OBSTETRICS & GYNECOLOGY

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- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*

**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: Dec 21, 2021
To: "Sarah Maheux-Lacroix" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-21-2134

RE: Manuscript Number ONG-21-2134

The Effect of Postoperative Hormonal Suppression on Fertility in Patients with Endometriosis: a Systematic Review and Meta-Analysis

Dear Dr. Maheux-Lacroix:

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).

Please be sure to address the Editor comments (see "EDITOR COMMENTS" below) in your point-by-point response.

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 Jan 11, 2022, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

This is a thorough and carefully conducted meta-analysis of hormonal suppression after surgical treatment of endometriosis in infertile women. This reviewer offers the following suggestions to improve the manuscript.
1. The authors should make clear the infertility status of research participants. in lines 92-93, the authors state that they include RCTs of patients with endometriosis, without specifying that these are all infertile patients. The reason I raise this issue is that on lines 152-153, the authors refer to "a proportion of participants ... seeking pregnancy (versus all participants)." Also, in Table 1, the word "infertile" is added parenthetically to the heading "Participants." The authors should make clear whether all the trials were restricted to infertile women with endometriosis who underwent treatment with the goal of pregnancy; if not, in the text and tables, a distinction should be made between infertile patients seeking treatment and other patients with endometriosis who may have undergone surgery to reduce pain of for some other reason.
2. The authors chose pregnancy rather than live birth as their primary endpoint. Live birth is the current standard for infertility studies. Had the authors chosen live birth as the primary outcome variable, their conclusion would be that hormonal suppression was not associated with a higher pregnancy rate. The authors do not provide a reason for choosing pregnancy rather than live birth. One might infer from the statement on line 202 that "only" seven of the 19 RCTs reported live births as contributing to their reasoning. But quality evaluations of the different studies are not provided (the "bias" assessments in Figure 2 are incomplete assessments of quality), so in is unclear whether the trials reporting live birth that show no impact of hormonal suppression have methodology problems such that their findings are less credible than the ones reporting pregnancy but not live birth. In fact, one might argue the reverse -- i.e., the trials that choose to focus on pregnancy and don't choose to report live birth are of lower quality because they don't follow current standards of outcome reporting in infertility studies.
3. Along these lines, I noticed that two studies reporting pregnancy but not live birth by Yang showed RRs strongly favoring suppression; these two reports are from China in low-impact journals with very limited exposition on randomization method and other aspects of design/methodology, and no independent data monitoring committee. The 2019 study reports that, 2 years after f/u, there was a 31% pregnancy rate in patients receiving post-operative treatment, and a 9% pregnancy rate in the control group, leading to an estimated RR >3. Studies of pregnancy following surgical treatment of endometriosis in the era before super ovulation/IUI/IVF (i.e., comparable to the control group) show cumulative pregnancy rates in the range of 45% after 2 years of f/u. How can this study be considered credible with a control group rate of 9%? The 2014 study, five years earlier, showed higher pregnancy rates but still estimated a 55% higher pregnancy rate in the treatment group.

4. Also of note, another study with a high RR favoring suppression is the one by Muller, a Russian study that provided postoperative suppression before IVF; it seems to this reviewer that the use of postoperative suppression prior to IVF is a very specific question that perhaps should not be lumped in (statistically in the meta-analysis) with the studies that follow patients after treatment without IVF. A meta-analysis assumes that, if the inclusion and exclusion criteria are the same, the design is the same and the outcome measure is the same, that data from several studies can be safely combined to improve the power of a test. In this case, the design is very different -- i.e., surgery and post-op suppression with f/u observation for pregnancy vs. surgery and post-op suppression done as a "pre-treatment" to improve IVF outcome.
5. The confidence limit for the RR of 1.22 for pregnancy comes close to including 1.0. If the questionable studies from China were excluded, the result would likely be not significant. There is no significant finding for live birth. Therefore, the discussion imho should be softened in terms of the firmness of the conclusions vis-a-vis patient counseling.
6. It would be helpful to know the control group prenancy rate against which the treatment group RR is being reported. Perhaps this can be added as a column in Table 1.

Reviewer #2:

Review of Manuscript ONG-21-2134 "The effect of postoperative hormonal suppression on fertility in patients with endometriosis: A systematic review and meta-analysis"

A systematic review and meta-analysis with a stated purpose of evaluating the potential impact of post-operative hormonal suppression on fertility outcomes in patients with endometriosis has been submitted. The majority of the included trials, all of which were performed outside of the United States, evaluated the role of post-operative GNRH agonist therapy. The authors correctly note the use of standard approaches for performing this review and included a PRSIMA checklist. I have the following questions and comments.

Title - Consider noting the surgeries were conservative.

Précis - No comments.

Abstract - Line 27 - did you consider looking at live births as your primary outcome rather than just pregnancy?
if your results (line 42) suggest an increase likelihood of pregnancy, why so lukewarm in the conclusion - line 49.

Introduction - Should provide more information on the potential role and benefits of different hormonal suppression.

Methods - Line 96 - Did you consider eliminating studies which included patients with an oophorectomy? Was there prior surgical interventions, if provided in the studies - say a prior USO and now additional non-definitive surgery - that could or should have been excluded?
Line 149 - How did you define doses of medication?

Results - Although evaluated for impact, in Line 161 would it have been cleaner to exclude those trials with post-therapy IVF/IUI?
Line 175 - Since the trials were open label, for patients not receiving therapy on study is there a chance they received therapy off of protocol?
Line 186 - Again not the primary purpose per say but since the studies predominantly evaluated GNRH agonist therapy would it have been better to restrict the systematic review to those trials?

Discussion - Line 233 - Other than the combination of medicine and surgery are there other potential explanations?

Tables - Table 1 - Do you have the St. Dev for the patients?
Table 2 - Consider noting in the legend that these were the criteria or variables from the included studies.
Per my count from table 1 it appears that 12 studies had follow-up of at least 1 year or greater but in table 2 it was noted as 7. Am I incorrect or was labeling incorrect in table 1 or did I misinterpret presented information?
Table 3 - No comments.

Figures - Figure 1&2 - No comment.

Reviewer #3:

This is a systematic review with meta-analysis of peer-reviewed RCTs of patients with surgical diagnosis and treatment of endometriosis with either post-op suppressive therapy vs no treatment/placebo. Overall, this is a thorough and well done review on a topic with little data. The authors state that their main conclusions are that >3months of suppressive therapy with Lupron can lead to improved pregnancy outcomes in patients with endometriosis.

The main issues with this data is that they are skewed toward the results - with 4 studies with less than 3 months suppression vs 15 studies with >3 months of suppression. 14 of the studies included used Lupron for suppression. There were only 3 studies which used progesterone for suppression, 1 that used OCPs for suppression, 2 that used androgens for suppression, and one that used letrozole. Clinically, Lupron is the least tolerated of these medications. There is also a lack of data regarding age of patients and ovarian reserve which would be informative for highest risk fertility patients. All of the confidence intervals for the Lupron data (except for the Yang and Rickies data) cross 1 which implies that there is no difference in the data points. The significant difference is only found once all of the data is pooled. In addition, the I2 statistic shows variability across the data. These issues should be addressed in the discussion to make the paper more complete.

This study is important, because it considers a question which has little data. This review will help focus this question for future studies. While the data suggests that suppression for greater than 3 months with Lupron will likely increase pregnancy rates, it would be really helpful to understand the role of more tolerated and accepted therapies such as progesterone, OCPs, Orilissa. It would also be helpful to better understand the role of ovarian reserve and age.

STATISTICAL EDITOR COMMENTS:

Fig 1: For the subsets other than GnRHa, the counts of pregnancy are fewer, the samples smaller, he CIs wider and the power less. There fore the NS findings re: those subsets are likely not generalizable.
Further, as shown in Table 3, those subsets had lower quality of evidence scores than pregnancy after GnRHa use.

Supplemental: Figs 2 and 3 are important and should be in main text. Fig 3 includes the funnel plot for the main outcome, while Fig 2 shows the comparison for < 3mos duration vs ≥ 3 mos. The data for < 3 months is limited, thus making the CIs wider and having lower stats power. So, the conclusion re: < 3 mos, like those involving treatments other than GnHRa, are limited.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology have increased 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. 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:

A. OPT-IN: Yes, please publish my point-by-point response letter.
B. OPT-OUT: No, please do not publish my point-by-point response letter.

2. When you submit your revised manuscript, please make the following edits to ensure your submission contains the required information that was previously omitted for the initial double-blind peer review:
* Include your title page information in the main manuscript file. The title page should appear as the first page of the document. Add any previously omitted Acknowledgements (ie, meeting presentations, preprint DOIs, assistance from non-

byline authors).
* Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and in the body text. For industry-sponsored studies, the Role of the Funding Source section should be included in the body text of the manuscript.
* Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable).
* Name the IRB or Ethics Committee institution in the Methods section (if applicable).
* Add any information about the specific location of the study (ie, city, state, or country), if necessary for context.

3. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA), which must be completed by all authors. When you uploaded your manuscript, each co-author received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please check with your coauthors to confirm that they received and completed this form, and that the disclosures listed in their eCTA are included on the manuscript's title page.

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 has adopted the use of the reVITALize definitions. Please access the obstetric data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

5. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Review articles should not exceed 6,250 words. Stated word limits include the title page, précis, abstract, text, tables, boxes, and figure legends, but exclude references.

7. Specific rules govern the use of acknowledgments in the journal. Please note 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 response in the journal's electronic author 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).
* If your manuscript was uploaded to a preprint server prior to submitting your manuscript to Obstetrics & Gynecology, add the following statement to your title page: "Before submission to Obstetrics & Gynecology, this article was posted to a preprint server at: [URL]."

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 limit for Reviews is 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. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%").

12. 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.

13. Please review examples of our current reference style at http://ong.editorialmanager.com (click on the Home button in the Menu bar and then "Reference Formatting Instructions" document under "Files and Resources). Include the digital object identifier (DOI) with any journal article references and an accessed date with website references. Unpublished data, in-press items, personal communications, letters to the editor, theses, package inserts, submissions, meeting presentations, and abstracts may be included in the text but not in the reference list.

In addition, the American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG documents in your manuscript, be sure the references you are citing are still current and available. Check the Clinical Guidance page at https://www.acog.org/clinical (click on "Clinical Guidance" at the top). If the reference is still available on the site and isn't listed as "Withdrawn," it's still a current document.

If the reference you are citing has been updated and replaced by a newer version, please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly (exceptions could include manuscripts that address items of historical interest). If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript.

14. Figures 1-2: Please upload as figure files on Editorial Manager.

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.

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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.

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If you choose to revise your manuscript, please submit your revision through Editorial Manager at http://ong.editorialmanager.com. Your manuscript should be uploaded as a Microsoft Word document. Your revision's cover letter should include the following:

* A confirmation that you have read the Instructions for Authors (http://edmgr.ovid.com/ong/accounts/authors.pdf), and
* A point-by-point response to each of the received comments in this letter. Do not omit your responses to the Editorial Office or Editors' comments.

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

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 Jan 11, 2022, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

John O. Schorge, MD
Deputy Editor, Gynecology

2020 IMPACT FACTOR: 7.661
2020 IMPACT FACTOR RANKING: 3rd out of 83 ob/gyn journals

January 1st, 2022

Dr. Dwight J. Rouse, MD, MSPH
Dr. Jason D. Wright, MD
John O. Schorge, MD
Editor-in-Chief, Editor-in-Chief Elect, Deputy Editor
Obstetrics and Gynecology

Dear Dr. Rouse, Dr. Wright and Dr Schorge,

Here is a point-by-point response to each of the received comments.

Reviewer #1:

This is a thorough and carefully conducted meta-analysis of hormonal suppression after surgical treatment of endometriosis in infertile women. This reviewer offers the following suggestions to improve the manuscript.

1. The authors should make clear the infertility status of research participants. in lines 92-93, the authors state that they include RCTs of patients with endometriosis, without specifying that these are all infertile patients. The reason I raise this issue is that on lines 152-153, the authors refer to "a proportion of participants ... seeking pregnancy (versus all participants)." Also, in Table 1, the word "infertile" is added parenthetically to the heading "Participants." The authors should make clear whether all the trials were restricted to infertile women with endometriosis who underwent treatment with the goal of pregnancy; if not, in the text and tables, a distinction should be made between infertile patients seeking treatment and other patients with endometriosis who may have undergone surgery to reduce pain of for some other reason.

** In most included trials, all patients are infertile. Nonetheless, since some trials include patients wishing to conceive that are not infertile, we agree that it is very important to clarify this point. In the abstract (lines 75-76), we replaced "patients seeking pregnancy" by "infertile patients or patients wishing to conceive". In line 145, we clarified this point by changing the sentence to "We included peer-reviewed randomized clinical trials of infertile patients or wishing to conceive with surgical diagnosis and treatment of endometriosis, comparing postoperative suppressive hormonal treatment with an inactive control (placebo or no treatment after surgery)." In lines 206-207 (previously 152-153), we refer to trials in which not all participants wished to conceive after surgery and for whom pregnancy after surgery was not an outcome. These patients were not pooled in our study, but post-hoc subgroup analyses were performed for the trials in which this was the case. In Table 1, the heading "Participants (infertile)" was modified to "Participants (number infertile)". This column shows the number of infertile participants or wishing to conceive in each study and in parentheses the number of infertile participants.*

2. The authors chose pregnancy rather than live birth as their primary endpoint. Live birth is the current standard for infertility studies. Had the authors chosen live birth as the primary outcome variable, their conclusion would be that hormonal suppression was not associated with a higher pregnancy rate. The authors do not provide a reason for choosing pregnancy rather than live birth. One might infer from the statement on line 202 that "only" seven of the 19 RCTs reported live births as contributing to their

reasoning. But quality evaluations of the different studies are not provided (the "bias" assessments in Figure 2 are incomplete assessments of quality), so in is unclear whether the trials reporting live birth that show no impact of hormonal suppression have methodology problems such that their findings are less credible than the ones reporting pregnancy but not live birth. In fact, one might argue the reverse -- i.e., the trials that choose to focus on pregnancy and don't choose to report live birth are of lower quality because they don't follow current standards of outcome reporting in infertility studies.

**This is an excellent point. This is a question that we reflected on before conducting the study. We decided to choose pregnancies as a primary outcome because we were concerned that choosing live births as our primary outcome would lead to a lack of power since it requires greater resources to follow up participants until delivery. We are very aware of this weakness and this is why we mention in the discussion (lines 338-340) that "Future research should focus on changes in live births instead of only pregnancy, which better represents the targeted effect in fertility. Unfortunately, very few trials assessed live births leading to a lack of power." One of the objectives of our study is to guide future research on the subject since there is very little data. Therefore, one of our conclusions is that more studies assessing live births are required. This point was added at the end of the discussion in lines 345-346 "and to assess the effect of postoperative suppression on live births." To clarify this point, we also added the sentence "Pregnancy was chosen as primary outcome to maximize power" in line 181. The tool used for risk of bias assessment is the revised Cochrane risk-of-bias tool for randomized trials. Unfortunately, we could not classify trials not reporting live births as a high risk of bias trial according to the criteria of this tool. If there is any other tool that you would like us to use for risk of bias assessment, we will be pleased to make this modification.*

3. Along these lines, I noticed that two studies reporting pregnancy but not live birth by Yang showed RRs strongly favoring suppression; these two reports are from China in low-impact journals with very limited exposition on randomization method and other aspects of design/methodology, and no independent data monitoring committee. The 2019 study reports that, 2 years after f/u, there was a 31% pregnancy rate in patients receiving post-operative treatment, and a 9% pregnancy rate in the control group, leading to an estimated RR >3. Studies of pregnancy following surgical treatment of endometriosis in the era before super ovulation/IUI/IVF (i.e., comparable to the control group) show cumulative pregnancy rates in the range of 45% after 2 years of f/u. How can this study be considered credible with a control group rate of 9%? The 2014 study, five years earlier, showed higher pregnancy rates but still estimated a 55% higher pregnancy rate in the treatment group.

**We agree that these studies have very limited credibility for the reasons you mention. In our study, we report that Yang 2019 is at high risk of bias. We agree that there is very limited information on randomization in the trial Yang 2014, which is why we decided to modify its risk of bias to high for the "bias arising from the randomization process" dimension. We made all the changes in the manuscript and in the subgroup analyses to report Yang 2014 as a high risk of bias trial (Figure 2, Table 2, line 269). After this modification, for the pregnancy outcome, subgroup analysis taking into account the risk of bias of included studies did not modify the results. Furthermore, we looked at the effect of excluding Yang 2014 and Yang 2019 from the main outcome (pregnancy) analysis, from the treatment duration subgroup (less than 3 months or at least 3 months) and from the hormonal treatment class subgroup. If Yang 2014 and Yang 2019 are excluded from the main analysis, we obtain a relative risk of 1.13 with a*

confidence interval of [1.01, 1.26] (see image 1 below). If Yang 2014 and Yang 2019 are excluded from the subgroup "at least 3 months" for the treatment duration, we obtain a relative risk of 1.17 with a confidence interval of [1.04, 1.33] (see image 2). Finally, if we exclude Yang 2014 and Yang 2019 from the GnRH agonist subgroup, we obtain a relative risk of 1.16 with a confidence interval of [1.03, 1.31] (see image 3). We can conclude that the exclusion of those studies does not modify our results. Nonetheless, we agree that these studies are at high risk of bias, have very low credibility and have many methodological issues, but we do not have a motive to exclude them and their inclusion does not modify our results.

Image 1.

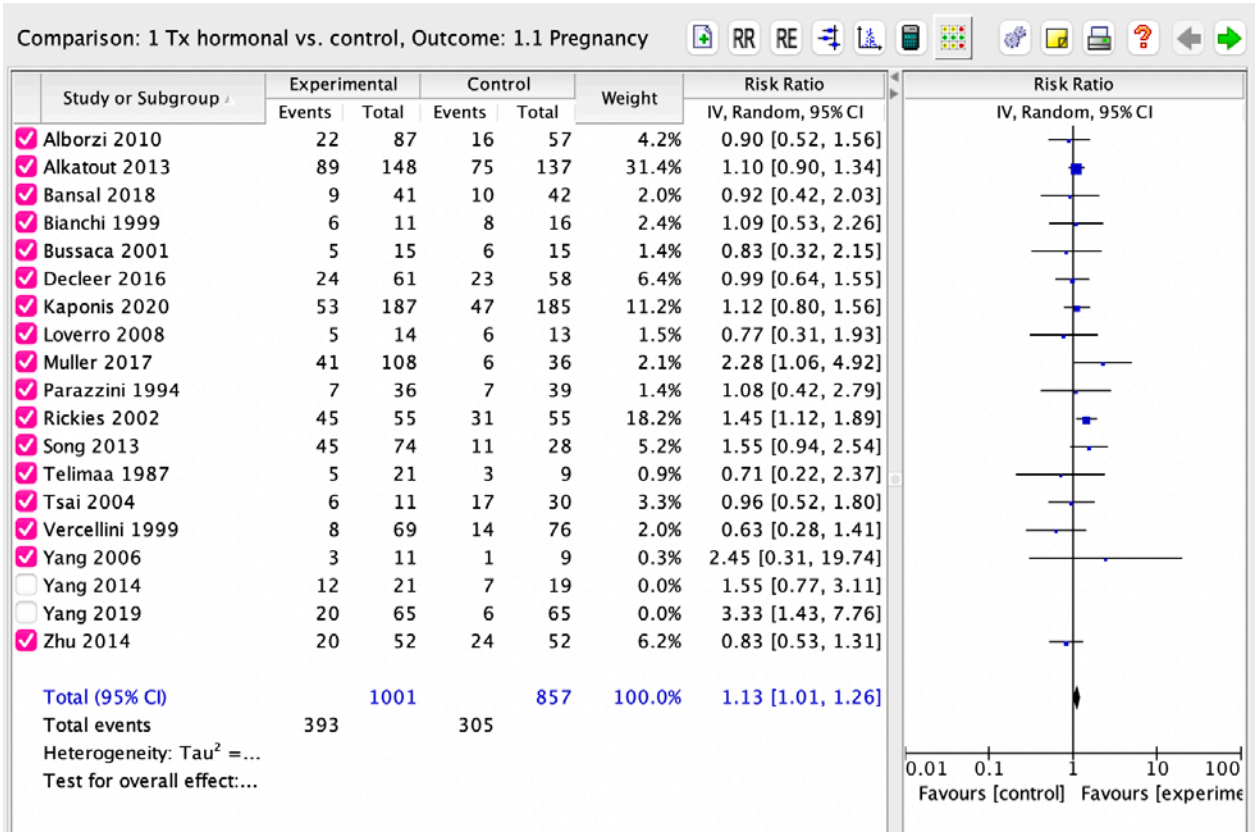


Image 2.

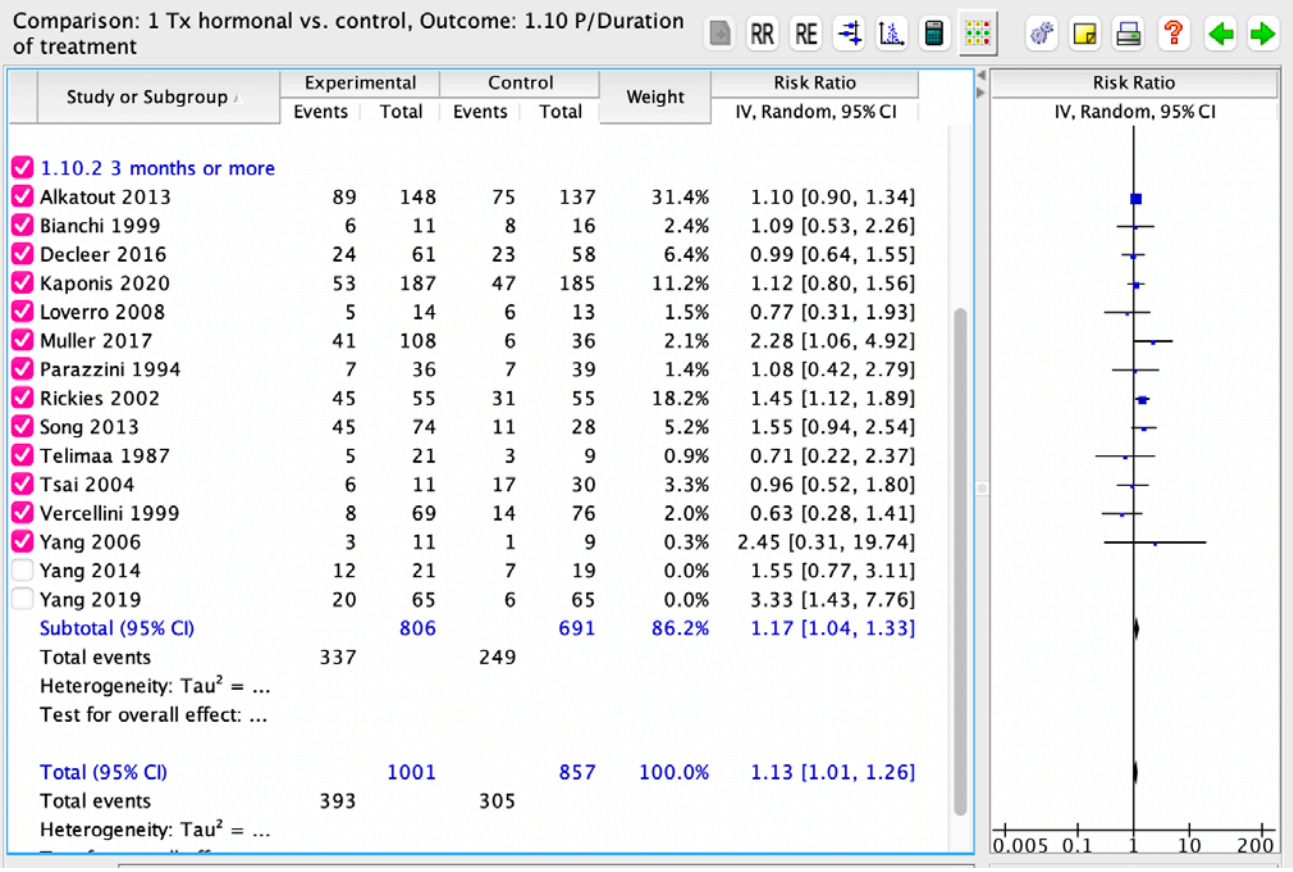
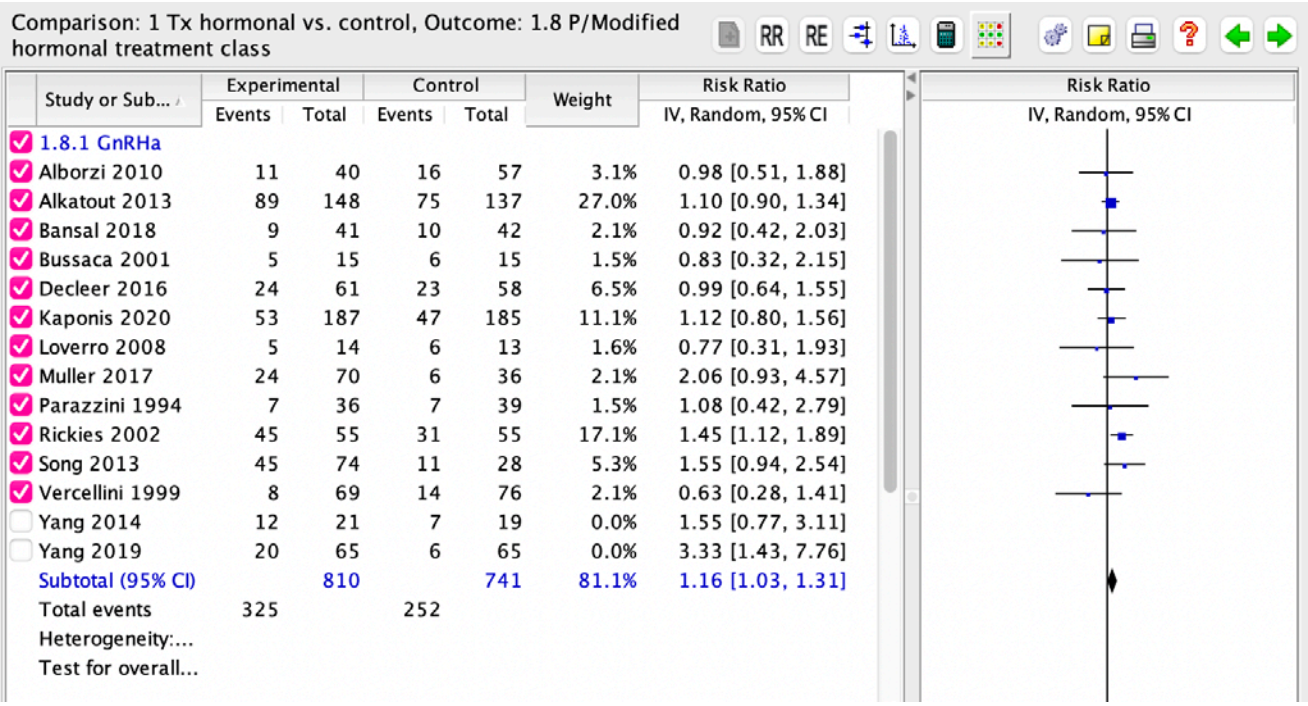


Image 3.



4. Also of note, another study with a high RR favoring suppression is the one by Muller, a Russian study that provided postoperative suppression before IVF; it seems to this reviewer that the use of postoperative

suppression prior to IVF is a very specific question that perhaps should not be lumped in (statistically in the meta-analysis) with the studies that follow patients after treatment without IVF. A meta-analysis assumes that, if the inclusion and exclusion criteria are the same, the design is the same and the outcome measure is the same, that data from several studies can be safely combined to improve the power of a test. In this case, the design is very different -- i.e., surgery and post-op suppression with f/u observation for pregnancy vs. surgery and post-op suppression done as a "pre-treatment" to improve IVF outcome.

**We agree that those two populations are completely different. Nonetheless, in other studies published in high impact journals[1, 2], those two populations are combined. We decided to include trials assessing fertility treatment (IVF/IUI) since they corresponded to our previously established inclusion criteria. Nonetheless, since we are very aware that the two populations are very different and that their inclusion could potentially modify our results, we performed a subgroup analysis to compare trials assessing pregnancy after fertility treatment and trials assessing spontaneous pregnancy. Trials in which all or some patients underwent fertility treatment after surgery had a relative risk of pregnancy of 1.22 [1.00, 1.50] whereas trials assessing spontaneous pregnancy had a relative risk of pregnancy of 1.10 [0.90, 1.34] (Table 2). Even if it seems that fertility treatments might favor pregnancy, the results of this subgroup are not statistically significant. Moreover, the I^2 for subgroup differences between those two subgroups is 0%, which suggests that the use of fertility treatment after surgery is not a significant source of heterogeneity between studies.*

[1] *Maheux-Lacroix S, Nesbitt-Hawes E, Deans R, Won H, Budden A, Adamson D, et al. Endometriosis fertility index predicts live births following surgical resection of moderate and severe endometriosis. Hum Reprod. 2017;32(11):2243-2249. doi:10.1093/humrep/dex291*

[2] *Ferrier C, Roman H, Alzahrani Y, Mathieu d'Argent E, Bendifallah S, Marty N, et al. Fertility outcomes in women experiencing severe complications after surgery for colorectal endometriosis. Hum Reprod. 2018;33(3):411-415. doi:10.1093/humrep/dex375*

5. The confidence limit for the RR of 1.22 for pregnancy comes close to including 1.0. If the questionable studies from China were excluded, the result would likely be not significant. There is no significant finding for live birth. Therefore, the discussion imho should be softened in terms of the firmness of the conclusions vis-a-vis patient counseling.

**Refer to response to comment #3.*

6. It would be helpful to know the control group prenancy rate against which the treatment group RR is being reported. Perhaps this can be added as a column in Table 1.

**This information is presented in figure 1.*

Reviewer #2:

Review of Manuscript ONG-21-2134 "The effect of postoperative hormonal suppression on fertility in patients with endometriosis: A systematic review and meta-analysis"

A systematic review and meta-analysis with a stated purpose of evaluating the potential impact of post-operative hormonal suppression on fertility outcomes in patients with endometriosis has been submitted. The majority of the included trials, all of which were performed outside of the United States, evaluated the role of post-operative GNRH agonist therapy. The authors correctly note the use of standard

approaches for performing this review and included a PRSIMA checklist. I have the following questions and comments.

Title - Consider noting the surgeries were conservative.

**The title was changed to "The Effect of Postoperative Hormonal Suppression on Fertility in Patients with Endometriosis after conservative surgery: a Systematic Review and Meta-Analysis."*

Précis - No comments.

Abstract - Line 27 - did you consider looking at live births as your primary outcome rather than just pregnancy?

**Yes. Ideally, live births would be our primary outcome since it better represents the targeted effect in fertility. Please refer to our answer to the second comment of the first reviewer.*

if your results (line 42) suggest an increase likelihood of pregnancy, why so lukewarm in the conclusion - line 49.

**The abstract conclusion was changed to: "Postoperative hormonal suppression should be considered on a case-by-case basis in order to enhance fertility while balancing this benefit with the risks of delaying conception. If chosen, gonadotropin-releasing hormone agonists would be the treatment of choice and a duration of at least three months should be favored." We decided to soften the conclusion since our primary outcome is not live births.*

Introduction - Should provide more information on the potential role and benefits of different hormonal suppression.

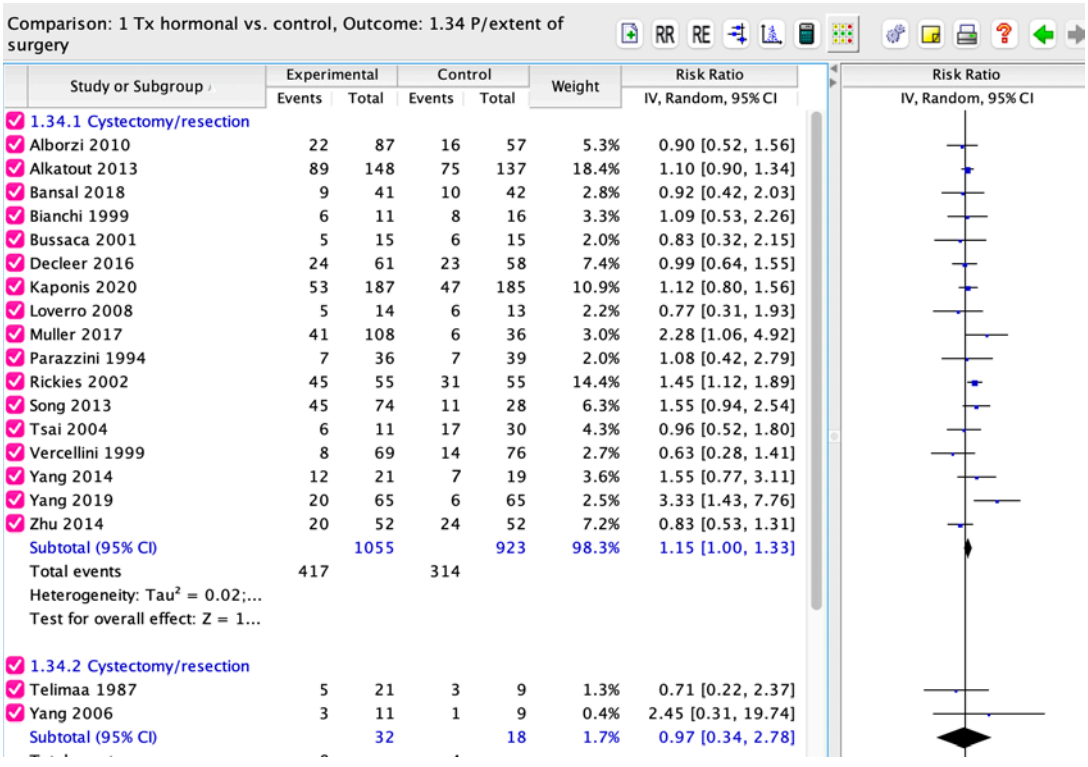
**This is a very good point. This information is very relevant since it is in direct correlation with the objective of our study. We discussed the potential roles and benefits of the different hormonal treatments in the discussion (lines 289-296, "GnRH agonists suppress the hypothalamic pituitary ovarian axis and prevent ovulation, menses and growth of endometriotic implants[46]. In literature, GnRH agonists were associated with lower levels of inflammatory markers in the peritoneal cavity[47], which could decrease risk of adhesions, anatomical disturbances and improve subsequent fertility. In a similar way, other suppressive hormonal therapy could be beneficial on the fertility prognosis when administered postoperatively. In fact, progestins are also known to decrease inflammatory levels, cell proliferation, neovascularisation and neurogenesis in endometriosis[48]."*) *In the introduction, we state that postoperative hormonal suppression in general has the potential to reduce anatomical and pain recurrence after surgery and that it has the potential to improve fertility (lines 120-121, "It has been suggested that postoperative suppressive therapy could increase pregnancy rates by reducing the inflammatory environment and decreasing early recurrence of lesions[14]. Such hormonal treatments are generally contraceptive, but their short-term use in the immediate postoperative period before attempting to get pregnant could be a non-invasive way to improve the fertility outcomes. (...) In a recent systematic*

review, a variety of postoperative hormonal therapies were associated with a lower risk of recurrence of pain symptoms[15], but their effect on chances of conceiving was under-investigated.")

Methods - Line 96 - Did you consider eliminating studies which included patients with an oophorectomy? Was there prior surgical interventions, if provided in the studies - say a prior USO and now additional non-definitive surgery - that could or should have been excluded?

**Yes, we did consider excluding studies in which not all participants had a fertility potential. Only two studies (Telimaa 1987 and Yang 2006) included some patients with unilateral oophorectomy. According to those studies, the participants still had a fertility potential. In the context of a systematic review, we are limited by the information available in the trials that we included. Unfortunately, we do not have any information on previous surgical interventions of the participants. Since very little data on our research question is available and that nothing suggests that the included trials studied participants without any fertility potential, we decided to include those studies. Moreover, we performed a subgroup analysis (image 4) to compare trials in which some patients had unilateral oophorectomy and trials in which all patients had cystectomy or resection of visible endometriosis. According to this subgroup analysis, the inclusion of some participants with unilateral oophorectomy did not modify the results. This subgroup analysis was not planned, but we can include it in the final manuscript if necessary.*

Image 4.



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
1.34.1 Cystectomy/resection						
Alborzi 2010	22	87	16	57	5.3%	0.90 [0.52, 1.56]
Alkatout 2013	89	148	75	137	18.4%	1.10 [0.90, 1.34]
Bansal 2018	9	41	10	42	2.8%	0.92 [0.42, 2.03]
Bianchi 1999	6	11	8	16	3.3%	1.09 [0.53, 2.26]
Bussaca 2001	5	15	6	15	2.0%	0.83 [0.32, 2.15]
Decleer 2016	24	61	23	58	7.4%	0.99 [0.64, 1.55]
Kaponis 2020	53	187	47	185	10.9%	1.12 [0.80, 1.56]
Loverro 2008	5	14	6	13	2.2%	0.77 [0.31, 1.93]
Muller 2017	41	108	6	36	3.0%	2.28 [1.06, 4.92]
Parazzini 1994	7	36	7	39	2.0%	1.08 [0.42, 2.79]
Rickies 2002	45	55	31	55	14.4%	1.45 [1.12, 1.89]
Song 2013	45	74	11	28	6.3%	1.55 [0.94, 2.54]
Tsai 2004	6	11	17	30	4.3%	0.96 [0.52, 1.80]
Vercellini 1999	8	69	14	76	2.7%	0.63 [0.28, 1.41]
Yang 2014	12	21	7	19	3.6%	1.55 [0.77, 3.11]
Yang 2019	20	65	6	65	2.5%	3.33 [1.43, 7.76]
Zhu 2014	20	52	24	52	7.2%	0.83 [0.53, 1.31]
Subtotal (95% CI)		1055		923	98.3%	1.15 [1.00, 1.33]
Total events	417		314			
Heterogeneity: Tau² = 0.02;...						
Test for overall effect: Z = 1...						
1.34.2 Cystectomy/resection						
Telimaa 1987	5	21	3	9	1.3%	0.71 [0.22, 2.37]
Yang 2006	3	11	1	9	0.4%	2.45 [0.31, 19.74]
Subtotal (95% CI)		32		18	1.7%	0.97 [0.34, 2.78]

Line 149 - How did you define doses of medication?

**As shown in Table 1, all types of treatments, dosage, administration route and treatment duration were collected in every included trial. We planned on defining dosage as either "low", "standard" or "high" according to each molecule. Since every trial used a standard dosage, subgroup analysis could not be performed.*

Results - Although evaluated for impact, in Line 161 would it have been cleaner to exclude those trials with post-therapy IVF/IUI?

**Please refer to our answer to the fourth comment of the first reviewer.*

Line 175 - Since the trials were open label, for patients not receiving therapy on study is there a chance they received therapy off of protocol?

**Once again, we are limited by the information provided by the included studies. No study reports that any participant received off protocol therapy. We think that the probability that a significant number of participants received off protocol treatment is fairly low since the patient's medical team should be aware of the treatment (or the absence of treatment) received as part of the study. Moreover, we are doing a per-protocol analysis, which means that we analyze data according to what the trials had planned in their protocol.*

Line 186 - Again not the primary purpose per say but since the studies predominantly evaluated GNRH agonist therapy would it have been better to restrict the systematic review to those trials?

**When writing the protocol, we did not know that most of the studies on the subject would be evaluating GnRH agonists. The purpose of this study was to assess the effect of postoperative hormonal treatment in general. Therefore, this is why we state in our conclusion that more studies evaluating the effect of other hormonal therapies such as progestins are required. Since there is very little data on our research question, we also wanted to be as inclusive as possible.*

Discussion - Line 233 - Other than the combination of medicine and surgery are there other potential explanations?

**In this statement, we wanted to highlight that we do not think that the effect observed is exclusively related to the effect of the medication alone. Other factors that may have an impact on pregnancy rates such as fertility treatment (IVF/IUI), duration of treatment, type of hormonal treatment, etc. were analyzed with subgroup analyses.*

Tables - Table 1 - Do you have the St. Dev for the patients?

**The standard deviation for the patients age were added to Table 1.*

Table 2 - Consider noting in the legend that these were the criteria or variables from the included studies. Per my count from table 1 it appears that 12 studies had follow-up of at least 1 year or greater but in table

2 it was noted as 7. Am I incorrect or was labeling incorrect in table 1 or did I misinterpret presented information?

**Yes, there was a mistake in the order of the signs. This mistake was corrected. Thank you.*

Table 3 - No comments.

Figures - Figure 1&2 - No comment.

Reviewer #3:

This is a systematic review with meta-analysis of peer-reviewed RCTs of patients with surgical diagnosis and treatment of endometriosis with either post-op suppressive therapy vs no treatment/placebo. Overall, this is a thorough and well done review on a topic with little data. The authors state that their main conclusions are that >3months of suppressive therapy with Lupron can lead to improved pregnancy outcomes in patients with endometriosis.

The main issues with this data is that they are skewed toward the results - with 4 studies with less than 3 months suppression vs 15 studies with >3 months of suppression. 14 of the studies included used Lupron for suppression. There were only 3 studies which used progesterone for suppression, 1 that used OCPs for suppression, 2 that used androgens for suppression, and one that used letrozole. Clinically, Lupron is the least tolerated of these medications. There is also a lack of data regarding age of patients and ovarian reserve which would be informative for highest risk fertility patients. All of the confidence intervals for the Lupron data (except for the Yang and Rickies data) cross 1 which implies that there is no difference in the data points. The significant difference is only found once all of the data is pooled. In addition, the I2 statistic shows variability across the data. These issues should be addressed in the discussion to make the paper more complete.

This study is important, because it considers a question which has little data. This review will help focus this question for future studies. While the data suggests that suppression for greater than 3 months with Lupron will likely increase pregnancy rates, it would be really helpful to understand the role of more tolerated and accepted therapies such as progesterone, OCPs, Orilissa. It would also be helpful to better understand the role of ovarian reserve and age.

**The different points mentioned in this comment are very important. We agree that more data is needed on the effect of postoperative suppression for less than three months, for patients' age, for ovarian reserve and for the different types of hormonal therapies. Even though there is very little data on this subject, our systematic review is currently the most complete review on the subject. As you mention, we found that more data is required especially on other types of molecules such as progestins, OCP, GnRH antagonists, etc. which helps to guide further research on the subject. This point is mentioned in lines 296-301, "In our review, progestins were associated with a relative risk of 1.9 that did not reach statistical significance, likely due to a lack of power. This analysis had only 8% (power) chances of detecting a 20% increase in pregnancy (RR=1.2) and a sample size of 3710 patients would have been required to reach a power of 80%. Other classes of suppressive hormonal therapy such as oral*

contraceptives and GnRH antagonists were also under-evaluated, underlining that more studies are required to clarify their effect on fertility outcomes." In lines 325-327, we added that there is also a lack of data on patients ovarian reserve in included trials.

STATISTICAL EDITOR COMMENTS:

Fig 1: For the subsets other than GnRHa, the counts of pregnancy are fewer, the samples smaller, he CIs wider and the power less. There fore the NS findings re: those subsets are likely not generalizable. Further, as shown in Table 3, those subsets had lower quality of evidence scores than pregnancy after GnRHa use.

**We completely agree with this statement. More trials studying other hormonal therapies are required in order to assess their effect on fertility. This point is mentioned in the conclusion in lines 344-346.*

Supplemental: Figs 2 and 3 are important and should be in main text. Fig 3 includes the funnel plot for the main outcome, while Fig 2 shows the comparison for < 3mos duration vs ≥ 3 mos. The data for < 3 months is limited, thus making the CIs wider and having lower stats power. So, the conclusion re: < 3 mos, like those involving treatments other than GnHRa, are limited.

**We agree with this statement. Supplemental figures 2 and 3 will be added to the main text.*

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology have increased 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. 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:

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** A. OPT-IN: Yes, please publish my point-by-point response letter.*

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* Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable).
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***The title page including acknowledgements, funding information and PROSPERO registration number was added to the main manuscript file.*
***PROSPERO registration number was added at the end of the abstract.*

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**The authors were notified.*

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 has adopted the use of the reVITALize definitions. Please access the obstetric data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

**We agree with the reVITALize definitions of all the terms used in the study.*

5. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Review articles should not exceed 6,250 words. Stated word limits include the title page, précis, abstract, text, tables, boxes, and figure legends, but exclude references.

**Manuscript word count: 4879 words.*

7. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

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***Acknowledgements are presented in lines 30-35 (Title page). Our manuscript was not uploaded to a preprint server prior to submitting your manuscript to Obstetrics & Gynecology.*

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In addition, the abstract length should follow journal guidelines. The word limit for Reviews is 300 words. Please provide a word count.

**Abstract word count: 295 words.*

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**We previously used the abbreviation "GnRH". Since this abbreviation is not on the list, we changed "GnRH" to "gonadotropin-releasing hormone".*

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.

**Modification line 149. "/" was changed to "or".*

**Modification line 180. "And/or" was changed to "with or without".*

11. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%").

**Relative risks and number needed to treat were used. The presentation of the data was standardized.*

12. 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.

**The tables were modified to conform to journal style.*

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