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

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

**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: 03/25/2024
To: "Anna Denoble" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-24-374

03/25/2024

RE: ONG-24-374: COVID-19 Vaccination and Stillbirth in the Vaccine Safety Datalink: A Case-Control Study

Dear Dr. Denoble:

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

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

To facilitate our review, we prefer that the cover letter you submit with your revised manuscript include each reviewer and Editor comment below, followed by your response. That is, a point-by-point response is required to each of the EDITOR COMMENTS (if applicable), REVIEWER COMMENTS, and STATISTICAL EDITOR COMMENTS (if applicable) below. The revised manuscript should indicate the position of all changes made. Please use the "track changes" feature in your document (do not use strikethrough or underline formatting). Upload the tracked-changes version when you submit your revised manuscript.

Your submission will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by 04/15/2024, we will assume you wish to withdraw the manuscript from further consideration.

EDITOR COMMENTS:

Please note the following:

* Help us reduce the number of queries we add to your manuscript after it is revised by reading the Revision Checklist at https://journals.lww.com/greenjournal/Documents/RevisionChecklist_Authors.pdf and making the applicable edits to your manuscript.

* As of January 2024, only certain article types will appear in the print version of the journal. All accepted articles will continue to publish online. All articles will be indexed in PubMed as an official article of Obstetrics & Gynecology. Additional information is available in the Instructions for Authors (https://journals.lww.com/greenjournal/Pages/InformationforAuthors.aspx#II).

STATISTICAL EDITOR COMMENTS:

Table 1, lines 149-151: Should embolden or otherwise identify the SMD with values ≥ |.20| for the reader.

Table 2: While justification is provided for the sample size/power estimations regarding the primary outcome, many of the various subsets (e.g., by number or type of vaccine have smaller samples and are thus underpowered, as implied by their wide CIs. Should include this among limitations in Discussion.

lines 257-258: In addition to prior history of stillbirth, other aspects of the individual obstetric histories would be relevant. For example, were the groups equivalent in terms of parity, prior preterm, SGA or fetal growth restricted births? If the database does not contain or release individual-level medical information, that would also be relevant to mention among limitations. Also, is there information regarding the overall rates of abortion for the vaccinated vs unvaccinated cohorts generally? If so, then that might be relevant in terms of assessing the effect of competing risks.

REVIEWER COMMENTS:

Reviewer #1:

The question of the safety of COVID-19 continues to linger, and on this base the authors portend in a retrospective matched case-control study to assess the possible (although very unlikely) association between COVID-19 vaccination during pregnancy and still birth.

1. My main concerns with this submission relate to the study design.

A. The Vaccine Safety Datalink reflects data of approximately 4% of the US population.

B. Although 465 cases of stillbirth were noted the authors state that after "adjudication only 276 (59.4%) cases were confirmed, and matched with 830 singleton live birth controls. No information was provided regarding 189 (41.6%) still birth cases, which were not judged appropriate for inclusion.

C. Late in the Discussion section (see lines # 250-253, the authors acknowledge that their study design contains a potential bias in the event the control population differs systematically from the case group.

D. The authors acknowledge the inherent potential incomplete capture of potential additional confounders (including the history of previous stillbirth), and that they were unable to conduct chart reviews for matched controls and thus relied only on automated data files.

2. I note the critical absence of data regarding COVID-19 infection, which may have occurred.

3. I note the overall absence of substantiated, new, previously unpublished data.

Reviewer #2:

This manuscript, titled "COVID-19 Vaccination and Stillbirth in the Vaccine Safety Datalink: A Case-Control Study", presents the results of a case control study investigating the association between COVID-19 vaccination and stillbirth. 276 cases of antepartum stillbirths occurring in 1 year (Feb 2021-Feb 2022) were included and matched 1:3 with controls. The authors found no association between COVID-19 and stillbirth, nor any association with vaccine type, number of doses, or timing of vaccination relative to pregnancy outcome.

The presentation of the data is straightforward and the manuscript is well-written. The introduction is clear and concise. The methods are appropriate for the study's question and an excellent use of the VSD. Including the power analysis was helpful for interpretation of the results. These are critically important data for pregnant individuals considering mRNA vaccination. I have no major comments and recommend acceptance after addressing the following minor comments:

Minor comments:
-Please clarify the dates of inclusion (discrepancy between line 15 and 92)
-Please clarify the gestational age limit for stillbirth definition (Line 87 says 22 weeks but 100 says 20 weeks)

Reviewer #3:

Title: COVID-10 Vaccination and Stillbirth in the Vaccine Safety Datalink: A Case Control Study

Study Overview: This is an IRB approved retrospective matched case-control study comparing the association between stillbirth and COVID-10 vaccination. There is a clear study population, hypothesis, and inclusion/exclusion criteria. Power calculations and statistical analysis are clearly explained. There were a total of n= 276 stillbirth cases and n=830 livebirth controls (matched 3:1). The objective was to evaluate the association between COVID-19 vaccination and stillbirths. At the conclusion of this study, the authors find that there is no association between COVID-19 vaccinations and stillbirth.

Comments:
Abstract: The abstract is a good summary of the paper.

Introduction: The introduction is appropriate and well written. The hypothesis is clear.

Methods: Study Design is clear, there is clear inclusion/exclusion criteria, a clean study period. The adjucation process is

clear and improves accuracy of results. Matching is done well with good efforts at matching appropriate controls. The authors are thorough at obtaining vaccine details.

1. Line 67: If this data is on 4% of the U.S. population, consider including this as a limitation on generalizability of the results of this study to the general public.

2. Line 127-128: The authors mention a prior hospitalization within the last year as a potential confounder for health status. In the reproductive aged population, a prior hospitalization within the last year may reflect a prior pregnancy and may not be a confounder to health status. Consider removing this as a confounder.

Statistical Analysis: The analysis is very clear. I appreciate the explanation of the calculation of the power and the post hoc power analysis clarifying the power analysis.

Results: The results are clear and well stated.

Discussion: The discussion is well written

Tables: No comments

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Sincerely,
The Editors of Obstetrics & Gynecology

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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.

Yale SCHOOL OF MEDICINE

April 12, 2024

Editorial Board for *Obstetrics & Gynecology*

Dear Editors:

I am pleased to re-submit the enclosed manuscript entitled "**COVID-19 Vaccination and Stillbirth in the Vaccine Safety Datalink: A Case-Control Study**" solely for consideration of publication in *Obstetrics & Gynecology* with edits and responses to reviewers as below. It has not been submitted to any other journal for review.

Thank you for the opportunity to revise our manuscript. We have responded to the editor's and reviewers' comments below. As requested by the reviewers, the variable "hospitalization within the year prior to pregnancy" was removed. Due to removal of this variable, a few additional changes to the data emerged, including the exclusion of 8 live birth cases. Additional data regarding the comorbidity obesity was able to be obtained and is now included. However, the overall results and interpretation of the results remain unchanged with these updates.

STATISTICAL EDITOR COMMENTS:

1. Table 1, lines 149-151: Should embolden or otherwise identify the SMD with values ≥ |.20| for the reader.
    a. This change has been made as suggested in Table 1.

2. Table 2: While justification is provided for the sample size/power estimations regarding the primary outcome, many of the various subsets (e.g., by number or type of vaccine have smaller samples and are thus underpowered, as implied by their wide CIs. Should include this among limitations in Discussion.
    a. This limitation has been added as suggested to the limitations section, lines 373-376.

3. lines 257-258: In addition to prior history of stillbirth, other aspects of the individual obstetric histories would be relevant. For example, were the groups equivalent in terms of parity, prior preterm, SGA or fetal growth restricted births? If the database does not contain or release individual-level medical information, that would also be relevant to mention among limitations. Also, is there information regarding the overall rates of abortion for the vaccinated vs unvaccinated cohorts generally? If so, then that might be relevant in terms of assessing the effect of competing risks.
    a. The Vaccine Safety Datalink has not historically captured prior obstetric history due to difficulty ascertaining outcomes like prior stillbirth, gestational age of prior birth if it occurred outside of the healthcare system, and history of small-for-gestational-age. While we recognize the importance of these variables in the pathophysiology of stillbirth, this remains an acknowledged limitation of this work. In an overlapping cohort, our group has found no association between COVID-19 vaccination and spontaneous abortion, as indicated in the discussion. Additional recognition of this limitation has been added to the discussion section on lines 378-379.

Yale SCHOOL OF MEDICINE

REVIEWER COMMENTS:

Reviewer #1:
The question of the safety of COVID-19 continues to linger, and on this base the authors portend in a retrospective matched case-control study to assess the possible (although very unlikely) association between COVID-19 vaccination during pregnancy and still birth.

1. My main concerns with this submission relate to the study design.
    a. The Vaccine Safety Datalink reflects data of approximately 4% of the US population.
    b. Although 465 cases of stillbirth were noted the authors state that after "adjudication only 276 (59.4%) cases were confirmed, and matched with 830 singleton live birth controls. No information was provided regarding 189 (41.6%) still birth cases, which were not judged appropriate for inclusion.
        i. The cases that were adjudicated and deemed to have had an outcome other than stillbirth are presented in Supplemental Table 2. Additional details regarding these outcomes are now included in the text, lines 260-271.
    c. Late in the Discussion section (see lines # 250-253, the authors acknowledge that their study design contains a potential bias in the event the control population differs systematically from the case group.
        i. We would like to point the reviewer to table 1 to note that differences between stillbirth cases and live birth controls were only noted for non-Hispanic Black race and for pre-gestational diabetes.
    d. The authors acknowledge the inherent potential incomplete capture of potential additional confounders (including the history of previous stillbirth), and that they were unable to conduct chart reviews for matched controls and thus relied only on automated data files.
        i. Please see response to Statistical Editors comments regarding this concern.
    e. I note the critical absence of data regarding COVID-19 infection, which may have occurred.
        i. COVID-19 disease (as indicated by ICD-10 diagnosis from an inpatient, outpatient or emergency department visit) was included as a comorbidity in this study with no significant differences noted between stillbirths and livebirths, as indicated by the SMD <0.20. However, we acknowledge that we were unable to capture all COVID-19 infections given the high rate of home antigen testing at the time of data capture for this study. See updated clarifying language on line 387.
    f. I note the overall absence of substantiated, new, previously unpublished data.
        i. We hope that this study does provide additional reassurance to patients and providers through its thoughtful design using one of the largest, validated vaccine databases available in the U.S.

Reviewer #2:

This manuscript, titled "COVID-19 Vaccination and Stillbirth in the Vaccine Safety Datalink: A Case-Control Study", presents the results of a case control study investigating the association between COVID-19 vaccination and stillbirth. 276 cases of antepartum stillbirths occurring in 1 year (Feb 2021-Feb 2022) were included and matched 1:3 with controls. The authors found no association between COVID-19 and stillbirth, nor any association with vaccine type, number of doses, or timing of vaccination relative to pregnancy outcome.

The presentation of the data is straightforward and the manuscript is well-written. The introduction is clear and concise. The methods are appropriate for the study's question and an excellent use of the VSD. Including the power analysis was helpful for interpretation of the results. These are critically important data for pregnant individuals considering mRNA vaccination. I have no major comments and recommend acceptance after addressing the following minor comments:

Minor comments:

-Please clarify the dates of inclusion (discrepancy between line 15 and 92)

g. We recognize that there is some confusion between the study inclusion dates and the final dates when stillbirths actually occurred within the study period. The abstract now reflects the date range for when stillbirths actually occurred (line 15) . The methods and results have updated to reflect the study period during which stillbirths were identified in the Dynamic Pregnancy Algorithm and the actual dates during which stillbirths occurred. See lines 15, 146-147, and 259-260.

-Please clarify the gestational age limit for stillbirth definition (Line 87 says 22 weeks but 100 says 20 weeks)

1. Additional language has been added to the methods to clarify that the 22 week and 500g limit for inclusion of livebirths referred to livebirths and not stillbirths. This was used as an exclusion criteria for the livebirth controls as a birth at <22 weeks or <500g was deemed to have a low likelihood of survival. See lines 141-142.

Reviewer #3:

Title: COVID-10 Vaccination and Stillbirth in the Vaccine Safety Datalink: A Case Control Study

Study Overview: This is an IRB approved retrospective matched case-control study comparing the association between stillbirth and COVID-10 vaccination. There is a clear study population, hypothesis, and inclusion/exclusion criteria. Power calculations and statistical analysis are clearly explained. There were a total of n= 276 stillbirth cases and n=830 livebirth controls (matched 3:1). The objective was to evaluate the association between COVID-19 vaccination and stillbirths. At the conclusion of this study, the authors find that there is no association between COVID-19 vaccinations and stillbirth.

Comments:
Abstract: The abstract is a good summary of the paper.

Introduction: The introduction is appropriate and well written. The hypothesis is clear.

Methods: Study Design is clear, there is clear inclusion/exclusion criteria, a clean study period. The adjudication process is clear and improves accuracy of results. Matching is done well with good efforts at matching appropriate controls. The authors are thorough at obtaining vaccine details.

1. Line 67: If this data is on 4% of the U.S. population, consider including this as a limitation on generalizability of the results of this study to the general public.
    a. This limitation has been added on lines 381-384.

Yale SCHOOL OF MEDICINE

2. Line 127-128: The authors mention a prior hospitalization within the last year as a potential confounder for health status. In the reproductive aged population, a prior hospitalization within the last year may reflect a prior pregnancy and may not be a confounder to health status. Consider removing this as a confounder.
    a. This is an excellent observation. This has been removed as a confounder and the results of the conditional logistic regression updated. the overall results and interpretation of the results remain unchanged with these updates.

3. Statistical Analysis: The analysis is very clear. I appreciate the explanation of the calculation of the power and the post hoc power analysis clarifying the power analysis.

4. Results: The results are clear and well stated.

5. Discussion: The discussion is well written.

6. Tables: No comments.

Thank you for considering this study for publication.

Warm regards,

Anna Denoble, MD, MSCR
Assistant Professor
Section of Maternal-Fetal Medicine
Department of Obstetrics and Gynecology
Yale University School of Medicine