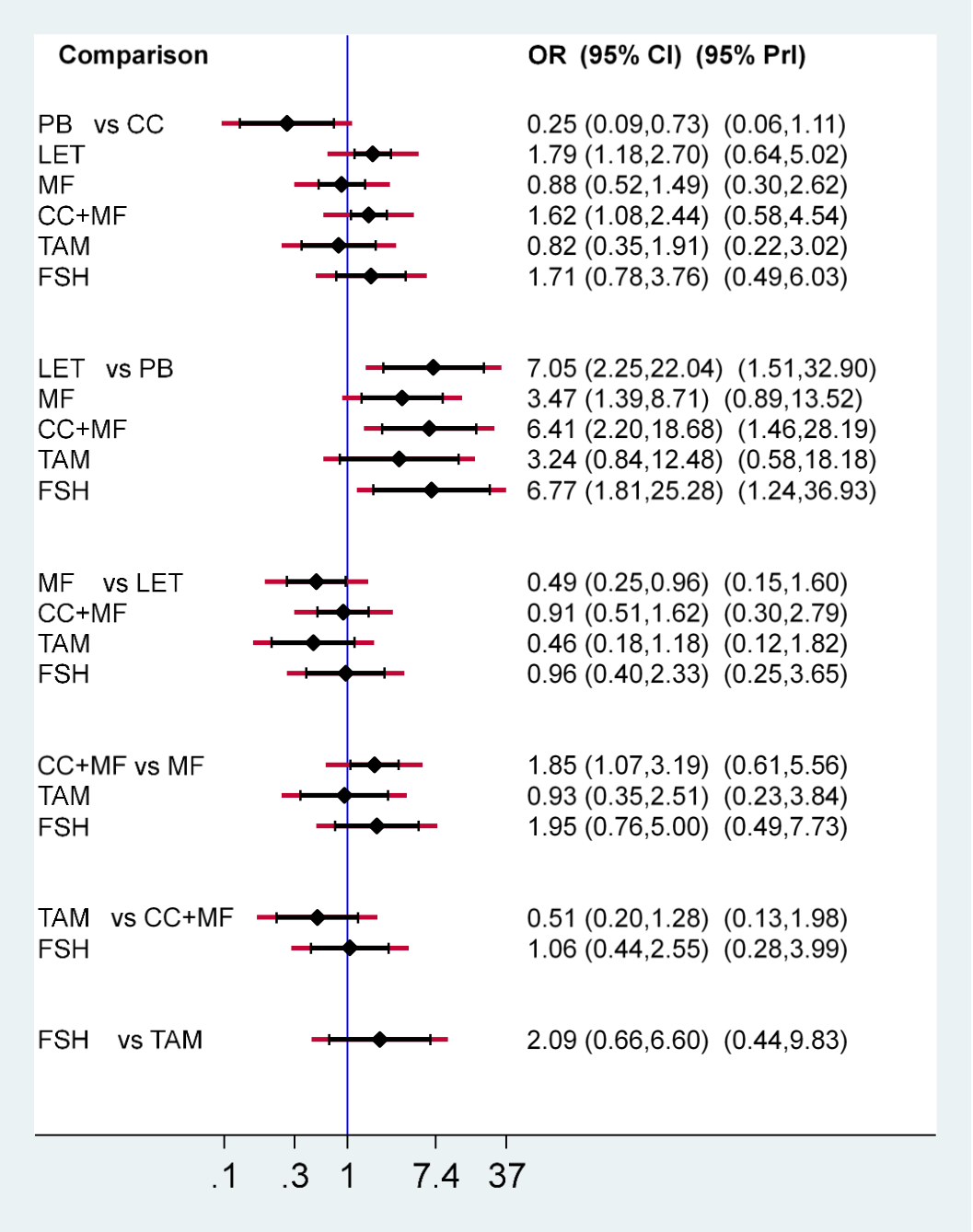


(1-clomiphene; 2-placebo/no treatment; 3-letrozole; 4-metformin; 5-clomiphene plus metformin; 6-tamoxifen; 7-FSH)

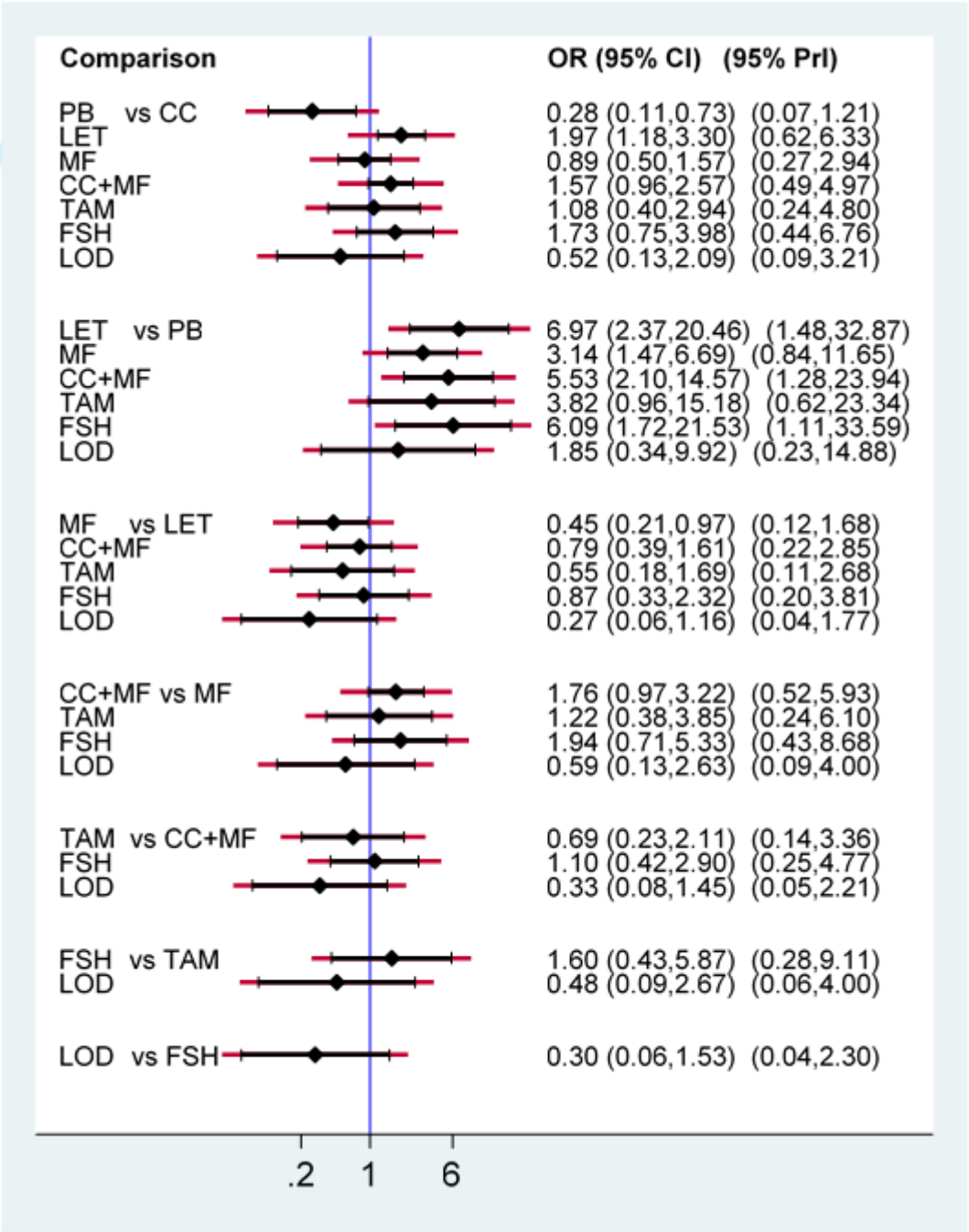
Appendix 30 Sensitivity analysis - RCTs with treatment naïve women



Appendix 31 Sensitivity analysis - RCTs reporting clinical pregnancy



Appendix 32 Sensitivity analysis - RCTs with low risk of randomisation & allocation bias



Appendix 33 List of excluded studies

1. Aboul Enien WM, Barghash NA, Mohamed Ali FS. Clinical, ultrasonographic and endocrine predictors of ovarian response to clomiphene citrate in normogonadotropic anovulatory infertility. Middle East Fertility Society Journal 2004;**9**(3):242-50
2. Alamolhoda S, Mirabi P. Metformin and/or Clomiphene do not adversely affect liver or renal function in women with polycystic ovary syndrome. Iranian Journal of Reproductive Medicine 2013;**11**:38
3. Al-Dahhan F. The role of Metformin in induction of ovulation in obese infertile patients with polycystic ovary syndrome. International Journal of Gynecology and Obstetrics 2009;**107**(Journal Article):S636
4. Amer SAK, Gopalan V, Li TC, et al. Long term follow-up of patients with polycystic ovarian syndrome after laparoscopic ovarian drilling: Clinical outcome. Human Reproduction 2002;**17**(8):2035-42
5. Ayaz A, Alwan Y, Farooq MU. Efficacy of combined metformin-clomiphene citrate in comparison with clomiphene citrate alone in infertile women with polycystic ovarian syndrome (PCOS). Journal of Medicine & Life 2013;**6**(2):199-201
6. Baillargeon JP, Jakubowicz DJ, Iuorno MJ, et al. Effects of metformin and rosiglitazone, alone and in combination, in nonobese women with polycystic ovary syndrome and normal indices of insulin sensitivity. Fertil Steril 2004;**82**(4):893-902 doi: 10.1016/j.fertnstert.2004.02.127[published Online First: Epub Date]|.
7. Baruah J, Roy KK, Rahman SM, et al. Endometrial effects of letrozole and clomiphene citrate in women with polycystic ovary syndrome using spiral artery Doppler. Archives of gynecology and obstetrics 2009;**279**(3):311-4 doi: 10.1007/s00404-008-0714-4[published Online First: Epub Date]|.
8. Basirat Z, Golsourkhtabar M, Kashifard M. Does metformin affect on pregnancy outcome in PCOs infertile women with different BMI? Iranian Journal of Reproductive Medicine 2012;**10**:76
9. Begum MR, Ferdous J, Begum A, et al. Comparison of efficacy of aromatase inhibitor and clomiphene citrate in induction of ovulation in polycystic ovarian syndrome. Fertility and sterility 2009;**92**(3):853-57 doi: 10.1016/j.fertnstert.2007.08.044 [doi][published Online First: Epub Date]|.
10. Beigi A, Zarrinkoub F. Randomized controlled trial comparing clomiphene citrate and metformin as the first-line treatment for ovulation induction in women with polycystic ovary syndrome. XVIII FIGO World Congress of Gynecology and Obstetrics 2006;**3**:177
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Appendix 34 Outcome data of included studies

34-1 Pregnancy

Study ID	n1	n2	n3	n4	n5	n6	n7	n8	r1	r2	r3	r4	r5	r6	r7	r8
Abuelghar 2013	32				34				2				3			
Amer 2009	36							36	14							9
Amer2015	79		80						34		49					
Atay 2006	55		51						5		11					
Ayaz 2013	21				21				6				13			
Aygen 2007	5		5						1		2					
Badawy 2009	220		218						94		82					
Badawy 2011	187					184			35					20		
Basirat 2012	167				167				41				48			
Bayar 2006	40		40						7		9					
Beigi 2006	35			35					8			9				
Boonstanfar 2001	47					48			6					10		
Boudhraa 2010	31				32				4				11			
Cudmore 1966	13	9							1	0						
Dasari 2009	24				16				2				4			
Dehbashi 2009	50		50						7		13					
El-Biely 2001	45				45				4				13			
Fleming 2002		19		23						1		4				
Garcia 1985	26	23							8	2						
Homburg 2012	143						159		59						80	
Jahan 2015	156		152	152					26		31	24				
Johnson 1966	33	32							5	0						

Johnson 2010A		33		32			5		7			
Johnson 2010B	36			35	35		14			14	19	
Kar 2012	51		52				4		11			
Kar 2015	35			35	35		10			13	12	
Karimzadeh 2007		100		100				11		40		
Karimzadeh 2010	90			90	88		11			13	13	
Keikha 2011	58		58				3		11			
Khorram 2006	15				16		0				5	
Leanza 2014	28				28		8				15	
Legro 2007	209			208	209		50			18	65	
Legro 2014	376		374				81		117			
Liu 2015	67		67				22		29			
López 2004	38					38	9					16
Lord 2006		22		22				2		3		
Lorzadeh 2011	50		50				11		16			
Maged 2015	40				40		4			4		
Mobusher 2014	50		50				4		10			
Moll 2006	114				111		52				44	
Nazik 2012	33		31				8		7			
Palomba 2005	50			50			16			31		
Raja 2005	50				50		8				18	
Ray 2012	78		69				14		20			
Robinson 2003	25				23		10				11	
Roy 2012	108		104				28		43			
Sahin 2004	10				11		3				5	

Santonocito 2009	19		17				6		10					
Selim 2012	110	110					20	29						
Seyedoshohadaei 2012	50	50		50			32	25			20			
Sharief 2015	40	35					7	10						
Sh-El-Arab Elsedeek 2011	62	62					16	20						
Tang 2006		74	69					2	6					
Vegetti 1999	50			45			12				8			
Williams 2009	26		29				8			12				
Zain 2009	41		42	41			6		3	8				
Zeinalzadeh 2010	57	50					8	10						

(n - number of patients in each group; r - number of events in each group; 1- clomiphene; 2 - lacebo/no treatment; 3 - letrozole; 4 - metformin; 5 - clomiphene plus metformin; 6 - tamoxifen; 7 – follicle-stimulating hormone; 8: laparoscopic ovarian drilling)

34-2 Live birth

Study ID	n1	n2	n3	n4	n5	n6	n7	r1	r2	r3	r4	r5	r6	r7
Amer2015	79		80					28		39				
Bayar 2006	40		40					7		8				
Beigi 2006	35			35				5			8			
Boonstanfar 2001	47					48		1					3	
Boudhraa 2010	31				32			4				11		
Dehbashi 2009	50		50					6		10				
Homburg 2012	143						159	53						72
Jahan 2015	156		152	152				24		28	12			
Johnson 2010A		33		32					2		5			

Johnson 2010B	36			35	35				13				10	15		
Kar 2015	35			35	35				9				9	10		
Legro 2007	209			208	209				47				15	56		
Legro 2014	376		374						72		103					
Liu 2015	67		67						13		19					
López 2004	38						38		6							11
Moll 2006	114				111				31					21		
Palomba 2005	50			50					9				26			
Ray 2012	78		69						13		20					
Roy 2012	108		104						21		39					
Sahin 2004	10				11				3					4		
Santonocito 2009	19			17					4				9			
Seyedoshohadaei 2012	50		50			50			22		21				17	
Zain 2009	41			42	41				6				3	7		

(n - number of patients in each group; r - number of events in each group; 1- clomiphene; 2 - lacebo/no treatment; 3 - letrozole; 4 - metformin; 5 - clomiphene plus metformin; 6 - tamoxifen; 7 – follicle-stimulating hormone)

34-3 Ovulation

Study ID	n1	n2	n3	n4	n5	n6	n7	n8	r1	r2	r3	r4	r5	r6	r7	r8
Abuelghar 2013	32				34				20				20			
Amer 2009	36							36	24							21
Atay 2006	55		51						35		42					
Ayaz 2013	21				21				8				16			
Badawy 2011	187					184			120					95		
Beigi 2006	35			35					22			23				

Boonstanfar 2001	47				48		30				26			
Boudhraa 2010	31			32			10			17				
Cudmore 1966	13	9					8	2						
Dehbashi 2009	50		50				16		30					
Garcia 1985	26	23					20	8						
Jahan 2015	156		152	152			92		104	36				
Johnson 1966	33	32					17	4						
Johnson 2010B	36			35	35		23			23	27			
Kar 2012	51		52				31		38					
Kar 2015	35			35	35		18			15	20			
Keikha 2011	58		58				18		22					
Khorram 2006	15				16		1				7			
Legro 2007	209			208	209		157			115	174			
Leanza 2014	28				28		20				24			
Legro 2014	376		374				288		331					
López 2004	38					38	30					35		
Maged 2015	40				40		16				18			
Mobusher 2014	50		50				30		36					
Moll 2006	114				111		82				71			
Palomba 2005	50			50			31			42				
Raja 2005	50				50		18				34			
Ray 2012	78		69				48		60					
Robinson 2003	25				23		20				15			
Roy 2012	108		104				84		92					
Selim 2012	110		110				64		72					

Seyedoshohadaei 2012	50	50			50		39	37			34			
Sharief 2015	40	35					25	29						
Sh-El-Arab Elsedeek 2011	62	62					35	41						
Williams 2009	26			29			20				17			
Zain 2009	41		42	41			23		9		26			
Zeinalzadeh 2010	57	50					43	43						

(n - number of patients in each group; r - number of events in each group; 1- clomiphene; 2 - lacebo/no treatment; 3 - letrozole; 4 - metformin; 5 - clomiphene plus metformin; 6 - tamoxifen; 7 – follicle-stimulating hormone; 8: laparoscopic ovarian drilling)

34-4 Miscarriage

Study ID	n1	n2	n3	n4	n5	n6	n7	r1	r2	r3	r4	r5	r6	r7
Badawy 2009	220		218					4		4				
Badawy 2011	187					184		5					4	
Bayar 2006	40		40					0		1				
Beigi 2006	35			35				3			1			
Boonstanfar 2001	47					48		0					1	
Dehbashi 2009	50		50					1		3				
Homburg 2012	143						159	5						7
Jahan 2015	156		152	152				3		1	0			
Johnson 2010A		33		32					2		1			
Johnson 2010B	36			35	35			0			4	3		
Kar 2012	51		52					1		0				
Kar 2015	35			35	35			0			4	2		
Karimzadeh 2007		100		100					3		4			
Leanza 2014	28				28			1				0		

Legro 2007	209		208	209			14		10	20			
Legro 2014	376	374					29	45					
López 2004	38				38		3					5	
Moll 2006	114			111			12			13			
Nazik 2012	33	31					1	1					
Palomba 2005	50		50				6		3				
Ray 2012	78	69					1	0					
Robinson 2003	25			23			3			2			
Roy 2012	108	104					7	4					
Sahin 2004	10			11			0			1			
Santonocito 2009	19		17				2		1				
Seyedoshohadaei 2012	50	50			50		10	4			3		
Zain 2009	41		42	41			0		0	1			

(n - number of patients in each group; r - number of events in each group; 1- clomiphene; 2 - lacebo/no treatment; 3 - letrozole; 4 - metformin; 5 - clomiphene plus metformin; 6 - tamoxifen; 7 – follicle-stimulating hormone)

34-5 Multiple pregnancy

Study ID	n1	n2	n3	n4	n5	n6	n7	r1	r2	r3	r4	r5	r6	r7
Atay 2006	55		51					1		0				
Badawy 2009	220		218					3		0				
Badawy 2011	187					184		2					0	
Dehbashi 2009	50		50					1		1				
Homburg 2012	143						159	0						2
Jahan 2015	156		152	152				6		2	0			
Johnson 2010A		33		32					1		0			

Johnson 2010B	36		35	35			1		1	1		
Karimzadeh 2010	90		90	88			2		0	1		
Legro 2007	209		208	209			3		0	2		
Legro 2014	376	374					6	4				
López 2004	38				38		1				3	
Lorzadeh 2011	50	50					1	0				
Mobusher 2014	50	50					1	0				
Moll 2006	114		111				3			1		
Nazik 2012	33	31					1	0				
Roy 2012	108	104					3	0				
Seyedoshohadaei 2012	50	50			50		1	0			1	
Sharief 2015	40	35					1	0				
Zeinalzadeh 2010	57	50					0	1				

(n - number of patients in each group; r - number of events in each group; 1- clomiphene; 2 - lacebo/no treatment; 3 - letrozole; 4 - metformin; 5 - clomiphene plus metformin; 6 - tamoxifen; 7 – follicle-stimulating hormone)