

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)*

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obgyn@greenjournal.org.

Date: Mar 28, 2019
To: "Leslie V Farland" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-325

RE: Manuscript Number ONG-19-325

Endometriosis and Risk of Adverse Pregnancy Outcomes

Dear Dr. Farland:

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

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

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Apr 18, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: This is a retrospective cohort study using the Nurses' Health Study II data base looking at obstetrical outcomes compared between women with laparoscopically proven endometriosis and those without. Nearly 117,000 women were included and nearly 200,000 pregnancies. The adverse pregnancy outcomes studied were spontaneous miscarriage (SAB), ectopic pregnancy, stillbirth, GDM, HTN DO of pregnancy, PRB and low birthweight. The study found that endometriosis was associated with a greater risk in all outcomes evaluated and varied by age, infertility and parity. The authors conclude that an association between laparoscopically-confirmed endometriosis and these adverse pregnancy outcomes should prompt further studies to focus on the potential biologic pathways to inform screening or preventative interventions. Ways in which this manuscript could be improved include:

1. Lines 106-108: I know this is a hard thing to quantify, but any data on the role of adenomyosis and these outcomes? It would be reasonable to hypothesize that myometrial endometriosis may be a potential mechanism as well.
2. Line 122: What is the data on visualized diagnosis and biopsy proven? I would guess there would have been no way to have that data with this data set, but I would comment her about the differences.
3. Lines 126-128: Did the questionnaire vary year by year, or was it standardized? I would make sure to clarify.
4. Line 163-164: Why did you use BW as opposed to EGA corrected SGA? This seems like an odd methodology? Is it utilized in any of the other studies you cite?
5. Line 256-257: This sentence is awkward, I would take out or re-word "for many years."
6. Line 260: Again what is the "gold standard." Biopsy or visualization?
7. Lines 275-278: How does your study improve on this study. What were the differences? I would expand.
8. Lines 317-321: Are these really valid assessment if EGA is not controlled for?
9. Lines 326-327: Is this because the date of laparoscopy was not elucidated?

Reviewer #2: 1.This is an interesting manuscript, however authors have made some assumptions and need some more information before they reach their conclusion.

2. There is no information about the controls in this study, except for the fact that the comparison is between the patients with diagnosis of endometriosis with and without laparoscopic diagnosis.

3. There are no data about prior h/o D&C, multiple gestation, placental abnormalities such as previa, accreta, associated fibroid uterus, incompetent cervix, prior termination of pregnancy and other co-morbidities that may exist.

4. This is a unique population, who may have different work schedules.

Besides, details of smoking, race and ethnicity stress factor, history over time period is also important.

5. They have given some data, but have neither given hypothesis nor the possible mechanism as to how those might lead to poor outcome.

6. Why did the authors describe BMI at age 18?

7. Difference of 96% and 54% in those who underwent laparoscopy and those who did not, may explain the degree of endometriosis in these groups.

8. Authors need to address all these factors to make the manuscript more appealing.

Reviewer #3: The authors present a large cohort study from the Nurses' Health Study II on the association between laparoscopically confirmed endometriosis and adverse pregnancy outcomes. The paper is overall well written and provides important data. I have only a few comments:

1) On page 9, under results: The last paragraph is difficult to understand. How can the data on predated endometriosis and non-laparoscopic confirmed endometriosis be reported and robust but also not tabulated? This requires clarification.

2) In table 1: Why aren't standard BMI categories for normal, overweight, obese, etc. used? Also the majority of subjects have a BMI <22.5 which is dramatically different than the general US population. How does the leanness of the population affect the results and generalizability of the study? Since obesity increases the risk for adverse pregnancy outcomes, the low average BMI of this study probably makes the associations even stronger, but absolutely needs to be addressed. I'm lucky if I see 1 patient a day with a BMI <22.5.

3) The majority of pregnancies occurred prior to 1989. Since then has the diagnostic criteria for endometriosis or any of the adverse outcomes studied such as preeclampsia changed that may have affected the results? This needs to be discussed.

4) Did they have any information on the stage of endometriosis?

STATISTICAL EDITOR'S COMMENTS:

1. lines 180-181, 68-70, 72-75: Since there were 116 K women, but 196 K pregnancies, the Author adjusted for repeat pregnancies for each individual. Should also report how many pregnancies there were per women in each cohort, since the results may be weighted towards women without endometriosis, if they had fewer pregnancies per woman.

2. lines 128: Were the follow-up rates statistically similar for endometriosis vs non or were there differential rates that might have biased the results?

3. lines 151-153: Since there were 7 outcomes of interest and the samples very large, should use a stricter inference threshold than 95% CIs. Several of the multivariable adjusted RRs in Table 2 (eg, stillbirth, PTB and LBW) would then not be statistically significant.

4. Tables: If there are any missing data, should enumerate (could be in supplemental material, but with reference to frequency in main text.)

5. Table 1: Should compare statistically the characteristics listed for any relevant baseline or current differences between the cohorts.

6. Table 2: Should include comparison of crude RR to inform reader of the results of the age adjustment of model RR (a). Also, should supplement this explanation of relative risks to include NNT(Harm) with CIs. This would give more context for the absolute magnitude of risk associated with endometriosis in this cohort.

7. Table 3: Although many of these stats tests were NS, in many cases, the denominators (counts of adverse events) were small, thus raising two issues: (1) inadequate power and (2) an overfitted model. The later is specifically an issue for ectopics, stillbirth, GDM (by maternal age) and LBW (by maternal age).

8. Supplemental table 1: Same issue of over fitted model for all except for spontaneous AB, pre-eclampsia, GHTN, PTB.

EDITORIAL OFFICE COMMENTS:

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

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

2. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Any author agreement forms previously submitted will be superseded by the eCTA. During the resubmission process, you are welcome to remove these PDFs from EM. However, if you prefer, we can remove them for you after submission.

3. Our journal requires that all evidence-based research submissions be accompanied by a transparency declaration statement from the manuscript's lead author. The statement is as follows: "The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained."

*The manuscript's guarantor.

If you are the lead author, please include this statement in your cover letter. If the lead author is a different person, please ask him/her to submit the signed transparency declaration to you. This document may be uploaded with your submission in Editorial Manager.

4. All submissions that are considered for potential publication are run through CrossCheck for originality. The following lines of text match too closely to previously published works. Variance is needed in the following sections:

a. LINES 123-142: Please cite the article "A prospective cohort study of endometriosis and subsequent risk of infertility" here, and note that these methods have been described previously.

5. 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 and gynecology data definitions at <https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize>. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

6. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) 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).

8. Provide a précis on the second page, for use in the Table of Contents. The précis is a single sentence of no more than 25 words that states the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstract's conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Please avoid phrases like "This paper presents" or "This case presents."

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

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

10. 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.

11. 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.

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.

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Please note that 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.

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

If you submit a revision, we will assume that it has been developed in consultation with your co-authors 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 Apr 18, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2017 IMPACT FACTOR: 4.982

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

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: <https://www.editorialmanager.com/ong/login.asp?a=r>) Please contact the publication office if you have any questions.

RE: ONG-19-325R1

Title: Endometriosis and Risk of Adverse Pregnancy Outcomes

Reviewer Comments:

Reviewer #1:

This is a retrospective cohort study using the Nurses' Health Study II data base looking at obstetrical outcomes compared between women with laparoscopically proven endometriosis and those without. Nearly 117,000 women were included and nearly 200,000 pregnancies. The adverse pregnancy outcomes studied were spontaneous miscarriage (SAB), ectopic pregnancy, stillbirth, GDM, HTN DO of pregnancy, PRB and low birthweight. The study found that endometriosis was associated with a greater risk in all outcomes evaluated and varied by age, infertility and parity. The authors conclude that an association between laparoscopically-confirmed endometriosis and these adverse pregnancy outcomes should prompt further studies to focus on the potential biologic pathways to inform screening or preventative interventions. Ways in which this manuscript could be improved include:

Thank you for your constructive comments. We hope the modifications we have made based on your feedback help to strengthen the manuscript.

1. Lines 106-108: I know this is a hard thing to quantify, but any data on the role of adenomyosis and these outcomes? It would be reasonable to hypothesize that myometrial endometriosis may be a potential mechanism as well.

We agree that adenomyosis may play a role in adverse pregnancy outcomes among women with endometriosis. Unfortunately, the Nurses' Health Study II did not collect information on this endpoint. However, adenomyosis can only be validly diagnosed at hysterectomy, which was infrequently and inconsistently utilized for the determination of presence or absence of adenomyosis during the study. Even current hospital-system based studies such as that based in Scotland, are impacted by the reality that the validity and reliability of an adenomyosis diagnosis is highly variable based on the hospital site, quality and gynecologic focus of the radiology and pathology staff, and direct attention and interest of the gynecologic specialists. As of now, the most widely used textbook for pathology education in US medical schools dedicates less than one full page to the hallmarks and diagnosis of adenomyosis. It is an area of women's health discovery that is critical to address in the coming years in both the scientific and clinical settings. It is quite likely that adenomyosis is an effect modifier of the relationship between endometriosis and pregnancy outcomes. We have added this briefly to the limitations section (Lines 364-366):

“Endometriosis was defined by surgical visualization. Within this large, geographically diverse cohort across multiple decades, information was not routinely nor uniformly available on endometriosis biopsy confirmed pathology, lesion location, rASRM stage, nor adenomyosis status.”

2. Line 122: What is the data on visualized diagnosis and biopsy proven? I would guess there would have been no way to have that data with this data set, but I would comment her about the differences.

Our study defined endometriosis by visualized surgical diagnosis. During the time period of this study and indeed, in many hospitals and clinics in the US now, pathology confirmation is not sought nor determined as having high enough specificity for endometriosis diagnosis (1). Within this cohort, a review of nearly 1,000 medical records from those self-reporting endometriosis confirmed the high validity of surgically visualized diagnosis but revealed that <10% of surgeries sought pathology confirmation. We have been more precise in our wording to clarify this in the study methods (Lines 135-137):

“Women were asked on each biennial questionnaire from 1993 onwards whether they had physician-diagnosed endometriosis. Participants who responded ‘yes’ indicated the year of diagnosis and whether it had been visually-confirmed by laparoscopy, the clinical gold standard for endometriosis diagnosis (2-4).”

Additionally, as outlined in response 1, we have added a discussion of this issue to the limitations section.

3. Lines 126-128: Did the questionnaire vary year by year, or was it standardized? I would make sure to clarify.

When items were asked on repeated questionnaires, they were worded / presented consistently. However, there are some domains and components of the Nurses’ Health Study II questionnaire that are added and removed from year to year. The questionnaires are built biennially through a lengthy large group process that includes extensive confirmation. All questionnaires from the original cohorts’ inception have been made publicly available since the existence of internet presence (<https://www.nurseshealthstudy.org/participants/questionnaires>), and these have been used as the basis for myriad studies across the US and globe. We have clarified this point in the methods text (Lines 126-129).

“At baseline and every two years thereafter, participants completed self-administered questionnaires, with questions that were consistent across biennial questionnaires as well as newly-added domains that varied by questionnaire, to capture detailed information on a variety of lifestyle and reproductive characteristics and to update health-related outcomes.”

4. Line 163-164: Why did you use BW as opposed to EGA corrected SGA? This seems like an odd methodology? Is it utilized in any of the other studies you cite?

We agree that small for gestational age is an important clinically relevant endpoint. Unfortunately, our questionnaire asked about birthweight and gestational age in categories. This improves the accuracy of recall, but prevents us from creating Z-scores to estimate small for gestational age. For our analysis of low birth weight, gestational

age was accounted for in the statistical multivariable models as has been done in previous NHSII analyses (5) (Lines 202-203).

The outcome of low birth weight has been of interest and reported in prior analyses. Indeed, the meta-analysis we compare to in the manuscript's discussion (Lines 336-338) is from twelve prior studies investigating the relationship between endometriosis and low birth weight (6), and we have applied those methodologic approaches.

5. Line 256-257: This sentence is awkward, I would take out or re-word "for many years."

We have modified this sentence (Lines 271-273):

"Recently, the relationship between endometriosis and adverse pregnancy outcomes has been an important topic of research (6-8) but has yielded mixed results."

6. Line 260: Again what is the "gold standard." Biopsy or visualization?

Visualization was considered the gold standard for our analysis. As discussed previously, this decision was borne out by the professional society guidelines of the day and current evidence of biopsy specificity, as well as the low prevalence of pathologic evaluation found in the medical records of the women who reported surgically confirmed endometriosis. We have modified the manuscript to add clarity around this issues as outlined in Response to Question #1 above.

7. Lines 275-278: How does your study improve on this study. What were the differences? I would expand.

We have added further discussion of this (Discussion Lines:288-290):

"While prior research on this topic has been mixed (9-11) possibly due to heterogeneity in endometriosis definitions and populations, our data, using a prospective cohort study investigating surgically confirmed endometriosis cases, support the findings of a recent meta-analyses that found that women with endometriosis had a 75% greater risk of SAB (n=9 studies) (8) and a 29% greater risk of stillbirth (n=7 studies) (6) compared to women without endometriosis."

8. Lines 317-321: Are these really valid assessment if EGA is not controlled for?

As discussed in Response to Question #4, we are unable in our data to to investigate SGA. However, for the analysis of the outcome of low birth weight, gestational age was accounted for in the analysis applying the methods most commonly utilized in the existing literature (5).

9. Lines 326-327: Is this because the date of laparoscopy was not elucidated?

Correct, for pregnancies occurring before 1989, the date of endometriosis diagnosis was not documented.

Reviewer #2:

1.This is an interesting manuscript, however authors have made some assumptions and need some more information before they reach their conclusion.

Thank you for your helpful and constructive comments to strengthen this manuscript.

2.There is no information about the controls in this study, except for the fact that the comparison is between the patients with diagnosis of endometriosis with and without laparoscopic diagnosis.

For this cohort study, the comparison group was women without a diagnosis of endometriosis. In Table 1, we describe the study population at baseline stratified by endometriosis diagnosis status. In the results section, we discuss the differences between women with and without a diagnosis of endometriosis. Moreover, we treat these differences as potential confounders and account for these differences utilizing the multivariable adjusted models. If there is additional information you would like for us to provide, we would be happy to accommodate.

3.There are no data about prior h/o D&C, multiple gestation, placental abnormalities such as previa, accreta, associated fibroid uterus, incompetent cervix, prior termination of pregnancy and other co-morbidities that may exist.

Utilizing the GEE models for multiple pregnancies contributed per woman, our analysis of hypertensive disorders of pregnancy and preterm birth accounted for prior obstetric outcomes for which we had data (Lines 203-204). You are correct; unfortunately, we were unable to quantify placenta previa, accreta, or incompetent cervix due to lack of adequate data. As you suggest, these are important factors to consider when studying pregnancy outcomes. They are unlikely to confer a confounding effect but may mediate the relationship between endometriosis and subsequent or concurrent obstetric outcomes. We have added a discussion of this issue to our limitation section (Lines 366-369):

“Additionally, we did not have sufficient sample size nor details to investigate the pregnancy endpoints placenta previa, accreta, or incompetent cervix, which may influence the adverse pregnancy outcomes reported.”

4.This is a unique population, who may have different work schedules. Besides, details of smoking, race and ethnicity stress factor, history over time period is also important.

We have previously explored rotating shift work and the distribution by and association with endometriosis, observing associations only among those with

concurrent infertility (12). The associations observed within this cohort for dozens of other health outcomes (13) have been replicated in other populations, with few suggesting that this cohort is wholly unique. However, we certainly agree that race/ethnicity, smoking, and stress are associated with adverse pregnancy outcomes. While stress data was not collected in NHS2 until after the majority of pregnancies occurred and therefore could not be incorporated into these analyses, we did adjust finely for race and ethnicity and cigarette smoking exposures to account for potential confounding. Unfortunately, our population is majority non-Hispanic white – representative of the nursing population across the US at enrollment in 1989, and thus we do not have sufficient statistical power to evaluate effect modification by race or ethnicity.

5. They have given some data, but have neither given hypothesis nor the possible mechanism as to how those might lead to poor outcome.

We described hypothesized mechanisms of association between endometriosis and all adverse outcomes in the introduction lines (99-108):

“There are many hypothesized mechanisms through which endometriosis may be associated with adverse pregnancy outcomes (14). Endometriosis has been hypothesized to alter the uterine environment through progesterone resistance of the endometrium and to influence oocyte quality, which could contribute to adverse embryo development and implantation (6, 7, 14). Additionally, research has shown that women with endometriosis have greater levels of inflammation locally, in the peritoneal cavity, and systemically (15, 16). Inflammation has long been hypothesized in the etiology of adverse pregnancy outcomes including gestational diabetes, hypertensive disorders of pregnancy (gestational hypertension and preeclampsia), and preterm birth (17-19). Women with endometriosis have also been hypothesized to have inadequate uterine contractility (20) and deficient placentation, both of which may influence implantation, fetal growth, and gestation length (7).”

Additionally, in the discussion we outline possible mechanism for each adverse pregnancy outcome discussed.

6. Why did the authors describe BMI at age18?

BMI at age 18 is the standard anthropometric measurement utilized in longitudinal studies to reflect early life body size, as it is the age at which most women have achieved their terminal height and also when their adolescent / early adulthood weight is quantified. In addition to myriad associations with cardiovascular and cancer outcomes (21), BMI at 18 has consistently been shown to be associated with risk of endometriosis (22, 23), with lean women being at higher risk of endometriosis. Thus, we felt it was important to enumerate.

7. Difference of 96% and 54% in those who underwent laparoscopy and those who did not, may explain the degree of endometriosis in these groups.

These proportions are not a difference among those who underwent laparoscopy and do not reflect endometriosis phenotype. Given the possibility of misclassification of endometriosis among women who did not undergo laparoscopy (54% concordance with medical record documentation), our main analysis was restricted to those with laparoscopic visually confirmed endometriosis (96% concordance with medical record documentation). We have clarified this more in the text. Among those with laparoscopic diagnosis and a recorded rASRM stage, 60% were determined to be stage I or II at the time of surgery and thus not skewed toward higher stages of endometriosis (24). As we have found in most other studies of endometriosis, when our analyses were expanded to include all self-reported endometriosis diagnoses, the patterns of association remained consistent but precision was diminished, presumably with the addition of misclassified endometriosis.

8. Authors need to address all these factors to make the manuscript more appealing.

Thank you for your helpful comments. We hope we have adequately addressed the limitations that you have outlined to add clarity for the readers of the Green journal.

Reviewer #3:

The authors present a large cohort study from the Nurses' Health Study II on the association between laparoscopically confirmed endometriosis and adverse pregnancy outcomes. The paper is overall well written and provides important data. I have only a few comments:

Thank you for your feedback. We appreciate your comments and are glad you felt the manuscript provided important data.

1) On page 9, under results: The last paragraph is difficult to understand. How can the data on predated endometriosis and non-laparoscopic confirmed endometriosis be reported and robust but also not tabulated? This requires clarification.

We apologize for the confusion. The data in the sensitivity analyses were consistent with the main results. We do not present the data in the tables. We have clarified this information in the text (Lines 263-266):

“Reported relationships for all adverse outcomes were consistent in sensitivity analyses where endometriosis was pre-dated by 4 or 6 years to account for diagnostic delay and where the definition of endometriosis was expanded to include non-laparoscopically-confirmed endometriosis cases to assess diagnostic bias (data not presented).”

2) In table I: Why aren't standard BMI categories for normal, overweight, obese, etc. used? Also the majority of subjects have a BMI <22.5 which is dramatically different than the general US population. How does the leanness of the population affect the results and generalizability of

the study? Since obesity increases the risk for adverse pregnancy outcomes, the low average BMI of this study probably makes the associations even stronger, but absolutely needs to be addressed. I'm lucky if I see 1 patient a day with a BMI <22.5.

Given the consistent relationship between lean body size and endometriosis (22, 23), we felt it was important to present the lower BMI spectrum, and therefore extended the categorization to include the WHO cutpoints for lean BMI below the clinically oft-used normal category. For BMI at age 18, we used the WHO determined cut-off of 22.5+ for BMI, because the majority of the cohort was below 22.5 (~78-80%) at age 18. This is consistent with general population distributions. When we report current BMI in 1989 (at which time the women were between the ages of 25 and 42), again the cohort has a similar distribution of BMI and obesity compared to the US population at that time (25), and indeed reflective (although still a bit leaner as the US population has become more obese since 1989) of your current patient population among whom leanness is less common.

3) The majority of pregnancies occurred prior to 1989. Since then has the diagnostic criteria for endometriosis or any of the adverse outcomes studied such as preeclampsia changed that may have affected the results? This needs to be discussed.

This is a very important point for a long-term cohort study. In the multivariable model, we adjusted for year of pregnancy to finely account for patterns of change over calendar time. Additionally, in the sensitivity analyses presented in Supplemental Table 1, we restricted to pregnancies occurring after 1989 and compared and contrasted these associations with those observed among pregnancies occurring in all years of the study population. There likely were more missed cases of endometriosis in earlier years than more recent years, which would have biased associations to the null by including those with undiagnosed endometriosis in the comparison group. Overall, the standards for diagnosis of the pregnancy outcomes remained consistent, however there may have been diagnostic trends or changes in awareness over time. This is true for all longitudinal studies, and we completely agree that this needs to be accounted for in analyses where possible, but more importantly, needs to be considered with respect to results interpretation and potential directions and magnitudes of bias. We have added a discussion of this issue to the limitations (Lines 368-370):

“All models were adjusted for year of pregnancy and we conducted sub-analyses that stratified by calendar year; however, we may not be fully accounting for temporal patterns in recognition of endometriosis and adverse pregnancy outcomes over time.”

4) Did they have any information on the stage of endometriosis?

We did not have information on endometriosis stage. As is true currently, given the lack of association with symptom presentation, treatment response, or prognosis, most clinicians do not incorporate rASRM stage into care determination, and, as we found in the review of hundreds of medical records for participants in this cohort, many do not document sufficient information at surgery to determine rASRM stage. In addition, theoretically, the stage would be reflective of the time of diagnosis, with it being impossible to determine

changes in stage proximal to pregnancy. As understanding of endometriosis emerges, we may find that symptoms spectrum or presence or absence of endometrioma or deep endometriosis is more informative than superficial peritoneal disease phenotype. We have added a discussion of this limitation to the manuscript (Lines 364-366):

“Endometriosis was defined by surgical visualization. Within this large, geographically diverse cohort across multiple decades, information was not routinely nor uniformly available on endometriosis biopsy confirmed pathology, lesion location, rASRM stage, nor adenomyosis status.”

STATISTICAL EDITOR'S COMMENTS:

1. lines 180-181, 68-70, 72-75: Since there were 116 K women, but 196 K pregnancies, the Author adjusted for repeat pregnancies for each individual. Should also report how many pregnancies there were per women in each cohort, since the results may be weighted towards women without endometriosis, if they had fewer pregnancies per woman.

We recognize that if cluster size is informative, our model may over-weight certain groups. In Table 1 we report that at cohort baseline in 1989, women with endometriosis had mean (SD) 1.7 (1.1) pregnancies where women without endometriosis had a mean 2.0 (1.2) pregnancies. However, at the end of study follow-up, the mean (SD) and median number of pregnancies were similar between women without endometriosis (mean:1.97 (1.21); median: 2.0) and women with endometriosis (mean:1.49 (1.18); median:2.0). This information has been added to the results (lines 230-232).

2. lines 128: Were the follow-up rates statistically similar for endometriosis vs non or were there differential rates that might have biased the results?

Overall, the women of the NHSII have been exceptional study participants, with follow-up remaining >90% after 30 years. With respect to endometriosis status, follow-up rates were similar between groups.

3. lines 151-153: Since there were 7 outcomes of interest and the samples very large, should use a stricter inference threshold than 95% CIs. Several of the multivariable adjusted RRs in Table 2 (eg, stillbirth, PTB and LBW) would then not be statistically significant.

Given the recent commentaries raising into question the dichotomization of statistical significance (26-28), in conjunction with a broader discussion by the American Statistical Association about the appropriateness of p-values and statistical significance (29), we would prefer not to modify our inference threshold from the standard / ubiquitous 95% to minimize the type I error (30), as we have discussed in previous commentaries for the reproductive clinical audience (31). If the editor prefers, we can add a discussion of this issue to the manuscript.

4. Tables: If there are any missing data, should enumerate (could be in supplemental material, but with reference to frequency in main text.)

We have added a description of how we addressed missing data to the study methods. Specifically, for pregnancy outcomes, those with missing data were excluded. To address this issue more clearly, we have added a discussion of this point to the manuscript's methods (Lines 167-169).

“Women who reported pregnancy on previous questionnaires, but who were missing pregnancy outcome information on the 2009 pregnancy-questionnaire were excluded (2.5% of pregnancies).”

For covariates, an indicator variable was created to address missing values. We have added information on this to the manuscript (Lines 183-184). In the multivariable model, the missing indicator method creates a specific and separate variable for missing data.

“For covariates with missing data, missing indicator variables were created.”

5. Table 1: Should compare statistically the characteristics listed for any relevant baseline or current differences between the cohorts.

As our team has previously summarized in a commentary directed to reproductive medicine, it is not valid to quantify p-values or attribute statistical significance to population characteristics presented in the typical Table 1 (31). The purpose of Table 1 is to describe the demographic make-up of the women with and without endometriosis in our analytic population. Given the large sample size, unimportant correlations may achieve the threshold for statistical significance without biologic significance or relevance. Therefore, we prefer not to add p-values to compare our baseline characteristics as we have discussed in previous commentary (21), based on guidance from the American Statistical Association. Our choice of potential confounders was based on *a priori* hypothesized relationships between the confounder and adverse pregnancy outcomes.

6. Table 2: Should include comparison of crude RR to inform reader of the results of the age adjustment of model RR (a). Also, should supplement this explanation of relative risks to include NNT(Harm) with CIs. This would give more context for the absolute magnitude of risk associated with endometriosis in this cohort.

The “crude” RR currently presented in our model is adjusted for age, year of pregnancy, and an interaction term between year of pregnancy and our exposure. We chose to include these covariates as the minimum “crude” model purposefully, as is the accepted practice for longitudinal studies. Age is the strongest predictor of adverse pregnancy outcomes. Moreover, given the time range of our pregnancies, it was important to include adjustment for year. We do not feel a model with no adjustment would be informative to the readership, given the importance of these covariates.

We agree that there is an important clinical-translational benefits from presenting absolute values. Therefore, we have provided absolute numbers in the tables. Additionally, in the manuscript text we have added absolute values.

Pregnancy Loss (Lines 235-239)

Gestational diabetes and hypertensive disorders of pregnancy (Lines 245-247)

Preterm birth (255-257)

Low birth weight (Lines 260-261)

7. Table 3: Although many of these stats tests were NS, in many cases, the denominators (counts of adverse events) were small, thus raising two issues: (1) inadequate power and (2) an overfitted model. The later is specifically an issue for ectopics, stillbirth, GDM (by maternal age) and LBW (by maternal age).

We agree that there may be limited power for some of these less common outcomes. Our goal was not to create a prediction model, where overfitting would be of concern, but rather our choice of confounders and potential effect modifiers (maternal age) were based on *a priori* hypotheses and not on statistical significance thresholds. However, it is worth noting that our study included more pregnancies to women with endometriosis than 31 of the 33 studies included in a recent meta-analysis on the topic (6). We have added a discussion of this issue to the manuscript's limitation section (Lines 370-371):

“For some endpoints of interest, there were small number of events that may result in limited statistical power.”

8. Supplemental table 1: Same issue of over fitted model for all except for spontaneous AB, pre-eclampsia, GHTN, PTB.

As described in the response to question #7, the conceptualization of overfitting does not apply to these analyses or results interpretation. However, we certainly agree that our sample size was small for many of these outcomes, despite the large size of our cohort population. It is good for the health of women and infants that these outcomes are rare, but that increases the challenge of scientific discovery. Indeed, compared to the existing literature as evidenced by recent meta-analyses, this study is larger by far than those previously published. We feel that this table is nonetheless important to comprehensively describe to the reader the magnitude of the observed associations and to suggest appropriate interpretation in the context of the sample size and analyses that were feasible. We present age and multivariable adjusted effect estimates in this table.

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