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

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ABSTRACT

OBJECTIVE

To compare the effectiveness of alternative first line treatment options for 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, up to 11 April 2016.

STUDY SELECTION

Randomised controlled trials comparing eight ovulation induction treatments in women with WHO group II anovulation: clomiphene, letrozole, metformin, clomiphene and metformin combined, tamoxifen, gonadotropins, laparoscopic ovarian drilling, and placebo or no treatment. Study quality was measured on the basis of the methodology and categories described in the Cochrane Collaboration Handbook. Pregnancy, defined preferably as clinical pregnancy, was the primary outcome; live birth, ovulation, miscarriage, and multiple pregnancy were secondary outcomes.

RESULTS

Of 2631 titles and abstracts initially identified, 54 trials reporting on 7173 women were included. All pharmacological treatments were superior to placebo or no intervention in terms of pregnancy and ovulation. Compared with clomiphene alone, both letrozole and the combination of clomiphene and metformin showed higher pregnancy rates (odds ratio 1.69, 95% confidence interval 1.33 to 2.14; 1.71, 1.28 to 2.27; respectively). Letrozole led to higher live birth rates when compared with clomiphene alone (1.67, 1.11 to 2.49). Metformin led to lower multiple pregnancy rates compared with clomiphene alone (0.22, 0.05 to 0.93).

CONCLUSIONS

In women with WHO group II anovulation, letrozole and the combination of clomiphene and metformin are superior to clomiphene alone in terms of pregnancy. Compared with clomiphene alone, letrozole is the only treatment showing a significantly higher rate of live birth.

SYSTEMATIC REVIEW REGISTRATION

PROSPERO CRD42015027579.

READERS' NOTE

This is the second version of this paper. The original version was corrected following the retraction of two studies and removal of another which were ineligible (references 40, 41, and 75 of the original paper). These studies are not shown in this version. A tracked changes version of the original version is attached as a supplementary file to the correction notice, which explains the issue further.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Clomiphene is the longstanding first line treatment for WHO group II anovulation

Existing pairwise meta-analyses are limited to comparisons of two treatments

WHAT THIS STUDY ADDS

This study compares all of the most common regimens of ovulation induction with each other, using direct and indirect means

All pharmacological ovulation inductions were superior to placebo or no treatment in terms of ovulation and pregnancy in women with WHO group II anovulation

Letrozole was the most effective treatment in terms of live birth, and one of the top three treatments in terms of pregnancy and ovulation

Clomiphene and metformin combined was the most effective treatment in terms of pregnancy but not live birth; the potential higher chances of side effects should also be taken into account in decision making

Metformin and letrozole were associated with the lowest rates of multiple pregnancy

Introduction

Infertility affects one in seven couples, and ovulation disorders account for a quarter of all cases.[1] Normogonadotrophic anovulation, also classified as World Health Organization group II anovulation, is the most common category of anovulatory infertility. 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 several different ways, the diagnostic criteria for PCOS, agreed jointly by the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine, 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, and not just obstetricians and gynaecologists. The clinical manifestations of PCOS include oligomenorrhoea or amenorrhoea, hirsutism, and frequently infertility.[7] From conception, women with PCOS and their infants are at increased risk of perinatal complications, including gestational diabetes, pre-eclampsia, preterm labour, 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, which is invasive, expensive, and associated with potentially higher chances

of perinatal complications and congenital abnormalities.[11-14] Several medical options are used to treat ovulation disorders and infertility, including oestrogen receptor modulators (such as clomiphene and tamoxifen), aromatase inhibitors (such as letrozole), insulin sensitising 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 the comparison of two interventions for ovulation induction.[15-20] However, many of these treatment strategies have not been compared directly in previous randomised controlled trials. 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, compares multiple treatments in one statistical model,[21-23] and provides 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, clomiphene and metformin combined, tamoxifen, gonadotropins, laparoscopic ovarian drilling, and placebo or no treatment, in women with WHO group II anovulation, and to identify the best strategy for first line treatment.

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Methods

Search strategy and selection criteria

We conducted and reported the study according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) extension statement for network meta-analyses.[26] 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 11 April 2016.

We included published and unpublished randomised controlled trials 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. Treatments were categorised according to the initial randomised allocation, although subsequent clinical management might have included further doses or an alternative treatment.

Studies were excluded if they were not randomised controlled trials; only included treatment resistant women; or failed to report on clinical pregnancy, live birth, or pregnancy. Participants in the included studies were classified as: treatment naive women, a combination of treatment naive and treatment exposed women, and women whose treatment status was unknown. Crossover trials were also included if pre-crossover data were available. We also excluded those studies that 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 conducting the research. We plan to involve Fertility Network UK, PCOS Challenge, RESOLVE, and Access Australia's National Infertility Network 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 (RW and BVK) independently assessed the eligibility of all identified citations, and extracted data from original trial reports using a specifically designed form that captured 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 (BWJM) to reach consensus.

We chose pregnancy, defined preferably as clinical pregnancy, as the primary outcome. Clinical pregnancy was defined as pregnancy diagnosed by ultrasonographic visualisation of one or more gestational sacs.[27 28] Comparing the effectiveness of a treatment based on either clinical pregnancy or live birth rate as endpoints often results in comparable conclusions.[29] Therefore, we used data on live birth or pregnancy (positive blood or urine test for human chorionic gonadotropin) as an 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 (RW and BVK) using the methodology and categories described in the Cochrane Collaboration Handbook.[30] Again, in case of disagreement, a third reviewer (BWJM) was asked to reach consensus. Briefly, the tool for assessing

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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 graphs by Review Manager 5.3 software.[30]

Data synthesis and statistical analysis

A network meta-analysis was conducted to simultaneously compare seven treatment options for ovulation induction 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 one 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.[31]

All network meta-analyses were conducted within a random effects multiple regression model using the mvmeta package in Stata software [31 32] (version 12.0, Stata Corp). 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 an inconsistency plot. Studies with 0% or 100% events in all interventions were excluded from the analysis because these studies do not allow conclusions on relative effects. For studies with zero events in one arm only, we added a continuity correction of 0.5 to each cell. To avoid double counting of events, multi-intervention trials were analysed in their original form without the need to combine interventions.

For the network meta-analysis, we presented summary treatment effects (odds ratios) with their 95% confidence intervals as well as predictive intervals to facilitate interpretation of the results in the light of the magnitude of heterogeneity.[31] Predictive intervals can provide an interval within which the estimate of a future study is expected to be.[31] We applied the comparison adjusted funnel plot to assess small study effects in the network. We used the surface under the cumulative ranking curve to rank the treatments.[31 33] It 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 naive women, trials with low risk of randomisation and allocation bias, and trials reporting clinical pregnancy for sensitivity analysis.

Results

Characteristics of included studies

The literature search yielded 2631 publications, as shown in the PRISMA flowchart (fig 1). Fifty three[34-89] publications reporting on 54 trials fulfilled the eligibility criteria, as one study[56] included two individual trials (appendices 2 and 3).Five studies[35 36 47 52 67] were crossover studies and eight studies[35 44 54 61 66 77 86 87] were reported in conference abstracts. Publication dates ranged from 1966 to 2015, with 42 trials published in the last 10 years. The studies were conducted in various countries, and one study each was reported in French,[46] Italian,[80] Turkish,[39] and Persian.[69] The list of excluded studies is presented in appendix 4.

Of 54 trials, seven[54 56 58 60 64 82 88] had three comparison interventions and each of the remaining 47 trials had two. Overall, 7173 women with WHO group II anovulation were randomised to seven different treatment options (including clomiphene, letrozole, metformin, clomiphene and metformin combined, tamoxifen, gonadotropins, and laparoscopic ovarian drilling) and to placebo or no treatment. Appendix 5 presents the network plots for pregnancy, live birth, ovulation, miscarriage, and multiple pregnancy.

Risk of bias assessment results

There were 29 (54%) randomised controlled trials with low risk of bias on random sequence generation and 25 (46%) randomised controlled trials with low risk of bias on allocation concealment. Only 12 (22%) trials had low risk of bias on both blinding of participants and outcome assessment. Appendix 6 shows results from the risk of bias assessment.

Network meta-analysis results

Primary outcome—pregnancy

Our network meta-analysis included 54 randomised controlled trials reporting on 7173 women. Of these trials, 18 evaluated a combination of clomiphene and metformin (981 women). The remaining trials offered one treatment in each intervention, including clomiphene (49 trials;

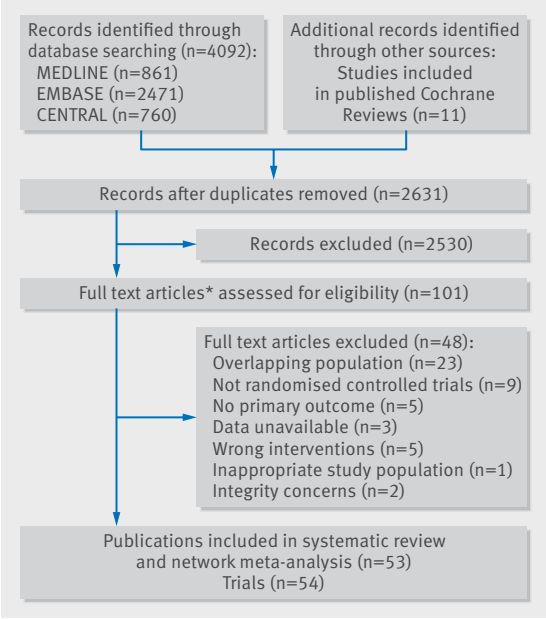

Fig 1 | PRISMA flow diagram of literature search for randomised controlled trials comparing eight ovulation induction treatments in women with WHO group II anovulation. *Full text articles=including abstract only publications

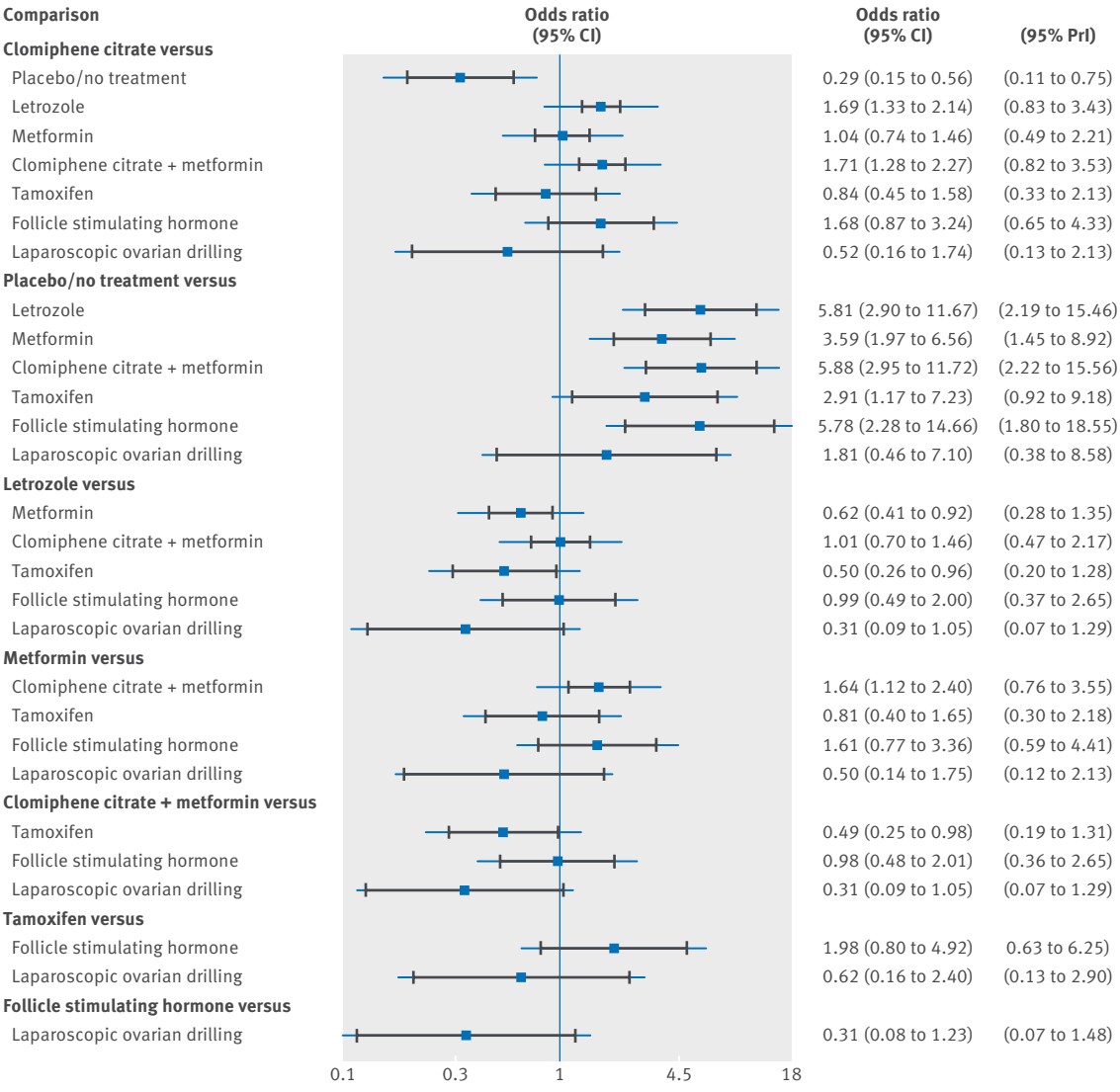

Fig 2 | Network meta-analysis of effectiveness of treatment options for pregnancy in women with WHO group II anovulation. Blue squares=estimate summary odds ratios of each comparison; black horizontal lines=confidence intervals; blue horizontal lines (overall length of lines)=predictive intervals (PrI); blue vertical line=line of no effect (odds ratio=1). Odds ratios less than 1 favour the first intervention; odds ratios greater than 1 favour the second intervention

3054 women), letrozole (20; 1540), metformin alone (14; 910), tamoxifen (three; 143), follicle stimulating hormone (two; 197), laparoscopic ovarian drilling (one; 36), and placebo or no treatment (eight; 312).

Figure 2 and table 1 show the network meta-analysis results. Compared with placebo or no intervention, all the treatment options (except for laparoscopic ovarian drilling) resulted in a significantly higher chance of pregnancy. Compared with clomiphene alone, letrozole as well as the combination of clomiphene and metformin led to significantly higher pregnancy rates (odds ratio 1.69, 95% confidence interval 1.33 to 2.14; 1.71, 1.28 to 2.27; respectively). Similar differences could be found when we compared these two interventions with tamoxifen. The combination of clomiphene and metformin also led to a significantly higher pregnancy when compared with metformin alone (1.64, 1.12 to 2.40).

When we considered predictive intervals in a network meta-analysis, clomiphene, letrozole, metformin, follicle stimulating hormone, and clomiphene and metformin combined still led to higher pregnancy rates compared with placebo or no intervention. For those interventions compared directly, the results from pairwise meta-analysis and network meta-analysis were consistent, apart from follicle stimulating hormone versus clomiphene (table 1 and appendix 7).

The surface under the cumulative ranking curve was 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 surface under the cumulative ranking curve values therefore correspond to more effective treatments.[31] The surface under the cumulative ranking curve values for the eight ovulation induction regimens were 85%, 82%, 84%, 47%, 43%, 35%, 20%, and 3%, for clomiphene and metformin combined, follicle stimulating hormone, letrozole, metformin, clomiphene, tamoxifen,

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Table 1 | Results from pairwise meta-analysis (where possible) and network meta-analysis for primary outcome (pregnancy) in women with WHO group II anovulation

	Pairwise meta-analysis		Network meta-analysis	
Treatment comparison*	No of studies	Odds ratio (95% CI)	Odds ratio (95% CI)	95% PrI
Clomiphene citrate versus:				
Placebo or no treatment	3	0.20 (0.05 to 0.74)	0.29 (0.15 to 0.56)	0.11 to 0.75
Letrozole	20	1.65 (1.40 to 1.95)	1.69 (1.33 to 2.14)	0.83 to 3.43
Metformin	9	1.10 (0.62 to 1.95)	1.04 (0.74 to 1.46)	0.49 to 2.21
Clomiphene citrate + metformin	18	1.49 (1.18 to 1.86)	1.71 (1.28 to 2.27)	0.82 to 3.53
Tamoxifen	3	0.73 (0.30 to 1.76)	0.84 (0.45 to 1.58)	0.33 to 2.13
Follicle stimulating hormone	2	1.57 (1.04 to 2.37)	1.68 (0.87 to 3.24)	0.65 to 4.33
Laparoscopic ovarian drilling	1	0.52 (0.19 to 1.44)	0.52 (0.16 to 1.74)	0.13 to 2.13
Placebo or no treatment versus:				
Letrozole	NA	NA	5.81 (2.90 to 11.67)	2.19 to 15.46
Metformin	5	3.58 (2.06 to 6.21)	3.59 (1.97 to 6.56)	1.45 to 8.92
Clomiphene citrate + metformin	NA	NA	5.88 (2.95 to 11.72)	2.22 to 15.56
Tamoxifen	NA	NA	2.91 (1.17 to 7.23)	0.92 to 9.18
Follicle stimulating hormone	NA	NA	5.78 (2.28 to 14.66)	1.80 to 18.55
Laparoscopic ovarian drilling	NA	NA	1.81 (0.46 to 7.10)	0.38 to 8.58
Letrozole versus:				
Metformin	1	0.73 (0.41 to 1.32)	0.62 (0.41 to 0.92)	0.28 to 1.35
Clomiphene citrate + metformin	NA	NA	1.01 (0.70 to 1.46)	0.47 to 2.17
Tamoxifen	1	0.67 (0.30 to 1.47)	0.50 (0.26 to 0.96)	0.20 to 1.28
Follicle stimulating hormone	NA	NA	0.99 (0.49 to 2.00)	0.37 to 2.65
Laparoscopic ovarian drilling	NA	NA	0.31 (0.09 to 1.05)	0.07 to 1.29
Metformin versus:				
Clomiphene citrate + metformin	5	1.92 (0.90 to 4.06)	1.64 (1.12 to 2.40)	0.76 to 3.55
Tamoxifen	NA	NA	0.81 (0.40 to 1.65)	0.30 to 2.18
Follicle stimulating hormone	NA	NA	1.61 (0.77 to 3.36)	0.59 to 4.41
Laparoscopic ovarian drilling	NA	NA	0.50 (0.14 to 1.75)	0.12 to 2.13
Clomiphene citrate + metformin versus:				
Tamoxifen	NA	NA	0.49 (0.25 to 0.98)	0.19 to 1.31
Follicle stimulating hormone	NA	NA	0.98 (0.48 to 2.01)	0.36 to 2.65
Laparoscopic ovarian drilling	NA	NA	0.31 (0.09 to 1.05)	0.07 to 1.29
Tamoxifen versus:				
Follicle stimulating hormone	NA	NA	1.98 (0.80 to 4.92)	0.63 to 6.25
Laparoscopic ovarian drilling	NA	NA	0.62 (0.16 to 2.40)	0.13 to 2.90
Follicle stimulating hormone versus:				
Laparoscopic ovarian drilling	NA	NA	0.31 (0.08 to 1.23)	0.07 to 1.48

PrI=predictive interval; NA=not available.
*Odds ratios less than 1 favour the first intervention; odds ratios greater than 1 favour the second intervention.

laparoscopic ovarian drilling, and placebo or no treatment, respectively (appendix 8). Further details of the analyses on the primary outcome are presented in appendices 9-11.

Secondary outcomes

Live birth—For the outcome live birth, 23 randomised controlled trials with 4206 women were included in the network meta-analysis. Letrozole resulted in a significantly higher live birth rate compared with clomiphene (odds ratio 1.67, 95% confidence interval 1.11 to 2.49) and metformin led to lower live birth rate than letrozole (0.54; 0.29 to 0.98). The other comparisons showed no significant differences (appendix 12).

In terms of live birth, letrozole had the highest surface under the cumulative ranking curve value (81%), followed by follicle stimulating hormone (74%), clomiphene and metformin combined (71%), tamoxifen (48%), clomiphene (36%), and metformin (30%), while placebo or no treatment (10%) had the lowest surface under the cumulative ranking curve value (appendix 13).

Ovulation—For the outcome ovulation per woman randomised, 38 randomised controlled trials 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 associations remained similar in the network meta-analysis including predictive intervals.

Letrozole (odds ratio 2.00, 95% confidence interval 1.39 to 2.88) led to a higher ovulation rate than clomiphene alone (appendix 14). The combination of clomiphene and metformin was superior to metformin alone (2.50, 1.43 to 4.36), while metformin was inferior to clomiphene alone (0.57, 0.36 to 0.92). Metformin (0.29, 0.16 to 0.51) was inferior to letrozole.

Follicle stimulating hormone had the highest surface under the cumulative ranking curve value (87%) in terms of ovulation, followed by letrozole (86%), clomiphene and metformin combined (70%), clomiphene (50%), tamoxifen (42%), laparoscopic ovarian drilling (38%), metformin (24%), and placebo or no treatment (1%; appendix 15).

Miscarriage—For the outcome miscarriage, after the exclusion of trials with 0% or 100% event rates in all interventions, we included 25 randomised controlled trials in the network meta-analysis. We did not find

Table 2 | Recommendations on first line ovulation induction from current guidelines and consensus

Guidelines/consensus	Condition	First line ovulation induction
WHO guideline, 2016[102]	PCOS	Clomiphene or letrozole
Australian National Health and Medical Research Council (NHMRC) guideline, 2015 updated[104]	PCOS	Clomiphene or letrozole
American Association of Clinical Endocrinologists, American College of Endocrinology, and Androgen Excess and PCOS Society Disease State Clinical Review, 2015[103]	PCOS	Clomiphene or letrozole
Italian Society of Endocrinology consensus, 2015[106]	PCOS	Clomiphene
European Society of Endocrinology position statement, 2014[105]	PCOS	Clomiphene
Endocrine Society, 2013[6]	PCOS	Clomiphene or letrozole
National Institute for Health and Care Excellence guideline, 2013[1]	WHO II anovulation	Clomiphene, metformin, or clomiphene and metformin combined
Society of Obstetricians and Gynaecologists of Canada guideline, 2010[109]	PCOS	Clomiphene
ESHRE/ASRM consensus, 2008[107 108]	PCOS	Clomiphene

PCOS=polycystic ovary syndrome; ESHRE/ASRM=European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine.

any significant difference between each comparison in terms of miscarriage per woman randomised or miscarriage per pregnancy in the network meta-analysis (appendices 16 and 17).

Multiple pregnancy—Eighteen trials assessed the outcome multiple pregnancy. When expressed per woman randomised, follicle stimulating hormone led to higher multiple pregnancy rates than metformin (odds ratio 16.17, 95% confidence interval 1.58 to 165.54). This difference remained significant in network meta-analysis including predictive intervals. Follicle stimulating hormone also led to a higher rate of multiple pregnancy when compared with letrozole (7.22, 1.00 to 51.84). Metformin (0.22, 0.05 to 0.93) led to lower rates of multiple pregnancy compared with clomiphene alone, but these differences were not significant in network meta-analysis including predictive intervals (appendix 18).

Follicle stimulating hormone had the highest surface under the cumulative ranking curve value (90%), followed by clomiphene (65%), tamoxifen (61%) placebo (47%), clomiphene and metformin combined (441%), letrozole (33%), and metformin (11%; appendix 19).

Further details of the analyses of the secondary outcomes are presented in appendices 20-32.

Sensitivity analysis results

When analyses were restricted to studies reporting clinical pregnancy (appendix 33), the results were consistent with the main findings: letrozole and the combination of clomiphene and metformin were superior to clomiphene alone. However, in studies with treatment naive women or studies with low risk of both randomisation and allocation bias, letrozole remained superior to clomiphene (odds ratio 1.80, 95% confidence interval 1.20 to 2.70; 1.97, 1.18 to 3.30; respectively), while the difference between clomiphene and metformin combined and clomiphene alone was not significant (1.65, 0.98 to 2.80; 1.57, 0.96 to 2.57; respectively) (appendices 34 and 35).

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. Firstly, all pharmacological treatments were more effective than placebo or no intervention in terms of achieving ovulation and pregnancy. Secondly, the combination of clomiphene and metformin as well as letrozole on its own were superior to clomiphene in terms of pregnancy, and letrozole was superior to clomiphene in terms of live birth. Lastly, metformin was associated with a lower risk of multiple pregnancy when compared with 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 one 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 90] but in our meta-analysis they contributed 21% (12/57) of studies and 16% (1321/8082) of women. Therefore, we believe that our analysis included all relevant published randomised controlled trials on ovulation induction in WHO group II anovulation, thus reducing publication bias as much as possible.

Our study also had limitations. Firstly, we only reported reproductive outcomes in our study and were unable to include other relevant outcomes such as side effects that were not reported in many of the primary publications, and the reporting strategies varied from study to study. Metformin, for example, is known to generate gastrointestinal side effects,[15] but this could not be analysed in our network meta-analysis because it was not systematically reported in all studies. The use of standardised outcomes in studies on ovulation induction would have improved this aspect of our systematic review.[27 28 91] Additional discussion on the side effects of clomiphene and metformin combined is available in appendices 36-38.

Secondly, we chose pregnancy, defined preferably as clinical pregnancy, as the primary outcome. Although the aim of infertile couples is to have a

healthy child, 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 the early 2000s or earlier usually followed up participants until pregnancy. To make full use of these data and 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,[92] in the same direction when based either on pregnancy or live birth, while conclusions based on pregnancy as an endpoint are more robust because they have more statistical power.[29] Ideally, future randomised controlled trials should adhere to the Harbin consensus on outcomes reporting in infertility trials.[27 28]

Thirdly, lifestyle intervention was not analysed in this study. Although lifestyle intervention is recommended in many countries because it leads to higher spontaneous ovulation rates[93] and natural conceptions rates,[94] 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,[94] whereas lifestyle modification with weight loss before ovulation induction improved ovulation and live birth in PCOS in a US study.[95]

Lastly, WHO group II anovulation is a heterogeneous condition with various clinical manifestations. Women with different genetic backgrounds or metabolic conditions might respond differently to treatment options. The current systematic review only allowed general comparisons among women with WHO group II anovulation. Owing to the various reporting strategies, we chose not to perform subgroup analysis, based on characteristics such as body mass index and hyperandrogenaemia status in this network meta-analysis. Apart from the logistical and governance issues associated with data sharing across different countries, asking the original authors to reanalyse the data can be challenging, in view of the substantial time and effort needed to perform secondary analysis. Additionally, there are several practical difficulties with post hoc selection of cut-off values for continuous variables like body mass index. If the distribution of participants according to biological cut-off values (body mass index 25 or 30) are not balanced across groups, the results of subgroup analysis using this cut-off value could be misleading. Individual participant data meta-analysis would be able to address this issue and allow a more personalised strategy for ovulation induction care.

Research implications

Traditionally, the effectiveness of a new treatment option comes from comparisons with placebo or current standard care. To date, no trials have compared letrozole with placebo in treatment naive women. The current network meta-analysis, however, provides insight in this comparison from indirect comparisons, and suggests that trials comparing letrozole with placebo are unnecessary and in our opinion even unethical. Evidence on a head-to-head comparison between letrozole and the combination of clomiphene and metformin is lacking. Therefore, new trials comparing these two interventions are needed. Future trials should also compare new treatment options or combinations with one of these two strategies to enrich the evidence on first line management of WHO group II anovulation.

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

Individual participant data 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 including anovulatory PCOS, expectant management is not recommended, because pharmacological ovulation induction significantly improves pregnancy rate (odds ratios 2.43-6.11) compared with placebo no treatment in the present study.

Letrozole can be recommended as first line treatment due to its higher ovulation, pregnancy, and live birth 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). Miscarriage is often discussed in the literature especially in women with PCOS, and data in relation to this are controversial.[97] In our study, there were no significant differences in miscarriage rates in different comparisons; therefore, the superiority of letrozole over clomiphene in terms of live birth does not seem to be related to a decreased miscarriage rate.

Clomiphene and metformin combined can also be recommended as first line treatment, despite the lack of evidence to improve live birth rates and the instability in sensitivity analyses.[29] Of 18 studies comparing clomiphene and metformin combined with clomiphene or metformin alone, only seven reported live birth. The reduced sample size in the analysis of live birth affected statistical power for this comparison, and could explain the lack of a significant difference between clomiphene and metformin combined and clomiphene alone. The potential higher chances of side effects should also be taken into account in decision making.

Clomiphene alone was not competitive in the network, in terms of effectiveness (pregnancy, live birth, and ovulation) or safety (multiple pregnancy). Gonadotropins, though an effective treatment option,

had the greatest probability of leading to multiple pregnancy. It is therefore not recommended to use gonadotropins as the first line treatment in treatment naive women with WHO group II anovulation. Further discussions on quality of evidence and interpretation of data is presented in appendix 36.

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.[98 99] The use of letrozole for ovulation induction is explicitly prohibited in many other countries[100 101] (eg, Denmark), except in approved clinical trials. Some guidelines[6 102-104] have recommended clomiphene citrate or letrozole as first line treatment, whereas letrozole has not been included in the scope of other guidelines,[1 105-109] including the National Institute for Health and Care Excellence guidelines in the UK (table 2).[1] Safety concerns about letrozole use in infertility were raised in a study presented at the American Society for Reproductive Medicine's 2005 annual meeting, which showed a higher risk of locomotor malformations and cardiac anomalies in newborns.[110] However, this study was criticised on account of its methodological limitations, including small sample size of the letrozole group and inappropriate choice of control group.[111] This study has not been subsequently published as a peer reviewed paper. According to current evidence (appendix 39), letrozole use in infertility, including PCOS and unexplained infertility, does not increase the risk of congenital anomalies in newborns.[49 65 76 78 111-116] 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 subsequent guideline development.

Laparoscopic ovarian drilling was usually undertaken in clomiphene resistant women, and only one small randomised controlled trial on treatment naive 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.[117-122]

In conclusion, in women with WHO group II anovulation, both letrozole and the combination of clomiphene and metformin are superior to clomiphene alone in terms of pregnancy. Letrozole is the only treatment showing a significantly higher rate of live birth when compared with clomiphene alone.

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Appendices: Supplementary material