Dear BMJ Editorial Team, Dear Dr Georg Roeggla,

We would like to thank the two reviewers and the editorial committee for their valuable comments and for providing us with the opportunity of submitting a revised version. Please see below detailed answers to comments from the reviewers and the editorial committee.

We hope that the reviewers and editorial committee will find our revised manuscript satisfactory and look forward to hearing from you on a final decision.

Kind regards,

Rui Wang

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Manuscript ID: BMJ.2016.035343
Title: Treatment strategies for women with WHO group II anovulation - a systematic review and network meta-analysis

Reviewer: 1
This reviewer has many positive remarks on our manuscript, but has one minor reservation.
The aims have been to make a very comprehensive (Network) analysis. It you look at the studies, those on TAM, FSH and LOD are indeed few ….you may argue that the value of this "Network analysis" may add very little… why make such advanced analysis and statistics when the number of studies are 1, 2 and 4 on those treatment modalities. Without the "Network analysis" the conclusions would probably have been the same. Anyway, it is complete and comprehensive. Good.
Response: As the reviewer argues, we wanted to perform a complete and comprehensive review. Upfront, one cannot know whether particular treatments have been investigated. We therefore did not exclude interventions like TAM, FSH and LOD upfront.

The title includes the phrase: Network meta-analysis … I can read what it is in the text, but there may be clinicians like me who are not familiar with that concept. Why not chance the title to include the phrase: "multiple treatment comparison meta-analysis"
Response: Thank you for this suggestion. There have been more network meta-analyses published in recent years and the PRISMA extension statement for network meta-analyses was published to guide authors to report network meta-analyses[1]. According to PRISMA checklist, "network meta-analysis" is the recommended phase in the title. Articles published on the BMJ also use "network meta-analysis" as the terminology in the title, for instance, "Alfirevic Z, et al. Labour induction with prostaglandins: a systematic review and network meta-analysis. BMJ 2015; 350: h217". Therefore we propose to leave the title as it is to comply with the PRISMA statement for network meta-analyses.

Page 11, as I read it 8 papers were only available from published abstracts. According to Figure 1 it states "full text articles". Were the abstracts included in the analysis or not? It is not clear, so clarify please.

Response: The "full-text articles" in Figure 1 included abstract-only publications. In the revised version, we have now added a footnote in Figure 1 (Page 39): "*Full-text articles: including abstract-only publications".

Fig 2 a, b, c, d and e. A lot of space is used to present graphically the "Network plots". As I see this it simply shows that most studies are on clomiphene, metformin and letrozole, so to present 5 figures it not appropriate. I would let the figures be presented as supplementary material.
Response: We have now presented Figure 2 a-e as supplementary material (Appendix 5 Network plots of eligible comparisons for five outcomes). We are happy to make further adjustments according to the suggestions of reviewers or editors.

In the discussion the off-label used of letrozole is discussed and references are given to such off-label use. It should be added that off-label use in one issue, another is that in for instance Denmark use of letrozole for ovulation induction or IVF is explicitly prohibited by the Health Authorities, except if used in GCP approved clinical trial.
Response: We have now incorporated this issue in the discussion of off-label use of letrozole. We have added the following sentence: "The use of letrozole for ovulation induction is explicitly prohibited in many other countries, for example Denmark, except if used in approved clinical trials." (Page22, Line 14-16)

The superiority of letrozole versus clomiphene in terms of live birth rates does not seem to be related to a decreased miscarriage rate. At least the data showed no differences in miscarriage rates between the different treatment modalities. I would add in the discussion a few lines on miscarriages rates, as this issue is often discussed, in PCOS patients which will be the majority of the included type WHO type II patients.
Response: Thank you for this suggestion. We have added a paragraph on miscarriage rates in the "clinical implications and conclusion" section. It now reads: "Miscarriage is often discussed in the literature especially in women with PCOS, and data in relation to this are controversial. In our study, there were no significant differences in miscarriage rates in different comparisons and therefore the superiority of letrozole over clomiphene in terms of live birth does not seem to be related to a decreased miscarriage rate." (Page 21, Line 16-20)

In the discussion section I would abbreviate the methodological aspects that are presently 4 full pages. (Considering the extensive documentation given in all the supplementary data).
Response: We agree and have included "quality of evidence and interpretation of data" section as supplementary data (Appendix 36 Additional discussion). The methodological aspects now occupy less than two and a half pages. We are willing to make further adjustments according to suggestions of reviewer or editors.

There is no discussion of safety aspects on letrozole. Why is the drug prohibited in some countries? What is the problem with off-label use? Please refer to the papers earlier published after the debate on Letrozole safety.
Response: Thank you for this suggestion. We have discussed the safety aspects of letrozole in the revised manuscript. Also, according to the second reviewer's suggestion, we have summarised current evidence on the safety aspects of letrozole in a table (Appendix 39

Congenital malformations in newborns conceived through letrozole vs control). The text now reads: “Safety concerns about the use of letrozole in infertility were raised in a study, that showed a higher risk of locomotor malformations and cardiac anomalies in newborns [2]. However, this study was criticized on account of its methodologic limitations, including small sample size of letrozole group and inappropriate choice of control group [3]. This study has not been subsequently published as a peer-reviewed paper. According to current evidence (Appendix 39) [3-12], the use of letrozole in infertility, including PCOS and unexplained infertility, does not increase the risk of congenital anomalies in newborns.” (Page 22, Line 19 – Page23, Line4)

Reviewer: 2

This reviewer is also positive on the manuscript.

Limitations are well discussed. Perhaps the most important is the fact that the authors did not pursue aligned data from original authors to enable subgroup analysis, based on body mass index (BMI) and ethnicity. Whilst IPD could enable this, it is a massive body of work and an interim measure could have been to request data be reanalyzed and presented by original authors in a way to enable this analysis.

Response: We agree with the reviewer that BMI and ethnicity are important factors which could potentially modify the treatment effects. However, we did not plan subgroup analysis in our original protocol as this was in our opinion beyond the scope of our study and should be the focus of an IPD meta-analysis as mentioned in the manuscript (Page 20 Line 3). Moreover, apart from the logistic 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 analyses. Additionally, there are a number of practical difficulties with post hoc selection of cut-off values for continuous variables like BMI. If the distribution of participants according to biological cut-off values (25 or 30kg/m^2) are not balanced across groups, the results of subgroup analysis using this cut-off value could be misleading. Therefore, having considered this option, we decided not go down this route for this paper but have addressed this in our discussion (Page19, Line 15 - Page20, Line 2).

In the discussion the authors note that new trials evaluating ovulation induction should either compare letrozole to the combination of clomiphene and metformin. Further justification of why letrozole should be compared to metformin in future and what gaps this would address would be useful.

Response: We agree with the reviewer and have incorporated this issue in the revised manuscript. It now reads: “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. Additionally, future trials should also compare new treatment options or new combinations to one of these two strategies to enrich the evidence on first-line management of WHO group II anovulation.” (Page 20, Line 12-17)

The statement that" 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." may warrant clarification. One would presume this refers to women who have defined infertility following 12 months of

failing to conceive. The way this statement currently read could mislead readers to think that in women with PCOS, OI should be used firstline at the time fertility is desired without allowing time for spontaneous conception.

Response: Thank you for this comment. In the statement in our manuscript, we referred to WHO group II anovulation (including anovulatory PCOS), not all PCOS. Therefore the revised statement now reads: "In women with WHO group II anovulation including anovulatory PCOS, expectant management is not recommended, as pharmacological ovulation induction significantly improves pregnancy rate (ORs between 2.43 and 6.11) compared to placebo no treatment."(Page 21, Line 6-9)

In the discussion only the UK NICE guidelines are referred to. It would be useful to contextualize this work with the initial evidence based guidelines in PCOS which were recently updated and recommend both Clomiphene and Letrozole firstline (Teede et al) and the recent WHO guidelines on infertility management (Balen et al). Indeed, whilst there are many included tables and figure here, a table on current recommendations from key quality guidelines would be useful to contextualize the novelty and importance of this work. It would highlight the potential impact of the current work, whereby all guidelines would now need to be updated or modified in some way, based on this work, especially in relation to clomiphene + metformin vs clomiphene alone and letrozole.

Response: We have added a table (Table 2) summarising recommendations from current guidelines/consensus on WHO group II anovulation as well as PCOS. The revised sentence in the text reads: "As shown in Table 2, some guidelines recommended clomiphene citrate or letrozole as first-line treatment, while letrozole was not included in the scope of other guidelines including the NICE guideline in the UK." (Page 22, Line 16-19) Considering the need to limit the number of tables and figures, we are happy to make further adjustments to the table if necessary.

Table 2 Recommendations on the first-line ovulation induction from current guidelines and consensus.

Guidelines/Consensus	Condition	First-line ovulation induction
WHO guideline, 2016[13]	PCOS	CC or letrozole
Australian National Health and Medical Research Council (NHMRC) guideline, 2015 updated[14]	PCOS	CC or letrozole
American Association of Clinical Endocrinologists, American College of Endocrinology, and Androgen Excess and PCOS Society Disease State Clinical Review, 2015[15]	PCOS	CC or letrozole
Italian Society of Endocrinology consensus, 2015[16]	PCOS	CC
European Society of Endocrinology position statement, 2014[17]	PCOS	CC
The Endocrine Society, 2013[18]	PCOS	CC or letrozole
The National Institute for Health and Care Excellence (NICE) guideline, 2013[19]	WHO II anovulation	CC, metformin or CC+metformin
Society of Obstetricians and Gynaecologists of	PCOS	CC

Canada guideline, 2010[20]		
ESHRE/ASRM consensus, 2008[21 22]	PCOS	CC

Was it not possible to explore congenital abnormalities in this network meta-analysis as this is the main remaining concern in relation to letrozole?

Response: We agree with the reviewer that the congenital anomalies is a main concern with regard to letrozole. Of the 21 studies comparing clomiphene and letrozole included in our network meta-analysis, only nine studies reported live birth and four reported congenital anomalies. As two of the four studies reported that there were no congenital abnormalities in either group, the data are unsuitable for a meta-analysis for this outcome. However, we have listed these data, as well as the data from other studies (including observational studies) on the use of letrozole in infertility in a supplementary table. (Appendix 39 Congenital malformations in newborns conceived through letrozole vs control)

Appendix 39 Congenital malformations in newborns conceived through letrozole vs control

Study ID	Country	Study design	Congenital malformation	
			Control	Letrozole
Dehbashi 2009[8]	Iran	RCT	CC: 16.6% (1/6) [a]	0% (0/10)
Ray 2012[9]	India	RCT	CC: 0% (0/13)	0% (0/20)
Roy 2012[10]	India	RCT	CC: 0% (0/21)	0% (0/39)
Legro 2014[4]	USA	RCT	CC: 1.5% (1/66) [b]	3.9% (4/102) [c]
Diamond 2015[5]	USA	RCT	CC: 4.3% (3/70) [d]	3.6% (2/56) [e]
Tulandi 2006[7]	Canada	observational	CC/CC+FSH: 4.8(19/397) [f]	Letrozole/Letrozole+FSH: 2.4% (14/514) [g]
Forman 2007[3]	Canada	observational	2.6% (7/271) [h]	0% (0/94)
Sharma 2014[6]	India	observational	CC:4.0% (10/251) [i]; Natural conception: 2.9% (5/171)[k]	2.5% (5/201) [j]
Wu 2016[12]	China	RCT	Berberine: 0% (0/48)	Letrozole alone: 1.2%(1/84)l; Letrozole+Berberine: 1.2%(1/81)m
Tatsumi 2016[11]	Japan	observational	Natural cycle IVF/ICSI: 1.9% (44/2287)[n]	Letrozole + IVF/ICSI: 2.2%(15/694)[o]

Details of congenital malformations in these studies:

a. meningomyelocele.

b. atrial septal defect (ASD), ventricular septal defect (VSD), and pulmonary stenosis.

c. 1) cerebral palsy with arrested hydrocephalus with polycythemia and neutropenia; 2) imperforate anus with perineal fistula and spina bifida with a tethered spinal cord; 3) right hemimegalencephaly, and dysgenesis of the left frontal and temporal lobes but no hydrocephalus; 4) large cardiac VSD requiring surgical repair.

d. 1) Aortic arch hypoplasia; 2) Congenital hypothyroidism; 3) Renal duplicated right collecting system and ureterocele.

e. 1)Hypospadias; 2)Right facial hemangioma; Biventricular hypertrophy; Bifid uvula; Small cataracts bilaterally; Widening of the corneal horizontal diameter.
f. Major malformations (12 cases): 1) VSD (4 cases); 2) Transposition of great vessels; 3) Atresia of pulmonary valve and right ventricle; 4) Pulmonary valve atresia; 5) Pyelectasis; 6) Omphalocele; 7) Cleft palate; 8) Spinal muscular atrophy; 9) Down's syndrome.
Minor malformations (7 cases): 1) Preauricular skin tag (2 cases); 2) Horseshoe kidney; 3) Polydactyly (3 cases); 4) Unspecific hypotonia.
g. Major malformations (6 cases): 1) VSD; 2) Esophageal atresia; 3) Cleft palate; 4) Trisomy 18; 5) Down's syndrome; 6) Potter's syndrome.
Minor malformations (8 cases): 1) Preauricular skin tag; 2) Congenital ptosis; 3) Plagiocephaly; 4) Hydrocele; 5) Hypospadia; 6) Polydactyly; 7) Syndactyly (2nd and 3rd toes); 8) Umbilical and inguinal hernias.
h. 7 cases with major malformations but details not reported.
i. 1) patent ductus arteriosus (2 cases) and; 2) total anomalous venous connection; 3) Hypospadias (3 cases); 4) bilateral congenital talipus equino varus; 5) duplication of urethra; 6) cleft lip & palate; 7)inguinal hernia; 8)neural tube defect; 9) Down's syndrome (2 cases). Three babies with congenital heart disease were excluded from the analysis by the authors as they were born to diabetic mothers.
j. 1) combined ventricular and ASD; 2) paraumbilical hernia; 3) congenital deafness; 4) congenital talipus equino varus; 5) albinism.
k. 1) VSD; 2) Congenital talipus equino varus; 3)cleft lip; 4) imperforate anus; 5)polydactyly.
l. hydrocephalus.
m. major VSD and pulmonary stenosis.
n. major anomalies (34 cases), including chromosomal abnormalities (11 cases), cardiovascular abnormalities (13 cases) and musculoskeletal abnormalities (1 case).
o. major anomalies (13 cases): 1) ASD,VSD; 2)ASD,VSD, Down's syndrome; 3) Cleft lip without cleft palate; 4) Congenital hydronephrosis; 5) Diaphragmatic hernia; 6) Duodenal atresia; 7) Endocardial cushion defect, down syndrome; 8) Hypospadias; 9) Trisomy 18; 10) VSD (2 cases); 11)VSD, down syndrome; 12) Anencephalus.

Comments from The BMJ's manuscript committee meeting

• *We assume this is novel as it is the first NMA.*

Response: To our knowledge this is the first NMA on WHO group II anovulation.

• *The CI's are quite wide for many of the outcomes and we are not completely convinced that hanging the conclusions so definitively on the where the central estimate happens to sit.*
• *Many of the comparisons do not seem to reach statistical significance.*

Response: We agree with these two comments. The CIs were indeed wide and the results did not reach statistical significance in many comparisons in different outcomes. We therefore revised the conclusions as follows: "In women with WHO II group anovulation, letrozole and the combination of clomiphene and metformin are superior to clomiphene alone in terms of ovulation and pregnancy. Letrozole is the only therapy showing a statistically significant higher live birth rate than clomiphene alone."(Page 3, Line 7-9 and Page23, Line16-17)

• *This is potentially practice changing. However, interesting that clom/met combo is best for pregnancy but not live birth and you couldn't comment on side effects.*

Response: Thank you for this comment. We've incorporated the discussion on live birth in the revised manuscript. It reads: "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. Of the 19 studies comparing combined clomiphene-metformin to clomiphene and/or metformin alone, only 7 studies 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 statistical significant difference between combined clomiphene-metformin and clomiphene alone." (Page 21, Line 21 – Page 22, Line5)

As side effects were not reported in many of the primary publications and the reporting strategies varied from study to study, we were not able to incorporate this outcome in network meta-analysis. Considering the effectiveness of CC+metformin over CC, we have made further analysis and discussion on the side effect of CC+metformin versus CC in supplementary data (Appendix 36 Additional discussion). It now reads:

"We have summarised the side effects of the combination of clomiphene and metformin versus clomiphene alone in a supplementary table (Appendix 38). Of the 19 studies comparing these two interventions, 11 studies reported data on side effects or discontinuation due to side effects. Three studies including 714 women reported the number of participants who discontinued treatment due to side effects. In a pairwise meta-analysis for this outcome, we found that more women in the combination group discontinued the treatment due to side effects than women in clomiphene group (OR 2.34, 95% CI 1.04 to 5.30, Appendix 37). As the reporting strategies were diverse in different studies, we were not able to perform meta-analyses on overall side effects or any specific types of side effects. As shown in Appendix 38, gastrointestinal side effects were more frequent in combined clomiphene-metformin group than clomiphene group."

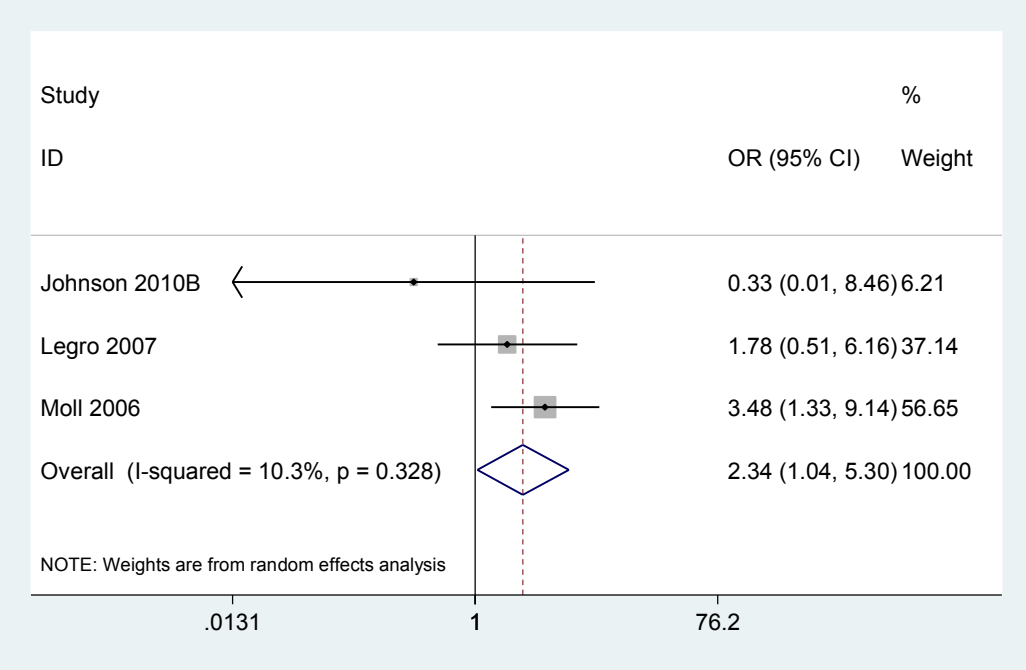
We have also added a sentence in "clinical implication" section after the recommendation of CC+metformin. It reads: "The potential higher chances of side effects should also be taken into account in decision making." (Page 22, Line 5-6).

Appendix 36 Side effects of the combination of clomiphene and metformin versus clomiphene alone.

Study ID	CC group				CC+Metformin group			
	Women with side effects	Details of side effects	discontinuation due to side	Sample size	Women with side effect	Details of side effect	discontinuation due to side	Sample size
Abuelghar 2013	6	Flushing: 4; gastrointestinal tract discomfort: 2	NA	32	11	Flushing: 2; gastrointestinal tract discomfort: 5; both: 1; diarrhoea: 3	NA	34
Ayaz 2013	NA	NA	0	21	NA	60% had complained of loss of appetite, 18% had nausea & vomiting	0	21
Basirat 2012	NA	No metformin related side effects.	NA	167	NA	No metformin related side effects.	NA	167
Dasari 2009	NA	NA	0	24	NA	NA[a]	0	16
Johnson 2010B	NA	Gastrointestinal symptoms: 5	1	36	NA	Gastrointestinal symptoms: 11; vasomotor: 1	0	35
Legro 2007	NA	Diarrhoea: 48; dyspepsia: 9; flatulence: 38; nausea: 82; stomach discomfort: 8; vomiting: 28; decreased appetite: 17[b]	4	209	NA	Diarrhoea: 126; dyspepsia: 14; flatulence: 30; nausea: 138; stomach discomfort: 16; vomiting: 72; decreased appetite: 33 [b]	7	209
Maged 2015	1	Nausea: 1	NA	40	1	Drowsiness:1	NA	40
Moll 2006	NA	NA	6	114	NA	NA	18	111
Raja 2005	NA	NA	NA	50	6	nausea and diarrhoea: 6	NA	50
Sahin 2004	NA	NA	0	10	NA	NA	0	11
Zain 2009	NA	NA	0	41	NA	NA[c]	0	41

NA: not available. a. The data of the 16 women in CC+ metformin group were not reported. But the authors reported that of the 25 participants who received metformin along with CC, 80% complained of loss of appetite and 24% had nausea and vomiting. The 25 participants was composed of 16 women in CC + metformin group and 9 women who did not conceive with six cycles of CC alone (given CC + metformin for an additional six cycles) at their request for further treatment. b. Main gastrointestinal side effects were summarised in this table. This study also reported data on other specific side effects but not the data on overall side effects. c. The data of CC+metformin group was not reported. Three patients with metformin complained of nausea, dizziness, and headache.

Appendix 37 Meta-analysis of CC + metformin versus CC for discontinuation due to side effects.



Boxes and horizontal lines represent ORs and 95% CIs of individual studies. The diamond represents the overall OR and 95% CI (Random-effect model). OR >1 means more women discontinue treatment due to side effect in CC+metformin group than CC group.

• *"Crossover trials were also included if pre-cross over data were available" – there should be a alter statement if any were included.*
Response: We have added the number of included crossover studies in results. It now reads "Five studies were crossover studies." (Page 11, Line 15)

• *Have you prepared the paper taking into account PRISMA for network meta-analysis?*
Response: Yes. We had submitted the PRISMA NMA checklist for network meta-analysis with our first draft last time. The revised PRISMA NMA checklist is also attached with the revised manuscript. Additionally, we have added a statement at the beginning of "methods" section in the revised manuscript. It now reads: "We conducted and reported the study according to the PRISMA extension statement for network meta-analyses[1]." (Page 7, Line3-4)

• *Table 1 – please clarify which way do ORs go?*
Response: We have now added the following footnote in Table 1: "OR > 1 favors the first intervention while OR <1 favors the second intervention". (Page 37)

• *Refer more than once to "arms" when they mean "interventions"*
Response: Thank you for this comment. We have replaced "arms" with "interventions". (Page 10 Line 13, 16, 17; Page 12 Line 16; Page 13 Line 7, 12; Page15 Line 13; and Appendix36)

• *p13: You use, as a secondary analysis, predictive intervals for evaluating vs zero – we are not sure this is a reasonable thing to do. It seems unduly conservative.*
Response: Thank you for this comment. Our interpretation on the predictive intervals in the first draft is indeed conservative and seems inappropriate. We have deleted this interpretation on page 13 to avoid confusion. The predictive interval reflects the variation in treatment effects over different settings, including what effect is to be expected in future patients, such as the patients that a clinician is interested to treat[23]. Considering that predictive interval is encouraged to be routinely presented in meta-analysis[23], we keep all the data on predictive intervals in the tables and figures, but we are happy to make further adjustments if required.

• *P16/46: not keen on use of "trend"*
Response: We have amended this sentence as "…, while the difference between combined clomiphene-metformin and clomiphene was not statistically significant (OR 1.65, 95% CI 0.98 to 2.80; OR 1.57, 95% CI 0.96 to 2.57)." (Page 16, Line 17-20)

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