NOTICE: This document contains correspondence generated during peer review and subsequent revisions but before transmittal to production for composition and copyediting:

- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*
- Email correspondence between the editorial office and the authors*

*The corresponding author has opted to make this information publicly available. Personal or nonessential information may be redacted at the editor’s discretion.

Questions about these materials may be directed to the Obstetrics & Gynecology editorial office: obgyn@greenjournal.org.
Date: Oct 26, 2018  
To: "Ashley Eskew"  
From: "The Green Journal" em@greenjournal.org  
Subject: Your Submission ONG-18-1800  

RE: Manuscript Number ONG-18-1800  

LETROZOLE VERSUS CLOMIPHENE CITRATE FOR UNEXPLAINED INFERTILITY: SYSTEMATIC REVIEW AND META-ANALYSIS  

Dear Dr. Eskew:  

Your manuscript has been reviewed by the Editorial Board and by special expert referees. Although it is judged not acceptable for publication in Obstetrics & Gynecology in its present form, we would be willing to give further consideration to a revised version.  

If you wish to consider revising your manuscript, you will first need to study carefully the enclosed reports submitted by the referees and editors. Each point raised requires a response, by either revising your manuscript or making a clear and convincing argument as to why no revision is needed. To facilitate our review, we prefer that the cover letter include the comments made by the reviewers and the editor followed by your response. The revised manuscript should indicate the position of all changes made. We suggest that you use the "track changes" feature in your word processing software to do so (rather than strikethrough or underline formatting).  

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Nov 16, 2018, we will assume you wish to withdraw the manuscript from further consideration.  

REVIEWER COMMENTS:  

REVIEWER #1:  

Thank you for your thoughtful review. Overall I find that it is extremely well done and your descriptions of your methodology are thoughtful and thorough.  

Specific comments:  

1. Intro: as you have targeted a more general audience in submitting to O&G, can you take some time in the introduction to relate this information to general practitioners, ie: why should we care about this study if we are just going to send this patient to REI, or is there information for me here too?  

2. Lines 144-59: the entire list of terms could be a supplement and be described in 1-2 sentences  

3. Lines 238-41: you are targeting a general audience in O&G, you will need to explain why injectables are being used with clomiphene or letrezole, as many of us do not use the injectables at all, only the oral medications, and will not be up on "standard practice" for stimulation. This might be best included in introduction.  

REVIEWER #2:  

1. Please justify the inclusion of patients with tubal factor (one blocked or absent tube) in the inclusion criteria definition of "unexplained infertility"?  

2. Were ovarian reserve markers similar between the two (CC vs LTZ) groups in all included studies?  

3. What were the outcomes when stratified by age group?  

REVIEWER #3:  

Abstract:  

1-Line 48: What do you mean by clinical effectiveness, please be more specific, is it live birth rate? Pregnancy rate?
2-Line 54-55 are repetitive from the data sources section above
3-Line 57: "patients" not couples...please change this throughout
4-Line 60: what is the difference between clinical pregnancy and pregnancy rate?
5-Line 62: "obtain"
6-Line 70-72: would delete from abstract and leave in manuscript results section

Introduction:
7-Line 97: what do you mean by being optimized?
8-Line 99: opportunity to introduce abbreviations for letrozole and clomiphene
9-Line 105: avoid common day vernacular, delete "classic" first line
10-Line 118: possibly less likely is clumsy, please edit

References, 7 and 9 refer to patients with PCOS, your study is for unexplained infertility. Would avoid complicating things and only stick to referencing articles for patients with unexplained infertility. They are not interchangeable.

12-Line 125-128: remove couples, and use patients, and I would re-word investigate, as you did not preform any formal investigation.

13-Line 144-159 can be removed and added to a supplemental appendix or table

Methods:
14-Very nicely written and organized. Study steps were very easy to follow and succinctly described.
15-Line 201 thru 205 may be better placed in the lines/paragraphs above were these initial steps were references, for ease of reading.
16-The inclusion of studies that used gonadotropins in both arms is a serious flaw in the methodology. If you are trying to be rigorous about CC vs LTZ, I would remove gonadotropins all together, regardless of their use in both arms.

Results:
17-I would like to see information re: cycle start dates and length of treatment for all of these studies
18-Line 258: how did you assess this?
19-Line 264: compares to what dose of clomiphene?

20-Line 270-276 & 277-285: these secondary outcomes were not mentioned in the methods section, I was surprised to see them described here. I think they are important to report, please edit methods section above to acknowledge their inclusion.

Discussion:
21-Inconsistent use of couples vs women vs patients
22-Line 289: positive pregnancy what? Rate? Test?
23-Line 290-293: See comments in results section. Ok to report but please update methods section.

Table:
24-Table 1: you mentioned chemical pregnancy, please make sure this is consistent throughout the manuscript, you use pregnancy rate in several locations. Also, why include adverse events in the table? Is it not a secondary outcome of yours.

Figures:
25-Not sure what figures 9-12 add to your manuscript? As I have mentioned before, they are not included as secondary outcomes and their being highlighted in manuscript in figures is kind of out of the blue. I would delete these figures.
STATISTICAL EDITOR’S COMMENTS:

1. Abstract: The primary outcome was pregnancy rate per patient among 8 RCTs. The results are cited as pooled RR, but this gives the reader no context for the actual rates. For at least the primary outcome, should also cite the pooled rates.

2. Fig 6: For the highest dose, there was only one study, so cannot generalize a conclusion.

3. Fig 9: Since there were only two studies compared here, cannot reliably estimate heterogeneity. Since only two studies, may also be subject to selection bias.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter, as well as subsequent author queries. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:
   1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
   2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.

2. This appears to have been presented at ASRM. On the title page, please disclose the name, dates, and location of the meeting.

3. Based on the forms that have been submitted, the following people have not met the criteria for authorship: Carolyn Stoll. On the third page of the agreement form, under the section labeled "Authorship," items #2-4, in addition to either 1a or 1b, MUST be checked off in order to qualify for authorship. Dr. Stoll should be moved to the acknowledgments, or they could resubmit a revised author agreement form if they filled it out erroneously the first time. All updated and missing forms should be uploaded with the revision in Editorial Manager.

4. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology will be transitioning as much as possible to use of the reVITALize definitions, and we encourage authors to familiarize themselves with them. The obstetric data definitions are available at http://links.lww.com/AOG/A515, and the gynecology data definitions are available at http://links.lww.com/AOG/A935.

5. Because of space limitations, it is important that your revised manuscript adhere to the following length. Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and appendixes).

Please limit your Introduction to 250 words and your Discussion to 750 words.

6. Specific rules govern the use of acknowledgments in the journal. Please edit your acknowledgments or provide more information in accordance with the following guidelines:

   * All financial support of the study must be acknowledged.
   * Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
   * All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your signature on the journal’s author agreement form verifies that permission has been obtained from all named persons.
   * If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

7. Provide a short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running foot.

8. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows:
Reviews, 300 words. Please provide a word count.

9. Only standard abbreviations and acronyms are allowed. A selected list is available online at http://edmgr.ovid.com/ong/accounts/abbreviations.pdf. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

10. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

11. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

12. The Journal's Production Editor and the following to say about the figures in your manuscript:

"1. Because the print Journal will not have room for all 12 of your figures, the Journal's editors ask that you move Figures 2-12 to the Supplemental Digital Content portion of your manuscript. Please rename those figures "Appendix #1-11," and rename all figures and citations accordingly.
2. Figures 2–12: Are these available at a higher resolution? Note that the text should be crisp when you zoom in to avoid looking blurry in print."

When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

When you submit your revision, art saved in a digital format should accompany it. Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file).

If the figures were created using a statistical program (eg, STATA, SPSS, SAS), please submit PDF or EPS files generated directly from the statistical program.

Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

Figures should be no smaller than the journal column size of 3 1/4 inches. Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce. Refer to the journal printer's web site (http://cjs.cadmus.com/da/index.asp) for more direction on digital art preparation.

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If you choose to revise your manuscript, please submit your revision via Editorial Manager for Obstetrics & Gynecology at http://ong.editorialmanager.com. It is essential that your cover letter list point-by-point the changes made in response to each criticism. Also, please save and submit your manuscript in a word processing format such as Microsoft Word.

If you submit a revision, we will assume that it has been developed in consultation with your co-authors, that each author has given approval to the final form of the revision, and that the agreement form signed by each author and submitted with the initial version remains valid.

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Nov 16, 2018, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2017 IMPACT FACTOR: 4.982
2017 IMPACT FACTOR RANKING: 5th out of 82 ob/gyn journals

In compliance with data protection regulations, please contact the publication office if you would like to have your personal information removed from the database.
Dear Dr. Chescheir,

I am writing to submit our revised manuscript entitled "Letrozole versus Clomiphene Citrate: Systematic Review and Meta-Analysis" PROSPERO ID: CRD42018094001 for the sole consideration for publication in Obstetrics and Gynecology.

We appreciate the valuable feedback from the reviewers and have addressed each comment individually. Changes made in response to reviewers’ comments are described by line number below as applicable. Due to compatibility issues with track changes when the PDF was generated, all changes in the text in response to the reviewers’ comments are highlighted in yellow. Please note that, to improve clarity and conform to word counts, we made additional small changes throughout the text that were not explicitly requested by the reviewers.

This manuscript describes original work and is not under consideration by any other journal. This manuscript will not be submitted elsewhere until a final decision is made by the editors of Obstetrics and Gynecology. All authors approved the manuscript, revisions and this resubmission. The authors have no financial disclosures. Institutional review board approval was not necessary for this systematic review and meta-analysis of de-identified, previously published data.

The lead author, Ashley Eskew, MD, affirms that this manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.
Signed by: [Signature]

Thank you for considering our manuscript for review. Please address all correspondence concerning this manuscript to [Redacted]. We appreciate your time and look forward to your response.

Sincerely,

[Signature]

Ashley Eskew MD
RE: Manuscript Number ONG-18-1800

LETROZOLE VERSUS CLOMIPHENE CITRATE FOR UNEXPLAINED INFERTILITY: SYSTEMATIC REVIEW AND META-ANALYSIS

REVIEWER COMMENTS:

REVIEWER #1:

Thank you for your thoughtful review. Overall I find that it is extremely well done and your descriptions of your methodology are thoughtful and thorough.

Thank you.

Specific comments:

1. Intro: as you have targeted a more general audience in submitting to O&G, can you take some time in the introduction to relate this information to general practitioners, ie: why should we care about this study if we are just going to send this patient to REI, or is there information for me here too?

Thank you for your comment. This is valuable feedback as part of our goal with submitting this to Obstetrics and Gynecology was to increase awareness of general OBGYNs in terms of options for ovulation induction in patients with unexplained infertility. Sentence added to line 102-104 to make clear why readers of Obstetrics and Gynecology should care about this study.

2. Lines 144-59: the entire list of terms could be a supplement and be described in 1-2 sentences

List of terms removed from manuscript and included as Appendix 1. The description in lines 121-123 encompass the key terms searched.

3. Lines 238-41: you are targeting a general audience in O&G, you will need to explain why injectables are being used with clomiphene or letrozole, as many of us do not use the injectables at all, only the oral medications, and will not be up on "standard practice" for stimulation. This might be best included in introduction.

Indications for and use of injectable gonadotropins explained more thoroughly in lines 98-99.

REVIEWER #2:
1. Please justify the inclusion of patients with tubal factor (one blocked or absent tube) in the inclusion criteria definition of "unexplained infertility"?

In general, it is thought that fertility is not substantially affected by one missing or blocked tube. This fits into the definition of unexplained infertility as if they ovulate from the side of the patent tube they can still successfully conceive spontaneously. In addition, ovum pickup can occur on the opposite side of the blocked tube.

2. Were ovarian reserve markers similar between the two (CC vs LTZ) groups in all included studies?

Only three of the studies included markers of ovarian reserve in their baseline characteristics and they each used different measures (one used cycle day 3 FSH/E2, another used day 2 FSH/E2 and the other used AMH and FSH/E2 but didn’t specify the cycle day it was drawn on). We added a comment to address this in line 201-203. There were no significant differences between the two groups in any of the studies including baseline ovarian reserve markers. Duration of infertility (also a marker of likelihood of success) was collected in six studies and included in Table 1.

3. What were the outcomes when stratified by age group?

Unfortunately, the individual studies do not present results stratified by age and we do not have access to individual patient data. Therefore, we are unable to provide this result for the purposes of a meta-analysis. Comment added to discussion as a way to improve future studies to be able to account for and stratify by patient age. See line 315. Mean age of participants in each group is included in Table 1.

REVIEWER #3:

Abstract:

1-Line 48: What do you mean by clinical effectiveness, please be more specific, is it live birth rate? Pregnancy rate?

Line 48-49: Added “as determined by positive pregnancy test” as this was our primary outcome.

2-Line 54-55 are repetitive from the data sources section above

We removed “electronic databases” to address redundancy.

3-Line 57: "patients" not couples..please change this throughout

“Couples” changed to “patients” throughout.

4-Line 60: what is the difference between clinical pregnancy and pregnancy rate?
These terms are defined in the study selection and results section (line 149-152). Pregnancy rate changed to "positive pregnancy test" throughout for clarity and consistency. Positive pregnancy test is defined by positive hCG two weeks post intrauterine insemination or timed intercourse. Clinical pregnancy is defined by ultrasound findings of pregnancy including a gestational sac or fetal pole with cardiac activity.

5-Line 62: 'obtain''
Corrected from “obtained” to “obtain”.

6-Line 70-72: would delete from abstract and leave in manuscript results section
Deleted from the abstract and left in results section.

Introduction:

7-Line 97: what do you mean by being optimized?
Sentence revised to reflect that an optimal protocol has yet to be identified for patients with unexplained infertility (line 95-96).

8-Line 99: opportunity to introduce abbreviations for letrozole and clomiphene
Introduced abbreviations at first opportunity and used throughout.

9-Line 105: avoid common day vernacular, delete "classic" first line
Deleted “classic” and replaced with “standard.”

10-Line 118: possibly less likely is clumsy, please edit
Sentence revised (line 110).

11-References, 7 and 9 refer to patients with PCOS, your study is for unexplained infertility. Would avoid complicating things and only stick to referencing articles for patients with unexplained infertility. They are not interchangeable.

Thank you for the comment. We agree that PCOS and unexplained infertility are not interchangeable, however, the studies completed in patients with PCOS demonstrate how use of aromatase inhibitors or LTZ may challenge the standard use of CC in patients with unexplained infertility. Reference to these studies demonstrates that there are populations (such as PCOS) in which LTZ is superior in terms of live birth rates which should motivate us to ask the clinically important question if it might also be more favorable in patients with unexplained infertility.
12-Line 125-128: remove couples, and use patients, and I would re-word investigate, as you did not perform any formal investigation.

*Couples replaced with patients. Re-worded “investigate” to “estimate” to more accurately reflect the process of this systematic review and meta-analysis.*

13-Line 144-159 can be removed and added to a supplemental appendix or table

*Removed from body of manuscript and added as supplemental Appendix 1.*

Methods:

14-Very nicely written and organized. Study steps were very easy to follow and succinctly described.

*Thank you.*

15-Line 201 thru 205 may be better placed in the lines/paragraphs above were these initial steps were references, for ease of reading.

*Thank you for your feedback. We agree this did seem out of place. After consideration, lines 201-205 were moved to the results section which improved the ease of reading and is more consistent with other meta-analyses published by Obstetrics and Gynecology.*

16-The inclusion of studies that used gonadotropins in both arms is a serious flaw in the methodology. If you are trying to be rigorous about CC vs LTZ, I would remove gonadotropins all together, regardless of their use in both arms.

*Thank you for your comment. We chose to include studies that employed the use of gonadotropins in both arms a priori as a part of our inclusion criteria as the impact of CC or LTZ should still be able to be assessed in terms of efficacy. Since gonadotropins were used in both arms of those studies, differences in outcomes are attributable to CC or LTZ. These studies accounted for a total n=321 which increase our sample size.*

*To assess for the potential impact of this decision on our results, we performed a sensitivity analysis in which we excluded the two studies that used injectable gonadotropins. We found that the pooled relative risks, pooled proportions and our conclusions were unchanged.*

Results:

17-I would like to see information re: cycle start dates and length of treatment for all of these studies
Information regarding cycle day start and length of treatment is provided in Table 1 under “LTZ regimen” and “CC regimen”. This includes dose, duration and cycle day (CD) start. We have now highlighted the references to Table 1 for these variables (line 199-208).

18-Line 258: how did you assess this?

Publication bias was assessed via constructed funnel plots with visual inspection and use of Egger test (described in study selection, line 181-182).

19-Line 264: compares to what dose of clomiphene?

The dose of clomiphene citrate was 100 mg in seven of the studies as shown in Table 1, but varied from 50-150 mg in Diamond et al. 2015. Dose per patient was not specified. This was a weakness of our meta-analysis that we discussed that we could not accurately identify the dose of clomiphene used in the Diamond et al. study, which is why it was included twice when we stratified by letrozole dose. They specified the outcome per cycle by dose of letrozole but not clomiphene (discussed in line 289-293 and line 313-315).

20-Line 270-276 & 277-285: these secondary outcomes were not mentioned in the methods section, I was surprised to see them described here. I think they are important to report, please edit methods section above to acknowledge their inclusion.

Methods section edited to acknowledge inclusion of secondary outcomes (line 153-155) and in the abstract (line 61-62).

Discussion:

21-Inconsistent use of couples vs women vs patients

Corrected to use only patients throughout the manuscript for consistency.

22-Line 289: positive pregnancy what? Rate? Test?

Clarified and changed to “positive pregnancy test” for consistency and clarity throughout the manuscript (see line 258 for correction specific to this comment).

23-Line 290-293: See comments in results section. Ok to report but please update methods section.

Methods sections updated to include secondary outcomes (line 153-155).

Table:

24-Table 1: you mentioned chemical pregnancy, please make sure this is consistent
throughout the manuscript, you use pregnancy rate in several locations. Also, why include adverse events in the table? Is it not a secondary outcome of yours.

“Chemical pregnancy” changed to “positive pregnancy test” to be consistent with the rest of the manuscript. Adverse events, while we considered them important, were inconsistently reported so they were not considered a secondary outcome. Adverse events were accordingly removed from the table.

Figures:

25-Not sure what figures 9-12 add to your manuscript? As I have mentioned before, they are not included as secondary outcomes and their being highlighted in manuscript in figures is kind of out of the blue. I would delete these figures.

*Based on this comment and the Editorial Office comments these figures were added as appendices.*

**STATISTICAL EDITOR’S COMMENTS:**

1. Abstract: The primary outcome was pregnancy rate per patient among 8 RCTs. The results are cited as pooled RR, but this gives the reader no context for the actual rates. For at least the primary outcome, should also cite the pooled rates.

*Pooled rates for the primary outcome of positive pregnancy test are now included in the abstract (line 66 and 67).*

2. Fig 6: For the highest dose, there was only one study, so cannot generalize a conclusion.

*Thank you for this comment. We agree. To clarify a sentence was added (line 307-309).*

3. Fig 9: Since there were only two studies compared here, cannot reliably estimate heterogeneity. Since only two studies, may also be subject to selection bias.

*We agree. Despite the small n we feel it is still important to include live birth as a secondary outcome because it is a critical clinical outcome for patients. Discussion point added to address this weakness in line 285-288.*

**EDITORIAL OFFICE COMMENTS:**

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you
choose to opt out, we will also be including your point-by-point response to the revision letter, as well as subsequent author queries. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:

1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.

1. OPT-IN: Yes, please publish the response letter and subsequent email correspondence related to author queries.

2. This appears to have been presented at ASRM. On the title page, please disclose the name, dates, and location of the meeting.

This information was added to the title page. Our findings were presented at the American Society for Reproductive Medicine Annual Meeting, Denver, CO, October 6-10, 2018.

3. Based on the forms that have been submitted, the following people have not met the criteria for authorship: Carolyn Stoll. On the third page of the agreement form, under the section labeled "Authorship," items #2-4, in addition to either 1a or 1b, MUST be checked off in order to qualify for authorship. Dr. Stoll should be moved to the acknowledgments, or they could resubmit a revised author agreement form if they filled it out erroneously the first time. All updated and missing forms should be uploaded with the revision in Editorial Manager.

This was erroneously filled out the first time. A revised authorship agreement form has been uploaded for Carolyn Stoll.

4. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology will be transitioning as much as possible to use of the reVITALize definitions, and we encourage authors to familiarize themselves with them. The obstetric data definitions are available at http://links.lww.com/AOG/A515, and the gynecology data definitions are available at http://links.lww.com/AOG/A935.

These standard definitions were reviewed and our manuscript complies where applicable.

5. Because of space limitations, it is important that your revised manuscript adhere to the following length. Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and appendixes).
Please limit your Introduction to 250 words and your Discussion to 750 words.

Revised introduction word count: 245 words
Revised discussion word count: 742 words

6. Specific rules govern the use of acknowledgments in the journal. Please edit your acknowledgments or provide more information in accordance with the following guidelines:

* All financial support of the study must be acknowledged.

All financial support of the study acknowledged on the title page.

* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.

Acknowledgment added to title page for editorial assistance provided with revisions (line 21-22).

* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your signature on the journal's author agreement form verifies that permission has been obtained from all named persons.

No additional persons contributed outside of the listed authors and scientific editor as noted above (line 21-22).

* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

This was added to the title page, lines 19-20. Our findings were presented at the American Society for Reproductive Medicine Annual Meeting, October 6-10, 2018, Denver, CO.

7. Provide a short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running foot.

Short title with 44 characters provided on line 23.

8. The most common deficiency in revised manuscripts involves the abstract. Be sure
there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Reviews, 300 words. Please provide a word count.

Revised abstract word count: 295 words.

9. Only standard abbreviations and acronyms are allowed. A selected list is available online at http://edmgr.ovid.com/ong/accounts/abbreviations.pdf. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

Abbreviations for clomiphene citrate (CC) and letrozole (LTZ) defined in both the abstract and manuscript updated throughout to address Reviewer #3, comment #7. These were originally not included throughout the manuscript as they weren’t on the standard abbreviations list, however, please let us know if we need to revise to remove them altogether.

10. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or;," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

Reviewed manuscript and found no text containing (/) that wasn’t being used to express data or a measurement.

11. Please review the journal’s Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

Table checklist reviewed for compliance with table 1 and table 2.

12. The Journal's Production Editor had the following to say about the figures in your manuscript:

"1. Because the print Journal will not have room for all 12 of your figures, the Journal's editors ask that you move Figures 2-12 to the Supplemental Digital Content portion of your manuscript. Please rename those figures "Appendix #1-11," and rename all figures and citations accordingly.

Figures 2-12 renamed to appendices 2-12 and legend updated accordingly."
2. Figures 2–12: Are these available at a higher resolution? Note that the text should be crisp when you zoom in to avoid looking blurry in print.

*Images re-saved as highest resolution .eps with TIFF preview files.*

When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

When you submit your revision, art saved in a digital format should accompany it. Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file).

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***
Dear Daniel,

Thank you so much for feedback and consideration.

I have reviewed and approve of all edits including those mentioned specifically on lines 54 and 122. I have added the information regarding heterogeneity from line 75 in the abstract to line 280 using the track changes features for consistency. I modified the sentence structures slightly in lines 278-283 with addition of the extra sentence.

I have attached my editing version here. Please let me know if there's anything else I can do or if you have any questions. Thank you so much for your time and consideration.

Kind Regards,

Ashley

Ashley Eskew, MD
Division of Reproductive Endocrinology and Infertility
Washington University, St. Louis

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Dear Dr. Eskew,

Thank you for submitting your revised manuscript. It has been reviewed by the editor, and there are a few issues that must be addressed before we can consider your manuscript further:

1. Please note the minor edits and deletions throughout. Please let us know if you disagree with any of these changes.
2. LINE 54: This phrase was added to the end of your Introduction. Do you approve?
3. LINE 75: Please be sure this is stated in the body of your paper. Statements and data that appear in the Abstract must also appear in the body text for consistency.
4. LINE 122: Added from abstract.
Please let me know if you have any questions. Your prompt response to these queries will be appreciated; please respond no later than COB on Thursday, December 6th.

Sincerely,
-Daniel Mosier

Daniel Mosier
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Hi Stephanie,

Only one small change with appendix 1. It was brought to my attention after I submitted my revised manuscript to change the title of Appendix 1 to "List of search terms in Ovid-Medline" to specify what the source was for those particular search terms so it could be replicated easily.

I have attached the revision as both a PDF and word doc. here.

I reviewed the other figures and did not identify any errors or inconsistencies.

Please let me know if I should resubmit the revised appendix in another format.

Kind Regards,

Ashley

Ashley Eskew, MD
Good Afternoon Dr. Eskew,

Your figure and appendices have been edited, and PDFs of the figure and appendices are attached for your review. Please review the figures CAREFULLY for any mistakes.

PLEASE NOTE: Any changes to the figures must be made now. Changes at later stages are expensive and time-consuming and may result in the delay of your article’s publication.

To avoid a delay, I would be grateful to receive a reply no later than Wednesday, 12/5. Thank you for your help.

Best wishes,