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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)*

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Date: Jun 28, 2022
To: "Nathalie Auger" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-22-1006

RE: Manuscript Number ONG-22-1006

Endometriosis and severe maternal morbidity: a retrospective cohort study

Dear Dr. Auger:

Thank you for sending us your work for consideration for publication in Obstetrics & Gynecology. Your manuscript has been reviewed by the Editorial Board and by special expert referees. The Editors would like to invite you to submit a revised version for further consideration.

If you wish to revise your manuscript, please read the following comments submitted by the reviewers and Editors. Each point raised requires a response, by either revising your manuscript or making a clear argument as to why no revision is needed in the cover letter.

To facilitate our review, we prefer that the cover letter you submit with your revised manuscript include each reviewer and Editor comment below, followed by your response. That is, a point-by-point response is required to each of the EDITOR COMMENTS (if applicable), REVIEWER COMMENTS, STATISTICAL EDITOR COMMENTS (if applicable), and EDITORIAL OFFICE COMMENTS below. Your manuscript will be returned to you if a point-by-point response to each of these sections is not included.

The revised manuscript should indicate the position of all changes made. Please use the "track changes" feature in your document (do not use strikethrough or underline formatting).

Your submission will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Jul 19, 2022, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: The authors present a cohort study evaluating the association between endometriosis and severe maternal morbidity in pregnancy. The authors conclude that endometriosis is associated with an increased risk of severe maternal morbidity. The strength of the study include large numbers in the database over a long period of time. Much of the findings have been previously reported but with smaller numbers. The authors focus on highest risk among women with active endometriosis. This group of patients is not clearly defined and leads to some confusion in the manuscript.

Abstract: The objective is presented clearly. The results and conclusion include the discussion of active endometriosis which is not noted in the methods.

Introduction is clear and concise

Methods:
Line 67- as this dataset includes women from 1989-2020 did all women have laparoscopic identified endoemtriosis? Did the authors include open procedures?

Line 69- why did the authors choose to include women with endometriosis after pregnancy? How is this clinically applicable?

Line 75-77 The definition of active endometriosis is confusing. Was the endometeriosis only documented in the patient's history? Was it actively treated in pregnancy? And why was "long-term management" included as "active." The manuscript focuses a great deal on these subgroups and they are not well defined. Perhaps the authors are stating "long standing or severe" endometriosis versus a milder subtype?

Line 95- the study contains large numbers, did the authors consider excluding patients with these confounders to strengthen the findings? Did they consider using only primiparous individuals to avoid confounding from multiple

pregnancies in the time period?

Line 113- the evaluation of patients with and without ART is a strength of the study.

Results:
Line 122- the largest group was actually diagnosed after delivery. What was the average time period to from pregnancy to diagnosis of endometriosis? As the authors conclude that these findings may help guide pregnancy management this is not necessarily possible if the majority of patients did not have this diagnosis prior to pregnancy.

Table 1- additional characteristics that would be helpful to include are cesarean history and history of ART.

Table 3- bold or starring of the statistically significant findings would make the table more readable.

Discussion
The discussion is somewhat lengthy and can be cut down and with increasing focus on the aspects that are similar and different from existing literature. The conclusions are well supported by the data.

Line 269- why was BMI, race and ethnicity unattainable? Is this due to the current form of data collection? If so an additional limitation would be of the accuracy of discharge data.

Reviewer #2: This is a large retrospective cohort study quantifying the association between endometriosis and severe maternal morbidities. Although the associations of endometriosis in relation to some maternal morbidities have been studied before such as PIH, this study specifically looked at a group of severe comorbidities that could be life-threatening, the information is novel and has strong clinical implications. Another merit is the large sample size and a good representation of the target population in the study region. However, there are some concerns that need to be addressed.

1. One concern is the misclassification of the exposure. Endometriosis could be seriously underdiagnosed although the proportion may present variations across regions. I am concerned that only considering those who had laparoscopically-confirmed endometriosis as the exposure group brings significant information bias. Ideally, it would be helpful to classify those who have symptoms or are suspected to have endometriosis into a separate group, but not to assume that they are the non-exposure group. Another problem with the exposure assessment is the timing of endometriosis diagnosis. It is good that the delay in diagnosing endometriosis is considered so that post pregnancy diagnosis is included. But I am not convinced that endometriosis diagnosed 10 years after pregnancy is likely to affect the preceding pregnancy. Not defining a cut-off for post pregnancy brings concerns about the inverse temporal relationship. A further question is if it is possible to consider the severity of endometriosis in exposure assessment. Dividing the total population into two distinctive groups as the main analysis looks suboptimal.

2. For outcome, it would be interesting to know how the deceased women were handled in the analysis as severe maternal morbidity are life-threatening. Association between severe maternal morbidity and endometriosis should not be dependent on the condition that women will be alive. It would be helpful to clarify if a composite outcome of morbidities and mortality was used.

3. Line 104. Here said the prevalence of severe maternal morbidity was calculated. Incidence rather than prevalence should be reported because this is a cohort study and the endpoint occurs alongside follow up. Given the nature of follow up, person-time incidence rate should be reported.

4. More details regarding clustering of pregnancies need to be provided. It seems genearalized linear model with robust estimators was used. Does this imply it is not possible to link pregnancies to individuals? If so, this needs to be clarified and acknowledge as a limitation.

5. It is important to report how missing data were handled in a large study like this. If no measures were taken, report the proportion of missing and explain why it is safe to do so.

Minor issues.
1. Line 38-39. This sentence looks redundant.

2. Line 32. It is not accurate to state the follow up time is 32-year as women enter the cohort in different years. This should be reported in results as median and range.

3. Line 116-117. Good to provide name of IRB, date and approval number.

4. Line 184-185. As this study is confined to associations. It is not justified to suggest active management of endometriosis could reduce severe maternal morbidity. Suggest removing.

5. As a good number of outcomes were tested, multiplicity should be considered. I suppose it is all right not to control for multiplicity given the exploratory nature of the study. But this should be acknowledged and warnings should be given regarding false positives.

Reviewer #3: This paper seeks to understand the relationship between inactive and active endometriosis and its impact on maternal morbidity. It is a novel and interesting topic that relates a relatively common gynecologic condition with very important obstetrics metrics. The strength of the study is that it includes a statistically impressive number of patients, has a good study design, and awareness of the limitations of the study. The weakness of the study is the overall low relative risk between maternal endometriosis and maternal morbidity. This translates to low clinical significance with the exception of the few categories that have a relatively high relative risk. It is also unclear how the diagnosis of active versus inactive in endometriosis can be made during pregnancy without laparoscopy to confirm disease activity during pregnancy. It seems that severe versus non-severe disease could be a different and more objective way of categorizing endometriosis. It could then be implied that severe disease (defined as requiring surgical intervention) May indicate that there are more inflammatory cytokines and markers that could contribute to increased maternal morbidity. Lastly, given that endometriosis is relatively progesterone resistant it may be worth considering the association between endometriosis and miscarriage and preterm birth as a future research endeavor.

Endometriosis as a risk factor for severe maternal morbidity is an interesting and novel association. As mentioned in the paper, hypertensive disorders of pregnancy and endometriosis have been investigated. This association may have more clinical Importance given relatively common incidence of hypertension in pregnancy. Using maternal morbidity with a relative risk association does not translate into clinical significance with relative risk of less than two given me uncommon nature of severe maternal mortality. It would be helpful to include the absolute increased risk in the calculations to see the clinical impact endometriosis has a maternal and morbidity.

Notably, two of the maternal morbidity categories have a relatively impressive relative risk, namely maternal status asthmaticus and placental abnormalities. Given the large relative risks associated with these conditions it would be worth spending more time exploring this in the discussion. This is a powerful part of the study that deserves more attention. This could be a fruitful area for future research.

STATISTICAL EDITOR COMMENTS:

Table 1: Should include column totals at top or bottom of columns.

Tables 3, 4: Suggest emboldening or otherwise identifying the RRs and aRRs that were statistically significant.

General: The study includes data from a 32-year period. Need to include year of pregnancy or categories by increments of years to include any temporal changes. Also, the unit of observation (lines 53-54) appears to be pregnancy, rather than by individual. That is, what adjustment was made for multiple pregnancies for an individual woman? There is likely some correlation of outcomes, i.e., the events are not independent. Thus, there is the potential for bias and imprecision in the estimates. Need to address by either (1) randomly choosing one pregnancy per woman or (2) adjusting for intraclass correlation.

EDITORIAL OFFICE COMMENTS:

1. If your article is accepted, the journal will publish a copy of this revision letter and your point-by-point responses as supplemental digital content to the published article online. You may opt out by writing separately to the Editorial Office at em@greenjournal.org, and only the revision letter will be posted.

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:
* Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and at the end of the abstract. For industry-sponsored studies, describe on the title page how the funder was or was not involved in the study.

* 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's Copyright Transfer Agreement (CTA) must be completed by all authors. When you uploaded your manuscript, each coauthor received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please ask your coauthor(s) to complete this form, and confirm the disclosures listed in their CTA are included on the manuscript's title page. If they did not receive the email, they should check their spam/junk folder. Requests to resend the CTA may be sent to em@greenjournal.org.

4. ACOG uses person-first language. Please review your submission to make sure to center the person before anything else. Examples include: "People with disabilities" or "women with disabilities" instead of "disabled people" or "disabled women"; "patients with HIV" or "women with HIV" instead of "HIV-positive patients" or "HIV-positive women"; and "people who are blind" or "women who are blind" instead of "blind people" or "blind women."

5. The journal follows ACOG's Statement of Policy on Inclusive Language (https://www.acog.org/clinical-information/policy-and-position-statements/statements-of-policy/2022/inclusive-language). When possible, please avoid using gendered descriptors in your manuscript. Instead of "women" and "females," consider using the following: "individuals;" "patients;" "participants;" "people" (not "persons"); "women and transgender men;" "women and gender-expansive patients;" or "women and all those seeking gynecologic care."

6. 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.

7. Make sure your manuscript meets the following word limit. The word limit includes the manuscript body text only (for example, the Introduction through the Discussion in Original Research manuscripts), and excludes the title page, précis, abstract, tables, boxes, and figure legends, reference list, and supplemental digital content. Figures are not included in the word count.

Original Research: 3,000 words

8. For your title, please note the following style points and make edits as needed:
* Do not structure the title as a declarative statement or a question.
* Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles.
* Abbreviations, jargon, trade names, formulas, and obsolete terminology should not be used.
* Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," "A Systematic Review," or "A Cost-Effectiveness Analysis" as appropriate, in the subtitle. If your manuscript is not one of these four types, do not specify the type of manuscript in the title.

9. Specific rules govern the use of acknowledgments in the journal. Please review the following guidelines and edit your title page as needed:

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* 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.
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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 manuscript.

In addition, the abstract length should follow journal guidelines. Please provide a word count.

Original Research: 300 words

11. 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.

12. 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.

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

Express all percentages to one decimal place (for example, 11.1%"). Do not use whole numbers for percentages.

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

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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. In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript.

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15. Each supplemental file in your manuscript should be named an "Appendix," numbered, and ordered in the way they are first cited in the text. Do not order and number supplemental tables, figures, and text separately. References cited in appendixes should be added to a separate References list in the appendixes file.

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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 a point-by-point response to each of the received comments in this letter. Do not omit your responses to the EDITOR COMMENTS (if applicable), the REVIEWER COMMENTS, the STATISTICAL EDITOR COMMENTS (if applicable), or the EDITORIAL OFFICE COMMENTS.

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

Again, your manuscript will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Jul 19, 2022, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Jason D. Wright, MD

Editor-in-Chief

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

Dr. Jason D. Wright, MD
Editor-in-Chief
Obstetrics & Gynecology

19 July 2022

Re: Submission – Original research

Dear Dr. Wright,

We are pleased to submit a revised version of our article "Endometriosis and severe maternal morbidity: a retrospective-cohort study" to be considered for publication in *Obstetrics & Gynecology*. We incorporated the recommendations and comments of the Reviewers and Editors. Please find below a point-by-point response to each comment. We have also attached the manuscript with changes tracked and confirm that we have read the Instructions for Authors. Each author contributed to the revision and has approved the final version.

We hope that you will be pleased with the revised manuscript, and remain available for additional corrections if requested.

Thank you for considering our work for publication in *Obstetrics & Gynecology*. We look forward to hearing from you soon.

Kind regards,

Nathalie Auger MD

RESPONSE TO REVIEW

Reviewer #1:

R1.1. The authors present a cohort study evaluating the association between endometriosis and severe maternal morbidity in pregnancy. The authors conclude that endometriosis is associated with an increased risk of severe maternal morbidity. The strength of the study include large numbers in the database over a long period of time. Much of the findings have been previously reported but with smaller numbers. The authors focus on highest risk

among women with active endometriosis. This group of patients is not clearly defined and leads to some confusion in the manuscript.

Response: We thank the Reviewer for these comments. We have clarified that: "*We defined active endometriosis as endometriosis that required clinical management for pelvic pain or other related symptoms during pregnancy*" (lines 76-77).

R1.2. Abstract: The objective is presented clearly. The results and conclusion include the discussion of active endometriosis which is not noted in the methods.

Response: We revised the Abstract as follows: "*Patients were classified as having active endometriosis during pregnancy, inactive endometriosis during pregnancy, a diagnosis of endometriosis post pregnancy, or no endometriosis*" (lines 12-14).

Introduction is clear and concise

Methods:
R1.3. Line 67- as this dataset includes women from 1989-2020 did all women have laparoscopic identified endoemtriosis? Did the authors include open procedures?

Response: We confirm that we included open procedures, and revised the text as follows: "*We identified cases of laparoscopy or laparotomy-confirmed endometriosis*" (line 69). In the Abstract, we indicated that cases were "*surgically-confirmed*" (line 11).

R1.4. Line 69- why did the authors choose to include women with endometriosis after pregnancy? How is this clinically applicable?

Response: We clarified that "*We included endometriosis diagnosed post pregnancy because a proportion of these patients may have undiagnosed endometriosis at the time of pregnancy*" (lines 80-82).

R1.5. Line 75-77 The definition of active endometriosis is confusing. Was the endometeriosis only documented in the patient's history? Was it actively treated in pregnancy? And why was "long-term management" included as "active." The manuscript focuses a great deal on these subgroups and they are not well defined. Perhaps the authors are stating "long standing or severe" endometriosis versus a milder subtype?

Response: We clarified the definition of active endometriosis as follows: "*We defined active endometriosis as endometriosis that required clinical management for pelvic pain or other related symptoms during pregnancy*" (lines 76-77).

R1.6. Line 95- the study contains large numbers, did the authors consider excluding patients with these confounders to strengthen the findings? Did they consider using only primiparous individuals to avoid confounding from multiple pregnancies in the time period?

Response: We placed these sensitivity analyses in Appendix 3. We revised the text as follows: "*In sensitivity analyses, we examined the association between endometriosis and severe maternal morbidity in primiparous pregnancies, pregnancies conceived spontaneously without assisted reproductive technology, and singleton pregnancies without comorbidity*" (lines 117-119).

R1.7. Line 113- the evaluation of patients with and without ART is a strength of the study.

Response: We thank the Reviewer.

Results:
R1.8. Line 122- the largest group was actually diagnosed after delivery. What was the average time period to from pregnancy to diagnosis of endometriosis? As the authors conclude that these findings may help guide pregnancy management this is not necessarily possible if the majority of patients did not have this diagnosis prior to pregnancy.

Response: We added that "*The average time between delivery and diagnosis of endometriosis post pregnancy was 11.6 years*" (lines 128-129) and that "*In sensitivity analyses of post pregnancy endometriosis, endometriosis diagnosed within 5 years of delivery was more strongly associated with severe maternal morbidity, suggesting that some cases may have already been active during pregnancy (Appendix 4)*" (lines 179-182). We rewrote the conclusions to focus on active endometriosis, where the associations were strongest: "*Effective management of active endometriosis and closer follow-up during pregnancy could potentially mitigate these risks*" (lines 281-282). Post pregnancy endometriosis was less strongly associated with adverse maternal outcomes.

R1.9. Table 1- additional characteristics that would be helpful to include are cesarean history and history of ART.

Response: We added this information in Table 1. We also added the limitation that "*We lacked data on potential confounders such as race, prepregnancy body mass index, age at menarche, prior history of cesarean section, and prior use of assisted reproductive technology*" (lines 262-264).

R1.10. Table 3- bold or starring of the statistically significant findings would make the table more readable.

Response: We bolded the statistically significant findings and thank the Reviewer.

Discussion
R.1.11. The discussion is somewhat lengthy and can be cut down and with increasing focus on the aspects that are similar and different from existing literature. The conclusions are well supported by the data.

Response: We shortened the Discussion to highlight the main findings in relation to existing literature.

R.1.12. Line 269- why was BMI, race and ethnicity unattainable? Is this due to the current form of data collection? If so an additional limitation would be of the accuracy of discharge data.

Response: We clarified that "*These data were not collected in discharge records*" (lines 264-265).

Reviewer #2:

R2.1. This is a large retrospective cohort study quantifying the association between endometriosis and severe maternal morbidities. Although the associations of endometriosis in relation to some maternal morbidities have been studied before such as PIH, this study specifically looked at a group of severe comorbidities that could be life-threatening, the information is novel and has strong clinical implications. Another merit is the large sample size and a good representation of the target population in the study region. However, there are some concerns that need to be addressed.

Response: We thank the Reviewer for these comments.

R2.2. One concern is the misclassification of the exposure. Endometriosis could be seriously underdiagnosed although the proportion may present variations across regions. I am concerned that only considering those who had laparoscopically-confirmed endometriosis as the exposure group brings significant information bias. Ideally, it would be helpful to classify those who have symptoms or are suspected to have endometriosis into a separate group, but not to assume that they are the non-exposure group. Another problem with the exposure assessment is the timing of endometriosis diagnosis. It is good that the delay in diagnosing endometriosis is considered so that post pregnancy diagnosis is included. But I am not convinced that endometriosis diagnosed 10 years after pregnancy is likely to affect the preceding pregnancy. Not defining a cut-off for post pregnancy brings concerns about the inverse temporal relationship. A further question is if it is possible to consider the severity of endometriosis in exposure assessment. Dividing the total population into two distinctive groups as the main analysis looks suboptimal.

Response: We agree with the Reviewer, but did not have data on symptomatic patients with unconfirmed endometriosis. We clarified that "*Patients with undiagnosed endometriosis may have been misclassified as unexposed. Errors in classification of exposures or outcomes may dilute the difference between groups and attenuate the association between endometriosis and severe maternal morbidity towards the null*" (lines 265-268). Unfortunately, we did not have data on the severity of endometriosis. We added the limitation that "*We could not assess the severity of endometriosis in this study. Patients with active endometriosis during pregnancy may include the most severe cases*" (lines 268-270).

We further clarified that "*The average time between delivery and diagnosis of endometriosis post pregnancy was 11.6 years*" (lines 128-129) and that "*In sensitivity analyses of post pregnancy endometriosis, endometriosis diagnosed within 5 years of delivery was more strongly associated*

with severe maternal morbidity, suggesting that some cases may have already been active during pregnancy (Appendix 4)" (lines 179-182).

R2.3. For outcome, it would be interesting to know how the deceased women were handled in the analysis as severe maternal morbidity are life-threatening. Association between severe maternal morbidity and endometriosis should not be dependent on the condition that women will be alive. It would be helpful to clarify if a composite outcome of morbidities and mortality was used.

Response: We confirm that we included mortality in the outcome. We clarified that "*Severe maternal morbidity was measured as a composite outcome of severe preeclampsia, eclampsia, severe hemorrhage, cardiac complications, cerebrovascular accidents, embolism, shock, disseminated intravascular coagulation, sepsis, acute renal failure and dialysis, uterine rupture, hysterectomy, surgical complications, intensive care unit admission, assisted ventilation, and rare complications such as hepatic failure, respiratory distress syndrome, inverted uterus, and mortality.*[11]" (lines 87-92).

R2.4. Line 104. Here said the prevalence of severe maternal morbidity was calculated. Incidence rather than prevalence should be reported because this is a cohort study and the endpoint occurs alongside follow up. Given the nature of follow up, person-time incidence rate should be reported.

Response: We calculated the prevalence because we did not have person-time denominators. The denominator consisted of numbers of women in a fixed population and there was no time-to-event (Noordzij 2010).

Noordzij M, et al. Measures of disease frequency: prevalence and incidence. Nephron Clin Pract. 2010;115(1):c17-20

R2.5. More details regarding clustering of pregnancies need to be provided. It seems genearalized linear model with robust estimators was used. Does this imply it is not possible to link pregnancies to individuals? If so, this needs to be clarified and acknowledge as a limitation.

Response: We confirm that a woman could have more than one pregnancy and that pregnancies could be clustered. We clarified that "*As patients could have more than one pregnancy, we used generalized estimating equations with robust estimators to account for intraclass correlation*" (lines 113-115). Generalized estimating equations can be used when pregnancies can be linked within an individual, which was the case in this study (Hanley 2003; Hubbard 2010).

Hanley JA. et al. Statistical analysis of correlated data using generalized estimating equations: an orientation. Am J Epidemiol. 2003;157:364-75.

Hubbard AE. et al. To GEE or not to GEE: comparing population average and mixed models for estimating the associations between neighborhood risk factors and health. Epidemiology. 2010;21:467-74.

R2.6. It is important to report how missing data were handled in a large study like this. If no measures were taken, report the proportion of missing and explain why it is safe to do so.

Response: We revised the manuscript as follows: "*We had missing values for maternal socioeconomic status (5.9%) and place of residence (3.1%), and accounted for missing data as separate categories in the analysis*" (lines 103-105). Table 1 provides additional information on the missing data.

Minor issues.

R2.7. Line 38-39. This sentence looks redundant.

Response: We removed the sentence and thank the Reviewer.

R2.8. Line 32. It is not accurate to state the follow up time is 32-year as women enter the cohort in different years. This should be reported in results as median and range.

Response: We deleted this material from the manuscript during revision.

R2.9. Line 116-117. Good to provide name of IRB, date and approval number.

Response: We added ethics information as follows: "*we obtained an ethical waiver for data usage from the institutional review board of the University of Montreal Hospital Centre*" (lines 121-122).

R2.10. Line 184-185. As this study is confined to associations. It is not justified to suggest active management of endometriosis could reduce severe maternal morbidity. Suggest removing.

Response: We removed the text as suggested.

R2.11. As a good number of outcomes were tested, multiplicity should be considered. I suppose it is all right not to control for multiplicity given the exploratory nature of the study. But this should be acknowledged and warnings should be given regarding false positives.

Response: We added the following word of caution: "*Active endometriosis was strongly associated with the risk of status asthmaticus and placenta previa with transfusion. However, the reason for the association is unclear. The findings should be interpreted with caution as these outcomes are rare. We do not know the extent to which the results may be false positives, as we did not correct the data for multiple comparisons to minimize the chance of false negatives. These associations should be explored in future studies*" (lines 255-259).

Reviewer #3:

R3.1. This paper seeks to understand the relationship between inactive and active endometriosis and its impact on maternal morbidity. It is a novel and interesting topic that relates a relatively common gynecologic condition with very important obstetrics metrics. The strength of the study is that it includes a statistically impressive number of patients, has a good study design, and awareness of the limitations of the study. The weakness of the study is the overall low relative risk between maternal endometriosis and maternal morbidity. This translates to low clinical significance with the exception of the few categories that have a relatively high relative risk. It is also unclear how the diagnosis of active versus inactive in endometriosis can be made during pregnancy without laparoscopy to confirm disease activity during pregnancy. It seems that severe versus non-severe disease could be a different and more objective way of categorizing endometriosis. It could then be implied that severe disease (defined as requiring surgical intervention) May indicate that there are more inflammatory cytokines and markers that could contribute to increased maternal morbidity. Lastly, given that endometriosis is relatively progesterone resistant it may be worth considering the association between endometriosis and miscarriage and preterm birth as a future research endeavor.

Response: We thank the Reviewer for these comments. We clarified that we "*defined active endometriosis as endometriosis that required clinical management for pelvic pain or other related symptoms during pregnancy*" (lines 76-77). We confirm that active endometriosis may include more severe cases, however we could not test this possibility. We added the limitation that "*We could not assess the severity of endometriosis in this study. Patients with active endometriosis during pregnancy may include the most severe cases*" (lines 268-270). We also added that "*Further research is required to understand the relationship between endometriosis and risk of miscarriage and preterm birth*" (lines 272-273).

R.3.2. Endometriosis as a risk factor for severe maternal morbidity is an interesting and novel association. As mentioned in the paper, hypertensive disorders of pregnancy and endometriosis have been investigated. This association may have more clinical Importance given relatively common incidence of hypertension in pregnancy. Using maternal morbidity with a relative risk association does not translate into clinical significance with relative risk of less than two given me uncommon nature of severe maternal mortality. It would be helpful to include the absolute increased risk in the calculations to see the clinical impact endometriosis has a maternal and morbidity.

Response: We placed the absolute prevalence of outcomes in Appendix 2, to provide an estimate of the absolute increased risk for endometriosis relative to no exposure. In the results, we wrote that "*The most common morbidities among patients with active endometriosis were sepsis (16.3 per 1,000 deliveries), severe preeclampsia and eclampsia (13.9 per 1,000 deliveries), and severe hemorrhage (10.9 per 1,000 deliveries) (Appendix 2)*" (lines 144-146).

R3.3. Notably, two of the maternal morbidity categories have a relatively impressive relative risk, namely maternal status asthmaticus and placental abnormalities. Given the large relative risks associated with these conditions it would be worth spending more time exploring this in the discussion. This is a powerful part of the study that deserves more attention. This could be a fruitful area for future research.

Response: We agree that these findings are interested and have added that "*Active endometriosis was strongly associated with the risk of status asthmaticus and placenta previa with transfusion. However, the reason for the association is unclear. The findings should be interpreted with caution as these outcomes are rare. We do not know the extent to which the results may be false positives, as we did not correct the data for multiple comparisons to minimize the chance of false negatives. These associations should be explored in future studies*" (lines 255-259).

STATISTICAL EDITOR COMMENTS:

E1.1. Table 1: Should include column totals at top or bottom of columns.

Response: We included column totals at the bottom of Tables 1 and 2.

E1.2. Tables 3, 4: Suggest emboldening or otherwise identifying the RRs and aRRs that were statistically significant.

Response: We bolded the statistically significant findings as suggested by the Editor.

E1.3. General: The study includes data from a 32-year period. Need to include year of pregnancy or categories by increments of years to include any temporal changes.

Response: We included year of pregnancy in categories in Table 1, and adjusted for this variable in all regression models.

E1.4. Also, the unit of observation (lines 53-54) appears to be pregnancy, rather than by individual. That is, what adjustment was made for multiple pregnancies for an individual woman? There is likely some correlation of outcomes, i.e., the events are not independent. Thus, there is the potential for bias and imprecision in the estimates. Need to address by either (1) randomly choosing one pregnancy per woman or (2) adjusting for intraclass correlation.

Response: We confirm that individuals may have had multiple pregnancies, and clarified that "*As patients could have more than one pregnancy, we used generalized estimating equations with robust estimators to account for intraclass correlation*" (lines 113-115). In addition, we clarified that "*In sensitivity analyses, we examined the association between endometriosis and severe maternal morbidity in primiparous pregnancies*" (lines 117-118). We used the first pregnancy rather than a random pregnancy to rule out parity as a confounder.

EDITORIAL OFFICE COMMENTS:

E2.1. If your article is accepted, the journal will publish a copy of this revision letter and your point-by-point responses as supplemental digital content to the published article online. You may opt out by writing separately to the Editorial Office at em@greenjournal.org, and only the revision letter will be posted.

Response: We accept to publish the point-by-point responses.

E2.2. 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:
*** Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and at the end of the abstract. For industry-sponsored studies, describe on the title page how the funder was or was not involved in the study.**
*** 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.**

Response: We confirm that the revised manuscript now includes funding and ethics information.

E2.3. Obstetrics & Gynecology's Copyright Transfer Agreement (CTA) must be completed by all authors. When you uploaded your manuscript, each coauthor received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please ask your coauthor(s) to complete this form, and confirm the disclosures listed in their CTA are included on the manuscript's title page. If they did not receive the email, they should check their spam/junk folder. Requests to resend the CTA may be sent to em@greenjournal.org.

Response: We confirm that each coauthor completed their authorship form.

E2.4. ACOG uses person-first language. Please review your submission to make sure to center the person before anything else. Examples include: "People with disabilities" or "women with disabilities" instead of "disabled people" or "disabled women"; "patients with HIV" or "women with HIV" instead of "HIV-positive patients" or "HIV-positive women"; and "people who are blind" or "women who are blind" instead of "blind people" or "blind women."

Response: We confirm that we used person-first language.

E2.5. The journal follows ACOG's Statement of Policy on Inclusive Language (HYPERLINK). When possible, please avoid using gendered descriptors in your manuscript. Instead of "women" and "females," consider using the following: "individuals;" "patients;" "participants;" "people" (not "persons"); "women and transgender men;" "women and gender-expansive patients;" or "women and all those seeking gynecologic care."

Response: We confirm that we respected the American College of Obstetricians and Gynecologists' Statement of Policy on Inclusive Language.

E2.6. 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 HYPERLINK. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

Response: We confirm that Obstetric Data definitions were used in this manuscript.

E2.7. Make sure your manuscript meets the following word limit. The word limit includes the manuscript body text only (for example, the Introduction through the Discussion in Original Research manuscripts), and excludes the title page, précis, abstract, tables, boxes, and figure legends, reference list, and supplemental digital content. Figures are not included in the word count.

Original Research: 3,000 words

Response: We confirm that the manuscript respects the word limit.

E2.8. For your title, please note the following style points and make edits as needed:
*** Do not structure the title as a declarative statement or a question.**
*** Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles.**
*** Abbreviations, jargon, trade names, formulas, and obsolete terminology should not be used.**
*** Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," "A Systematic Review," or "A Cost-Effectiveness Analysis" as appropriate, in the subtitle. If your manuscript is not one of these four types, do not specify the type of manuscript in the title.**

Response: We confirm that we followed manuscript guidelines.

E2.9. Specific rules govern the use of acknowledgments in the journal. Please review the following guidelines and edit your title page as needed:

*** 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 or indicate whether the meeting was held virtually).**

*** 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]."**
*** Do not use only authors' initials in the acknowledgement or Financial Disclosure; spell out their names the way they appear in the byline.**

Response: We confirm that we acknowledged the appropriate entities.

E2.10. Be sure that each statement and any data in the abstract are also stated in the body of your manuscript, tables, or figures. Statements and data that appear in the abstract must also appear in the body text for consistency. Make 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 manuscript.

In addition, the abstract length should follow journal guidelines. Please provide a word count.

Original Research: 300 words

Response: We confirm that we followed guidelines for the abstract.

E2.11. Only standard abbreviations and acronyms are allowed. A selected list is available online at HYPERLINK. 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.

Response: We confirm that we followed guidelines for abbreviations.

E2.12. 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.

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

Express all percentages to one decimal place (for example, 11.1%"). Do not use whole numbers for percentages.

Response: We confirm that we followed these guidelines.

E2.13. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available at HYPERLINK.

Response: We confirm that the tables conform to journal style.

E2.14. Please review examples of our current reference style at HYPERLINK. 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 formal reference list. Please cite them on the line in parentheses.

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 HYPERLINK (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. In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript.

Please make sure your references are numbered in order of appearance in the text.

Response: We confirm that we followed these guidelines.

E2.15. Each supplemental file in your manuscript should be named an "Appendix," numbered, and ordered in the way they are first cited in the text. Do not order and number supplemental tables, figures, and text separately. References cited in appendixes should be added to a separate References list in the appendixes file.

Response: We confirm we formatted the supplemental files as requested.

E2.16. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at HYPERLINK.

If your article is accepted, you will receive an email from the Editorial Office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.

Response: We thank the Editor.

Date: Aug 02, 2022
To: "Nathalie Auger" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-22-1006R1

RE: Manuscript Number ONG-22-1006R1

Endometriosis and severe maternal morbidity: a retrospective cohort study

Dear Dr. Auger:

Your revised manuscript has been evaluated by the Editors. We thank the authors for their responsiveness to the prior review and clarifications. However, the fact that the average lag time between pregnancy and post-delivery endometriosis was 11.6 years raises concern as to the biologic plausibility that endometriosis was present during pregnancy. Given this limitation, we ask the authors to consider revising their primary analysis limiting the cases of post pregnancy endometriosis to those diagnosed in a shorter time frame (perhaps 1-2 years) after delivery. The present analysis including all patients with post delivery endometriosis could be included as a sensitivity analysis.

You will receive an edited MS Word version of your manuscript from Randi Zung (rzung@greenjournal.org). This file contains additional queries and style edits from the Editorial Office. Please address these queries in addition to the Editor's request above.

The queries from the manuscript are as follows:

1. Title: Please note the edits to the title.

2. References: Please check your References list against the manuscript text to make sure they are cited in order at first mention and not duplicative.

If the editor has deleted text from your manuscript, review the references to ensure they aren't affected. If they are, please renumber them as needed.

3. Appendix: The latest version of your Appendix file is being returned to you in case you need to make additional edits.

If you submit a revision, we will assume that it has been developed in consultation with your coauthors and that each author has given approval to the final form of the revision. The next version of your manuscript should be uploaded to Editorial Manager by Aug 23, 2022.

Sincerely,

Jason D. Wright, MD
Editor-in-Chief

Dr. Jason D. Wright, MD
Editor-in-Chief
Obstetrics & Gynecology

16 August 2022

Re: Submission – Original research

Dear Dr. Wright,

We are pleased to submit a revised version of our article "Association of Endometriosis and Severe Maternal Morbidity". We incorporated the requested corrections and provide below a point-by-point response to each comment. We hope that you will be pleased with the changes.

Thank you for considering our work for publication in *Obstetrics & Gynecology*. We look forward to hearing from you.

Kind regards,

Nathalie Auger MD

RESPONSE TO REVIEW

Editor-in-Chief:

E1.1. Your revised manuscript has been evaluated by the Editors. We thank the authors for their responsiveness to the prior review and clarifications. However, the fact that the average lag time between pregnancy and post-delivery endometriosis was 11.6 years raises concern as to the biologic plausibility that endometriosis was present during pregnancy. Given this limitation, we ask the authors to consider revising their primary analysis limiting the cases of post pregnancy endometriosis to those diagnosed in a shorter time frame (perhaps 1-2 years) after delivery. The present analysis including all patients with post delivery endometriosis could be included as a sensitivity analysis.

Response: We restricted post pregnancy endometriosis to the 2 years following delivery and provide results for endometriosis diagnosed anytime post pregnancy in Appendix 4.

EDITORIAL OFFICE COMMENTS:

E2.1. Title: Please note the edits to the title.

Response: We agree with the revised title and thank the Editor.

E2.2. References: Please check your References list against the manuscript text to make sure they are cited in order at first mention and not duplicative.

If the editor has deleted text from your manuscript, review the references to ensure they aren't affected. If they are, please renumber them as needed.

Response: We confirm that the references were not affected and are correctly cited.

E2.3. Appendix: The latest version of your Appendix file is being returned to you in case you need to make additional edits.

Response: We have updated the Appendix file.