OBSTETRICS & GYNECOLOGY

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

**The corresponding author has opted to make this information publicly available.*

Personal or nonessential information may be redacted at the editor's discretion.

Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office: obgyn@greenjournal.org.

Date: Mar 11, 2022
To: "Alessandra J Ainsworth" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-22-220

RE: Manuscript Number ONG-22-220

Women with a History of Primary Infertility have Increased Rates of Bilateral Oophorectomy

Dear Dr. Ainsworth:

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

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

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

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Apr 01, 2022, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

The purpose of this manuscript was to report "a population-based sample of women with primary infertility, and age-matched referents to evaluate the association between primary infertility and subsequent risk of gynecologic surgery, specifically hysterectomy and/or oophorectomy." This was a retrospective, cohort study using the Rochester Epidemiology Project medical records.

1. Could the authors provide more information on how the control (referent) group was selected for this study? The authors note that the referent group was "randomly selected." How did they randomly select the controls? Did they use a random number generator or other method? Was the referent group selected from a database of women residing in Olmsted county? How was this random sample identified? Were any of the control group infertile? Were the referent group all parous?

2. Could the authors discuss the reliability and validity of data in the Rochester Epidemiology Project medical records in the Materials and Method section?

3. The authors note that the "Baseline demographic data, as of the index date, was manually collected." Who manually collected this data? Did they review the medical records from the Rochester Epidemiology Project Medical records? Was the data extracted from the medical records and recorded on a piloted form? Was the data transferred to an electronic database? What was done to ensure accurate recording and transfer of data? What was done if there was missing data? How was data obtained for the referent group? Did they review the medical records of the referent subjects, did they call the referent subjects and obtain their data, or was the referent group's records also included in the Rochester Epidemiology Project medical records?

4. As this study was from Jan 1,1980 to Dec 31,1999, how many subjects and referents were lost to follow-up? Or was one of the inclusion criteria that they had to remain in Olmsted county during the duration of the study? If the subject or referent left Olmsted County how do they know that they did not have a hysterectomy/oophorectomy with a different medical system?

5. Why did they select the age range between "18-50"? Do the authors have access to the infertility treatments used in this sample? How many had ovulation induction with clomiphene, how many cycles of clomiphene, hMG, number of cycles of hMG, intrauterine insemination, in vitro fertilization, donor eggs or donor embryos (esp for the older cohort)? Was the

increased risk of having a hysterectomy and/or oophorectomy mainly in the patients who underwent IVF or after 6 cycles of clomiphene citrate?

6. How did the authors arrive at their 'n' of 1001 subjects and controls? Did they perform an 'a priori' sample size determination or some other method of determining their sample size? Was this all of the primary infertility patients in their database?

Reviewer #2:

Comments to author:
The authors present a retrospective cohort study looking at the long term risk of bilateral oophorectomy and or hysterectomy in patients with primary infertility compared to an age-matched population referent cohort from the same county in Minnesota. The time period of exposure was from 1980-1999. Cumulative incidence curves for each primary outcome were assessed. Cox proportional hazard models were used to estimated HR for association between primary infertility and outcomes of interest.

Abstract:
Line 7 The objectives should be association vs risk.
Line 11 Why was ratio of 1:1 chosen vs a more robust 1:2 or 1:4?
Line 25-26 The results section is confusion. In line 16-17 it is stated that there was an association between primary infertility and BSO aHR 1.69 CI 1.22-2.33. Please clarify.
Line 27-29 The study design limits conclusions about long term health outcomes.

Introduction:
Line 32-33 The wording of association should more appropriately be the medical conditions, especially DM and other CVD, are associated with infertility. The cause and effect is more in this direction. Ie Pt. with DM has higher chance of being anovulatory which could cause infertility.
Line 38 I would suggest using association vs effect for reasons stated in previous comments.
Line 39-40 The all cause mortality is comparing with or with oophorectomy from Nurses Health study reference 5. Reference 7 was much smaller case control study which did not address or all cause mortality. Be more specific with references and associations. The use of and or is confusing.

Methods:
Line 51-53 What was the total population from which the 1001 patients were chosen? Ie 1001/population-based MPIC cohort
Line 54 How was confirmation confirmed? Was there more than one reviewer and if so what if there was a discrepancy was there a third party to review for inclusion?
Line 59 Did the control cohort include those with 2nd infertility? What were the GnPn of the comparison group? Parity is known to decrease certain risk like ovarian cancer, uterine cancer that may lead to different risks for either BSO +/- hysterectomy.
Line 76-77 Using the last visit for the control may not accurately reflect if the patient moved or had a hysterectomy/BSO out of network. Expand on the data base used and potential risk for misclassification.

Results:
Line 108 Define specifically what is meant by endometriosis and uterine etiology? Did patients have surgically confirmed endometriosis? Was there also tubal factor associated with this?
Table 1 Given the dates of the cohorts do you have a break down of how salpingectomy was preformed? This may have had opportunistic reduction in ovarian cancer/cyst which may bias comparing the two cohorts.
Line 119-120 What is meant be censored? Were these patients excluded? The control group being from lower educational levels and socioeconomic category may never have chosen or could not afford a work up for infertility and this may be underestimated.
Table 2 Why was prior gyn surgery not also included in covariant adjustment? From table 1 this was different and may be related to the primary outcome of interest.
Line 128-130 The lower avg age for BSO is not surprising given the dates 1980-1999. Practices patterns were different without benefit of all cause mortality data from Nurse Health Study. This limits generalizability to modern practice.
Line 139-141 The weights for both groups are quite small. Given higher rates of hysterectomy for AUB and or fibroids this probably does not reflect current treatment options for both. Ie endometrial ablation, IUD, UFE.
Line 141-143 The numbers for comparison are small and there was no difference in pathology. As written it is overstated.
Line 146-151 This statement is confusing and sounds like your saying the same thing. If the infertility cohort had higher rates of hysterectomy with BSO they would have lower rates of hysterectomy with ovarian conservation. Much of this may be related to higher rates of endometriosis and surgical practice at the time. Was this controlled for?

Line 166-167 Were the pregnancy in the infertility cohort spontaneous or through ART?
Line 169-172 The effect of ever being pregnant and time as covariant don't seem to be associated with hysterectomy or BSO P=0.06 and P=0.08. Explain.

Discussion:
Line 184-185 It is not clear what is meant by competing outcomes and dividing them into three catagories. If the objective is more about all cause mortality any BSO should be interpreted together regardless of hysterectomy.
Line 186-187 State what searches were done to claim primacy in finding this association. Given the time period endometriosis was both associated with infertility and potential hysterectomy and BSO so it is not surprising to find this association in the data base.
Line 188-189 What would be done to mediate long term risk with this known association? The overwhelming number of patients in your cohort ended up pregnant. It is hard to make this conclusion by the nature of this study design.
Line 201-203 There is already a known association of many of the outcomes evaluated here. How do these finding differ? The rest of the discussion addresses many of the question in this review

Reviewer #3:

This study was conducted on a validated cohort of women who had undergone evaluation for infertility. The manuscript is well written, concise and clear. I have the following questions for the authors:

1. The study group had higher incidence of endometriosis compared to referent group which is not a surprise. The study group women with endometriosis were more likely to undergo hysterectomy and BSO which is also not a surprise. Is it not a logical conclusion that endometriosis results in hysterectomy and BSO and primary infertility happens to be incidental finding? If we had studied a group of women with endometriosis and compared to referent women, the study group would have increased risk for hysterectomy and BSO. How is this any different? I expected the authors to discuss this aspect thoroughly and openly.
2. Women in the study group underwent hysterectomy for fibroids less often than the women in the study group. I was searching for information on the number of women who underwent myomectomy in the study group. Although this information is available at the index presentation, it is surprisingly missing from data after that. I am confident that the hysterectomy for fibroids was lower in the study group because they underwent myomectomy rather than hysterectomy (some of them many myomectomies I would imagine as they are naturally desperate to keep their uterus and their hopes for a pregnancy in the future).
3. My conclusion on reviewing the data presented is that endometriosis is more prevalent in the infertile women and therefore it increases risk of hysterectomy with BSO subsequently. Hysterectomy for fibroids is lower but data is not presented so one can only surmise that women underwent myomectomy instead of hysterectomy in that group.

STATISTICS EDITOR COMMENTS:

Table 1: In retrospect, it would have been preferable to match on variables besides age, notable race/ethnicity, marital status, education, BMI, rather than having to adjust for those variables at a later stage of analysis.

Table 2: For some of the subsets, the counts of adverse outcomes are not favorable w.r.t. 5 adjustors in the aHR models. On the other hand, some of the CIs are wide, reflecting the small counts of adverse outcomes and limiting power to generalize any NS findings.

Fig 1: Should summarize all stats tests of the K-M curves, either in figure or figure legend. Also, should indicate along the x-axes, the "N" remaining in each group at the indicated time points.

Fig 2: Should indicate in figure legend any stats testing done to compare the cohorts.

Suppl Fig 1: Same comments as in Fig 1 re: stats tests and labelling the x-axes.

EDITORIAL OFFICE COMMENTS:

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

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

2. When you submit your revised manuscript, please make the following edits to ensure your submission contains the required information that was previously omitted for the initial double-blind peer review:
* Include your title page information in the main manuscript file. The title page should appear as the first page of the document. Add any previously omitted Acknowledgements (ie, meeting presentations, preprint DOIs, assistance from non-byline authors).
* Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and in the body text. For industry-sponsored studies, the Role of the Funding Source section should be included in the body text of the manuscript.
* Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable).
* Name the IRB or Ethics Committee institution in the Methods section (if applicable).
* Add any information about the specific location of the study (ie, city, state, or country), if necessary for context.

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

4. For studies that report on the topic of race or include it as a variable, authors must provide an explanation in the manuscript of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, the reasons that race/ethnicity were assessed in the study also should be described (eg, in the Methods section and/or in table footnotes). Race/ethnicity must have been collected in a formal or validated way. If it was not, it should be omitted. Authors must enumerate all missing data regarding race and ethnicity as in some cases, missing data may comprise a high enough proportion that it compromises statistical precision and bias of analyses by race.

Use "Black" and "White" (capitalized) when used to refer to racial categories. The nonspecific category of "Other" is a convenience grouping/label that should be avoided, unless it was a prespecified formal category in a database or research instrument. If you use "Other" in your study, please add detail to the manuscript to describe which patients were included in that category.

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 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.

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 5,500 words. Stated word limits include the title page, précis, abstract, text, tables, boxes, and figure legends, but exclude references.

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

* All financial support of the study must be acknowledged.
* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).
* If your manuscript was uploaded to a preprint server prior to submitting your manuscript to Obstetrics & Gynecology, add the following statement to your title page: "Before submission to Obstetrics & Gynecology, this article was posted to a preprint server at: [URL]."

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

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

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

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

11. ACOG avoids using "provider." Please replace "provider" throughout your paper with either a specific term that defines the group to which are referring (for example, "physicians," "nurses," etc.), or use "health care professional" if a specific term is not applicable.

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.

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

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

13. Line 186: Your manuscript contains a priority claim. We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

14. 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.

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

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

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

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

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

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

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

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

Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce.

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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 open access, you will receive an Open Access Publication Charge letter from the Journal's Publisher, Wolters Kluwer, and instructions on how to submit any open access charges. The email will be from publicationservices@copyright.com with the subject line, "Please Submit Your Open Access Article Publication Charge(s)." Please complete payment of the Open Access charges within 48 hours of receipt.

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

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

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

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Apr 01, 2022, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

John O. Schorge, MD
Deputy Editor, Gynecology

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

MAYO CLINIC

April 25, 2022

Jason D. Wright, MD

Editor-in-Chief, *Obstetrics & Gynecology*

Dr. Wright,

We are grateful for an opportunity to submit revisions for our manuscript entitled “Women with a History of Primary Infertility have Increased Rates of Bilateral Oophorectomy”.

The peer-review process has improved our manuscript in both clarity and depth. We hope our response to reviewers (below) and the substantial edits to our manuscript are now suitable for consideration of publication.

Please contact me if you have any questions. We look forward to your review.

Sincerely,

Alessandra J. Ainsworth
Mayo Clinic Department of Obstetrics and Gynecology
Division of Reproductive Endocrinology and Infertility
[redacted]

Response to Reviewers:

REVIEWER COMMENTS:

Reviewer #1:
The purpose of this manuscript was to report "a population-based sample of women with primary infertility, and age-matched referents to evaluate the association between primary infertility and subsequent risk of gynecologic surgery, specifically hysterectomy and/or oophorectomy." This was a retrospective, cohort study using the Rochester Epidemiology Project medical records.

1. Could the authors provide more information on how the control (referent) group was selected for this study? The authors note that the referent group was "randomly selected." How did they randomly select the controls? Did they use a random number generator or other method? Was the referent group selected from a database of women residing in Olmsted county? How was this random sample identified? Were any of the control group infertile? Were the referent group all parous?
Thank you for these points of clarification. Although this information was included in our cited manuscript, we appreciate that this creates unnecessary work for the reader and have updated our manuscript accordingly. We have added the following text to address these questions: “The matching process was made possible by the availability of a complete enumeration of the Olmsted County population using the REP Personal Timelines (i.e., the REP Census).[12] For each case with primary infertility, all age-matched (±1 y) women residing in Olmsted County on the index date were electronically identified. From that pool of potential referents, 1 age-matched woman was randomly selected based on a random number generator. Referent women were reviewed and replaced if they had a history of infertility at the time of index date. Referent women may have been parous or nulliparous at the time of matching.”

2. Could the authors discuss the reliability and validity of data in the Rochester Epidemiology Project medical records in the Materials and Method section?
Thank you for the recommendation to include this important level of detail. The Rochester Epidemiology Project (REP) has been well-studied and validated when comparing individuals identified by medical records to other population counts by random digit dialing, a list of residents of nursing homes and senior citizen complexes, a commercial list of residents, and manual review of records. The REP census has been comparable to multiple decennial US censuses. These correlations provide a meaningful sample for epidemiologic study. An abbreviated description of this has been added to our Methods section along with a reference.

3. The authors note that the "Baseline demographic data, as of the index date, was manually collected." Who manually collected this data? Did they review the medical records from the Rochester Epidemiology Project Medical records? Was the data extracted from the medical records and recorded on a piloted form? Was the data transferred to an electronic database? What was done to ensure accurate recording and transfer of data? What was done if there was missing data? How was data obtained for the referent group? Did they review the medical records of the referent subjects, did they call the referent subjects and obtain their data, or was the referent group's records also included in the Rochester Epidemiology Project medical records?

Additional detail has been provided in the manuscript to address these questions. Medical records were reviewed by up to three individuals and recorded information on a piloted form. To ensure consistency and refine the data collection tool, AA reviewed the first 50 charts in duplicate, with ES and LKR. Any charts with unclear data were subsequently reviewed by AA. All data was entered into an electronic piloted form within a secure electronic database. Outliers were re-reviewed by AA after the full dataset was reviewed. This chart review included medical records from both women with primary infertility and age-matched referents. Missing data was noted as such.

4. As this study was from Jan 1,1980 to Dec 31,1999, how many subjects and referents were lost to follow-up? Or was one of the inclusion criteria that they had to remain in Olmsted county during the duration of the study? If the subject or referent left Olmsted County how do they know that they did not have a hysterectomy/oophorectomy with a different medical system?
In the results section of the paper, we reported the median and interquartile range for the duration of follow-up, which we defined in the statistical methods as being calculated from the index date to the date of procedure of interest, or the last clinical visit to a REP-affiliated health care professional for those without the procedure of interest. The only residency restriction was at the time of the index date. Being that this was a retrospective study, patients have varying durations of follow-up and the outcome of interest is not known for all patients especially if they are no longer receiving care at the medical center or the outcome hasn't yet occurred in the period under study, often referred to as censored data. Therefore, we used time-to-event methodology appropriate for censored data to quantify the cumulative incidence of having a subsequent hysterectomy/oophorectomy.

5. Why did they select the age range between "18-50"? Do the authors have access to the infertility treatments used in this sample? How many had ovulation induction with clomiphene, how many cycles of clomiphene, hMG, number of cycles of hMG, intrauterine insemination, in vitro fertilization, donor eggs or donor embryos (esp for the older cohort)? Was the increased risk of having a hysterectomy and/or oophorectomy mainly in the patients who underwent IVF or after 6 cycles of clomiphene citrate?
The age range was selected to represent a meaningful cohort of women of reproductive age. Although few women achieve pregnancy in their late 40s we captured all potential subjects who may meet criteria for primary infertility and inclusion in our study.

The effect of infertility treatment type and number of cycles is an interesting point but outside the scope of this analysis. We may consider this in future studies.

6. How did the authors arrive at their 'n' of 1001 subjects and controls? Did they perform an 'a priori' sample size determination or some other method of determining their sample size? Was this all of the primary infertility patients in their database?
The sample size reflects inclusion of all women with a diagnosis of primary infertility, confirmed by chart review, identified within the timeframe of the study. As such, we did not perform any sample size determination in this population-based cohort. We have explained this in the methods section as part of our response to point #3 above and to Reviewer #2 below.

Reviewer #2:

Comments to author:
The authors present a retrospective cohort study looking at the long term risk of bilateral oophorectomy and or hysterectomy in patients with primary infertility compared to an age-matched population referent cohort from the same county in Minnesota. The time period of exposure was from 1980-1999. Cumulative incidence curves for each primary outcome were assessed. Cox proportional hazard models were used to estimated HR for association between primary infertility and outcomes of interest.

Abstract:
Line 7 The objectives should be association vs risk.
Thank you for this point. We have revised the objective as follows: "To evaluate the association of primary infertility with subsequent bilateral oophorectomy and hysterectomy, using a population-based cohort of women with primary infertility and age-matched referent women".

Line 11 Why was ratio of 1:1 chosen vs a more robust 1:2 or 1:4?
Given the number of women included in each group and the depth of manual chart review, we felt a 1:1 ratio was adequate for evaluation.

Line 25-26 The results section is confusion. In line 16-17 it is stated that there was an association between primary infertility and BSO aHR 1.69 CI 1.22-2.33. Please clarify.
The intent of this comment is unclear. We have presented an association with an increased aHR and a 95% CI that does not cross 1.00. Additional feedback is requested if the reviewer has a concern.

Line 27-29 The study design limits conclusions about long term health outcomes.
It is difficult to respond to this comment without additional explanation since a mean followup of 20 years is typically considered long term outcomes. We are happy to address if additional guidance is provided.

Introduction:
Line 32-33 The wording of association should more appropriately be the medical conditions, especially DM and other CVD, are associated with infertility. The cause and effect is more in this direction. Ie Pt. with DM has higher chance of being anovulatory which could cause infertility.
Thank you for this clarification. We have changed our word choice to 'association' as suggested.

Line 38 I would suggest using association vs effect for reasons stated in previous comments.
This has been updated to reflect 'long term health outcomes associated with infertility'.

Line 39-40 The all cause mortality is comparing with or with oophorectomy from Nurses Health study reference 5. Reference 7 was much smaller case control study which did not address or all cause mortality. Be more specific with references and associations. The use of and or is confusing.
Thank you for this thorough review and opportunity to improve our use of references. We have updated as you suggested. We have removed the use of and/or throughout the manuscript.

Methods:
Line 51-53 What was the total population from which the 1001 patients were chosen? Ie 1001/population-based MPIC cohort Line 54 How was confirmation confirmed? Was there more than one reviewer and if so what if there was a discrepancy was there a third party to review for inclusion?
Thank you for this comment which was shared by Reviewer #1. We have updated the manuscript to better summarize the cohort selection and process of manual chart review. 'A total of 3,489 women aged 18-50 with at least one diagnosis code of infertility were identified in the REP. By manual chart review, a cohort of 1,001 women had a confirmed diagnosis of primary infertility… The medical records of the women with confirmed primary infertility and their matched controls were manually reviewed between September 2019 and November 2020. Three individuals (AA, ES and LKR) completed all chart reviews. To ensure consistency and refine the data collection tool, AA reviewed the first 50 charts in duplicate, with ES and LKR. Any charts with unclear data were subsequently reviewed by AA. All data was entered into an electronic piloted form within a secure electronic database. Outliers were re-reviewed by AA after the full dataset was reviewed."

Line 59 Did the control cohort include those with 2nd infertility? What were the GnPn of the comparison group? Parity is known to decrease certain risk like ovarian cancer, uterine cancer that may lead to different risks for either BSO +/- hysterectomy.
The cohort did not include those with secondary infertility. We have added this important point of clarification "Secondary infertility was not included to reduce potential confounding variables, such as effects of prior treatment and prior parity on long-term outcomes." Additionally, referent women may have been parous or nulliparous at the time of matching.

Line 76-77 Using the last visit for the control may not accurately reflect if the patient moved or had a hysterectomy/BSO out of network. Expand on the data base used and potential risk for misclassification.
Because that this was a retrospective study, individual subjects and referents have varying durations of follow-up. However, the two groups have similar duration of followup and we have therefore we used time-to-event methodology appropriate for censored data to quantify the cumulative incidence of having a subsequent hysterectomy/oophorectomy. We have added a note to the discussion to indicate that the number of events we have identified may be an underestimate of the true number.

Results:
Line 108 Define specifically what is meant by endometriosis and uterine etiology? Did patients have surgically confirmed endometriosis? Was there also tubal factor associated with this?
Endometriosis was surgically confirmed. Uterine factor included uterine fibroids, prior myomectomy, and congenital uterine anomalies. Tubal factor infertility was considered separately. This has been added to the manuscript.

Table 1 Given the dates of the cohorts do you have a break down of how salpingectomy was preformed? This may have had opportunistic reduction in ovarian cancer/cyst which may bias comparing the two cohorts.

The surgical approach to salpingectomy was not captured in creation of this cohort. While we acknowledge the risk reducing potential of salpingectomy on ovarian cancer – this was not a common outcome in our study and did not differ between women with primary infertility and referent women. The impact of salpingectomy on ovarian cyst formation is less well known to the authors and we do not believe bias the comparison of these groups.

Line 119-120 What is meant be censored? Were these patients excluded? The control group being from lower educational levels and socioeconomic category may never have chosen or could not afford a work up for infertility and this may be underestimated.
When the follow-up of a patient is "censored" that means that the follow-up is ended at a particular date/time that is not the date/time of the outcome of interest. Women from the referent group who were later diagnosed with primary infertility, diagnosis made after index date, were included in the time-to-event analysis up until the point in time when they are no longer considered a referent.

The impact of lower educational levels and possible socioeconomic association was controlled for statistically. Socioeconomic status was not directly addressed and the role of female education as a direct marker for this is less robust in the time period studied than in more current evaluations.

Table 2 Why was prior gyn surgery not also included in covariant adjustment? From table 1 this was different and may be related to the primary outcome of interest.
We did not adjust for prior gynecologic surgery because although there was a difference overall, the frequency differed by surgery type and was not universally more common in a single group (women with primary infertility vs referent women). Additionally, the specific surgeries that were statistically different had small sample sizes.

Line 128-130 The lower avg age for BSO is not surprising given the dates 1980-1999. Practices patterns were different without benefit of all cause mortality data from Nurse Health Study. This limits generalizability to modern practice.
Thank you for this comment. We agree, generalizability to modern practice may be limited. However, in initial efforts to better understand long-term associations with infertility this is a limitation that is unavoidable. We think it is meaningful to include these potential confounders in current work evaluating long-term outcomes as this requires 20-40 years for full assessment. The length from infertility diagnosis to current long-term health outcomes must include women who were treated in prior practice eras and the impact of prior practice patterns such as bilateral salpingo-oophorectomy similarly included.

Line 139-141 The weights for both groups are quite small. Given higher rates of hysterectomy for AUB and or fibroids this probably does not reflect current treatment options for both. Ie endometrial ablation, IUD, UFE.
We agree current trends may differ in treatment for abnormal uterine bleeding, however, hysterectomy remains a very common treatment approach. In evaluating a historical cohort, such as that described in our manuscript, an effort to evaluate long-term outcomes requires acceptance of prior treatment options to study the outcomes of interest. We have not edited the manuscript in response to this point of consideration.

Line 141-143 The numbers for comparison are small and there was no difference in pathology. As written it is overstated.
We agree this may not be worth highlighting and have removed this sentence from the manuscript.

Line 146-151 This statement is confusing and sounds like your saying the same thing. If the infertility cohort had higher rates of hysterectomy with BSO they would have lower rates of hysterectomy with ovarian conservation. Much of this may be related to higher rates of endometriosis and surgical practice at the time. Was this controlled for?
Women undergoing hysterectomy with BSO did not undergo either hysterectomy without BSO or BSO alone. We have added analysis to address the appropriate comment regarding endometriosis and added an additional supplemental figure that adjusted for era of surgical procedure (1980-1989 vs 1990-1999) and found persistent associations.

Line 166-167 Were the pregnancy in the infertility cohort spontaneous or through ART?
Thank you for the opportunity for expanded description. We have added additional detail describing the number of women who conceived their first pregnancy with use of fertility medications or conceived spontaneously.

Line 169-172 The effect of ever being pregnant and time as covariant don't seem to be associated with hysterectomy or BSO P=0.06 and P=0.08. Explain.
We noted an interaction but not statistical significance and have more clearly described this. We have attempted to clarify this by stating that “the magnitude of the association” between ever being pregnant and the subsequent occurrence of each outcome was different for women with primary infertility compared to the referents.

Discussion:
Line 184-185 It is not clear what is meant by competing outcomes and dividing them into three catagories. If the objective is more about all cause mortality any BSO should be interpreted together regardless of hysterectomy.
We have restated the description from our methods section to better describe the competing risks as the ’first subsequent procedure per woman: i) concurrent hysterectomy and bilateral oophorectomy, ii) hysterectomy with ovarian conservation, and iii) bilateral oophorectomy’. The differentiation of bilateral oophorectomy at the time of hysterectomy as a separate procedure illustrates different surgical decision making and is relevant to full understanding of this topic.

Line 186-187 State what searches were done to claim primacy in finding this association. Given the time period endometriosis was both associated with infertility and potential hysterectomy and BSO so it is not surprising to find this association in the data base.
Thank you for this recommendation. We have removed this primacy claim and instead stated that ‘there is limited data on the association of infertility and subsequent gynecologic surgery’.

Line 188-189 What would be done to mediate long term risk with this known association? The overwhelming number of patients in your cohort ended up pregnant. It is hard to make this conclusion by the nature of this study design.

Our intent with this comment was to describe an additional factor which may contribute to long-term health risks previously associated with infertility, such as hypertension. We do not suggest a role to mitigate these outcomes, only to identify a potential contributor. We aimed to study primary infertility, not nulliparity, so the role of pregnancy is meaningful, but we do not believe limiting in our conclusions.

Line 201-203 There is already a known association of many of the outcomes evaluated here. How do these finding differ?
We have updated the results and discussion section to reflect the impact of a primary infertility, excluding women with infertility related to endometriosis, on the association of subsequent risk of bilateral oophorectomy. This is further described below, in response to Reviewer #3.

The rest of the discussion addresses many of the question in this review

Reviewer #3:
This study was conducted on a validated cohort of women who had undergone evaluation for infertility. The manuscript is well written, concise and clear. I have the following questions for the authors:

1. The study group had higher incidence of endometriosis compared to referent group which is not a surprise. The study group women with endometriosis were more likely to undergo hysterectomy and BSO which is also not a surprise. Is it not a logical conclusion that endometriosis results in hysterectomy and BSO and primary infertility happens to be incidental finding? If we had studied a group of women with endometriosis and compared to referent women, the study group would have increased risk for hysterectomy and BSO. How is this any different? I expected the authors to discuss this aspect thoroughly and openly.
We appreciate this thoughtful review and an opportunity for significant improvement to our manuscript. We have added additional analysis excluding women with primary infertility related to endometriosis. When excluding women with primary infertility related to endometriosis, we found a persistent association with bilateral oophorectomy and no difference in subsequent risk of hysterectomy. This has been added to both the results and discussion section. A new 'Supplemental Figure 1' has been added to illustrate these findings. We conclude that primary infertility, not specific to endometriosis, remains a meaningful mediator of long-term risk of bilateral oophorectomy.

2. Women in the study group underwent hysterectomy for fibroids less often than the women in the study group. I was searching for information on the number of women who underwent myomectomy in the study group. Although this information is available at the index presentation, it is surprisingly missing from data after that. I am confident that the hysterectomy for fibroids was lower in the study group because they underwent myomectomy rather than hysterectomy (some of them many myomectomies I would imagine as they are naturally desperate to keep their uterus and their hopes for a pregnancy in the future).
We appreciate this comment and regret that myomectomy was not captured after the index date. This is a valuable consideration and has been added to the discussion both for consideration and as a limitation to our study.

3. My conclusion on reviewing the data presented is that endometriosis is more prevalent in the infertile women and therefore it increases risk of hysterectomy with BSO subsequently. Hysterectomy for fibroids is lower but data is not presented so one can only surmise that women underwent myomectomy instead of hysterectomy in that group.
Thank you again for such an impactful review. We now present the impact of primary infertility, both with and without a diagnosis of endometriosis, as a risk factor for subsequent bilateral oophorectomy.

STATISTICS EDITOR COMMENTS:
Table 1: In retrospect, it would have been preferable to match on variables besides age, notable race/ethnicity, marital status, education, BMI, rather than having to adjust for those variables at a later stage of analysis.
While this would be most ideal, the ability to identify referent women matched on this number of variables in a retrospective study is not feasible as this data is not available prior to chart review.

Table 2: For some of the subsets, the counts of adverse outcomes are not favorable w.r.t. 5 adjustors in the aHR models. On the other hand, some of the CIs are wide, reflecting the small counts of adverse outcomes and limiting power to generalize any NS findings.
We agree that for some of the models presented in Table 2, particularly the strata with endometriosis as the primary indication for infertility, that the models were overfit considering the number of events in relation to the number of covariates included in the models. We have added the following statement to the limitations section in the Discussion: "In our analysis stratified by the primary infertility indication, particularly for those with endometriosis as the indication, some models may be considered overfit using the rule of thumb of 10-15 events per each covariate included in the regression model. This overfit is evident by the wider 95% CIs and therefore some results should be cautiously interpreted."

Fig 1: Should summarize all stats tests of the K-M curves, either in figure or figure legend. Also, should indicate along the x-axes, the "N" remaining in each group at the indicated time points.
The unadjusted hazard ratio and corresponding 95% CIs have been added to this figure. Because the analysis was done using age as the time scale, instead of years following the index date", we have reported the "number in the risk set on an age scale" along the x-axis, with women entering the risk set at their respective index ages.

Fig 2: Should indicate in figure legend any stats testing done to compare the cohorts.
We have inserted the p-values for the two comparisons that we evaluated.

Suppl Fig 1: Same comments as in Fig 1 re: stats tests and labelling the x-axes.
We have made the requested changes to this figure.

EDITORIAL OFFICE COMMENTS:
1. The Editors of Obstetrics & Gynecology have increased transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including

your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:
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* 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.
The above has been revised as required.

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Confirmed that all co-authors have submitted the electronic Copyright Transfer Agreement.

4. For studies that report on the topic of race or include it as a variable, authors must provide an explanation in the manuscript of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, the reasons that race/ethnicity were assessed in the study also should be described (eg, in the Methods section and/or in table footnotes). Race/ethnicity must have been collected in a formal or validated way. If it was not, it should be omitted. Authors must enumerate all missing data regarding race and ethnicity as in some cases, missing data may comprise a high enough proportion that it compromises statistical precision and bias of analyses by race.

Use "Black" and "White" (capitalized) when used to refer to racial categories. The nonspecific category of "Other" is a convenience grouping/label that should be avoided, unless it was a prespecified formal category in a database or research instrument. If you use "Other" in your study, please add detail to the manuscript to describe which patients were included in that category.
Race was self-reported on patient intake forms and included by chart review. The category of ‘Other’ was an option on these intake forms and represented only 1.3-1.4% of total responses.

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 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.
Manuscript reviewed and terms used in accordance with reVITALize definitions.

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 5,500 words. Stated word limits include the title page, précis, abstract, text, tables, boxes, and figure legends, but exclude references.
Word limits reviewed for title page, précis, abstract, text, tables, boxes, and figure legends (excluding references) and meet journal guidelines.

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In addition, the abstract length should follow journal guidelines. The word limit for Original Research articles is 300 words. Please provide a word count.
Abstract updated after major revisions complete. Updated abstract word count is 296 words.

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The virgule symbol has been removed from sentences with words. Similarly, we have rephrased all instances where and/or was used to simply 'and'.

11. ACOG avoids using "provider." Please replace "provider" throughout your paper with either a specific term that defines the group to which are referring (for example, "physicians," "nurses," etc.), or use "health care professional" if a specific term is not applicable.
We have updated the term provider to "health care professional" as requested.

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.
All results presented in the manner requested.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.
Not relevant to this study.

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

13. Line 186: Your manuscript contains a priority claim. We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.
This sentence has been updated and now states: "To our knowledge, there is limited data on the association of infertility and subsequent gynecologic surgery."

14. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here:
http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.
The Table Checklist has been reviewed and our manuscript updated to conform to journal style.

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