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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.*

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

Date: 04/14/2023
To: "Malini DeSilva" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-23-585

RE: Manuscript Number ONG-23-585

Medically Attended Acute Adverse Events in Pregnant Persons Following COVID-19 Booster Vaccination

Dear Dr. DeSilva:

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 14 days from the date of this letter. If we have not heard from you by 04/28/2023, 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.

* Figure 1: Please upload as a figure file on Editorial Manager and rename as Figure 1.

REVIEWER COMMENTS:

Reviewer #1:

The authors evaluated acute safety outcomes following mRNA monovalent COVID-19 booster vaccination in pregnancy. They conducted a multisite observational matched cohort study including 8 Vaccine Safety Datalink (VSD) sites. They found that receipt of a mRNA monovalent COVID-19 booster in pregnancy was associated with an increased risk for medically attended malaise or fatigue and lymphadenopathy or lymphadenitis, but was not associated with increased risk for serious acute adverse events.

The following are my comments and questions:

1. The authors should define the term medically attended for the reader? Was this in person visits, telephone documentation etc.

2. The authors use the term clinically attended as well as medically attended--do these signify the same thing?

3. Can the authors confirm that their cohort's medical histories are reliably captured in these health systems -- could care have been accessed outside these systems?

4. Can the authors elaborate on how pregnancy was confirmed in their dataset?

5. Were any pregnancy outcomes captured?

6. Can the authors elaborate on how they selected the baseline comorbidities. Certain common morbidities included but others (diabetes) not?

Reviewer #2:

In this research letter, the authors conducted an observational matched cohort study of over 80,000 pregnant persons who received a monovalent mRNA COVID-19 vaccination. They concluded that although mRNA monovalent vaccine in pregnancy was associated with an increased risk of medically attended malaise or fatigue within 7 days of vaccination, lymphadenopathy, and lymphadenitis within 21 days of vaccination; mRNA COVID-19 vaccination was not associated with adverse events - thrombocytopenia, myocarditis, venous thromboembolism, ischemic stroke, or other serious adverse events within 21-42 days of booster vaccination. The findings of this study are interesting and welcome, but there are several aspects of this manuscript that need to be revised before it can be published.

General comments:
1. The 'source-population' was not described in detail. Since the authors did a 'case-controlled study', a detailed description of 'the source population' is very essential.

2. Selection of cases and controls: Detailed description of how controls were selected was not adequately described by the authors. There was no description of incidence density sampling (the goal standard sampling technique in case-controlled studies). In incidence density sampling, each case is matched on sex, age group, etc. with controls using an incidence density sampling strategy.

Introduction:
Lines 23-25: What percentage of pregnant persons received COVID-19 booster doses during pregnancy, and how does this compare to non-pregnant persons? Can the authors state the reasons why pregnant persons are averse to receiving booster doses during pregnancy from these studies?

Lines 25-26: Are there other safety outcomes that have been evaluated or reported in other non-pregnant studies that the authors failed to report in this study? If there are, what were the reasons why the authors failed to report these outcomes?

Methods:
Lines 36-37. How did the authors treat participants who received only 1 dose of the COVID-19 vaccination? Were these pregnant participants excluded from the analysis? Did any participants receive the Janssen (Johnson & Johnson) monovalent Novavax booster dose iCOVID-19 Vaccine? If yes, was one dose of J&J vaccine considered as 'complete'?

Line 41 - Please describe in a little bit more detail how matching was done, since matching is the bedrock of case-controlled studies.

Lines 56-58: I understand the rationale for analysis using Poisson regression. However, conditional logistic regression is usually the traditional regression method used in analyses of case-controlled studies. Why did the authors choose Poisson regression instead?

Lines 21-61: Did the authors conduct analysis by subgroup based on the type of vaccine received - Moderna versus Pfizer versus Johnson & Johnson?

The issues that would strengthen the methods section of this paper which the authors did not discuss include:

1. Description of the source population - Since the authors conducted a case-controlled study, a detailed description of 'the source population' is very essential.

2. Selection of cases and controls: Detailed description of how controls were selected was not adequately described. There was no description of incidence density sampling, the goal standard sampling technique in case-controlled studies. In incidence density sampling, each case is matched on variables, e.g. sex and age group, with controls per case by the use of an incidence density sampling strategy.

4. Analytical approach - Provide a good justification for the use of Poisson regression analyses rather than conditional logistic regression analyses.

Results and discussion - The results and discussion sections of these manuscript was adequately discussed and described.

STATISTICAL EDITOR COMMENTS:

General: Should include (in supplemental material) a version of Figure 1 in Table format that includes the rates of events per 10,000 along with 95% CIs for those rates for both the vaccinated and unvaccinated groups.

Also, since several of the adverse events of interest occur rarely (e.g., VTE, PE, myocarditis), the counts in those instances range from 0-2, thus the CIs are wide, the stats power is low to generalize the NS finding in terms of expression as aRR. Should include in limitations and make reference to the new Table in supplemental that includes CIs for the rates.

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Sincerely,

Torri D. Metz, MD, MS
Deputy Editor, Obstetrics

The Editors of Obstetrics & Gynecology

_____

HealthPartners Institute
8170 33rd Avenue So.MS21112R
Bloomington, MN 55425

healthpartnersinstitute.org

Mailing Address:
Mailstop 21112R, PO Box 1524
Minneapolis, MN 55440-1524

April 18, 2023

Obstetrics & Gynecology
409 12th Street SW
Washington, DC 20024

Dear Dr. Metz:

Thank you for your thoughtful review of the manuscript, "Medically Attended Acute Adverse Events in Pregnant Persons Following COVID-19 Booster Vaccination" letter #22-05276. We have revised the research letter based on the reviewers' comments. I have listed the statistical reviewer's comments and our response below. The word count has increased to 788 in order to address all reviewer comments.

Reviewer #1:

1. The authors should define the term medically attended for the reader? Was this in person visits, telephone documentation etc.
    a. We have modified the second sentence of the third paragraph in the methods section to define medically attended. It now reads, "Briefly, outcomes were identified using diagnostic codes at inpatient, outpatient, or emergency department clinical encounters (i.e., medically attended) with outcome-specific exclusions applied (Appendix Table)."

2. The authors use the term clinically attended as well as medically attended--do these signify the same thing?
    a. It is the same thing, for clarity, we have changed "clinically attended" to "medically attended" in line 83.

3. Can the authors confirm that their cohort's medical histories are reliably captured in these health systems -- could care have been accessed outside these systems?
    a. Medical histories for active medical problems are reliably captured in the health systems included. In order to be part of the VSD cohort, a patient needs to be both a patient (receive care) at a health system and for 7/8 health systems, the patients also have health insurance which captures information about health care received outside the health system. For the 1 site without an associated health insurance, they have a system for determining whether the patient is empaneled at the system. Thus, if a patient has an active medical condition for which they receive care, it is likely captured by the site through care visits and/or insurance claims.

4. Can the authors elaborate on how pregnancy was confirmed in their dataset?
    a. The VSD uses the Dynamic Pregnancy Algorithm (DPA) to identify pregnancies. . The algorithm uses ICD-10-CM and CPT® codes from inpatient, outpatient and emergency department visits, supplemented with clinical data, with updates on a

HealthPartners Institute
8170 33rd Avenue So.MS21112R
Bloomington, MN 55425

healthpartnersinstitute.org

Mailing Address:
Mailstop 21112R, PO Box 1524
Minneapolis, MN 55440-1524

weekly basis, to identify ongoing and completed pregnancies. We have cited the manuscript which provides information about the validation of this algorithm in this brief report: Naleway AL, Crane B, Irving SA, Bachman D, Vesco KK, Daley MF, Getahun D, Glenn SC, Hambidge SJ, Jackson LA, Klein NP, McCarthy NL, McClure DL, Panagiotakopoulos L, Panozzo CA, Vazquez-Benitez G, Weintraub ES, Zerbo O, Kharbanda EO. Vaccine Safety Datalink infrastructure enhancements for evaluating the safety of maternal vaccination. Ther Adv Drug Saf. 2021 Jun 14;12:20420986211021233. doi: 10.1177/20420986211021233. PMID: 34178302; PMCID: PMC8207278.

5. Were any pregnancy outcomes captured?
    a. For this manuscript, we did not capture pregnancy outcomes or infant outcomes. Our group has separately published on spontaneous abortions (https://jamanetwork.com/journals/jama/fullarticle/2784193) as well as specific infant outcomes, preterm birth and small for gestational age (https://www.cdc.gov/mmwr/volumes/71/wr/mm7101e1.htm) following maternal COVID-19 vaccine. The cohorts included in these evaluations are different from that used in this evaluation. We are in the process of working on a separate study that will evaluate major structural birth defects in infants following maternal COVID-19 vaccination.

6. Can the authors elaborate on how they selected the baseline comorbidities. Certain common morbidities included but others (diabetes) not?
    a. All baseline comorbidities evaluated are shown in the supplemental figure (i.e, Diabetes, Cancer, hypertension, liver disease, immunocompromising disease, chronic kidney disease, systemic lupus, pulmonary disease, cardiovascular disease, obesity, smoking, previous COVID-19 infection, and alcohol or substance abuse). For the Table, we chose to show only selected comorbidities.

Reviewer #2:

1. The 'source-population' was not described in detail. Since the authors did a 'case-controlled study', a detailed description of 'the source population' is very essential.
    a. This is a matched cohort study, not a case-control study. The source population includes pregnant persons age 16-49 years with ≥2 prenatal care visits (including one prior to third trimester) seen at one of 8 Vaccine Safety Datalink sites. We have moved the sentence from lines 41 – 43 to the first paragraph of the methods to help clarify this description.

2. Selection of cases and controls: Detailed description of how controls were selected was not adequately described by the authors. There was no description of incidence density sampling (the goal standard sampling technique in case-controlled studies). In incidence density sampling, each case is matched on sex, age group, etc. with controls using an incidence density sampling strategy.

HealthPartners Institute
8170 33rd Avenue So.MS21112R
Bloomington, MN 55425

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Mailing Address:
Mailstop 21112R, PO Box 1524
Minneapolis, MN 55440-1524

a. This is not a case control study, rather it is a matched cohort study of pregnant persons. We have selected persons for inclusion based on their exposure (exposed = received COVID-19 vaccine; unexposed = did not receive COVID-19 vaccine) not on a known health outcome (e.g., Guillain-Barré syndrome).

Introduction:

3. Lines 23-25: What percentage of pregnant persons received COVID-19 booster doses during pregnancy, and how does this compare to non-pregnant persons? Can the authors state the reasons why pregnant persons are averse to receiving booster doses during pregnancy from these studies?
    a. This sentence has been modified. It now reads, "Despite preliminary data that booster doses are safe in pregnancy, half of pregnant people who had completed a primary COVID-19 vaccine series had not received a COVID-19 booster 6 months after booster dose authorization." A new reference has been used as the citation which is specifically focused on receipt of the monovalent booster during pregnancy in a well-defined cohort. The studies cited do not provide information about why pregnant persons are averse to receiving booster doses. One possible reason is due to lack of safety data of booster doses in pregnancy.

4. Lines 25-26: Are there other safety outcomes that have been evaluated or reported in other non-pregnant studies that the authors failed to report in this study? If there are, what were the reasons why the authors failed to report these outcomes?
    a. In this report, we evaluated major safety concerns that had been identified in non-pregnant persons including myocarditis/pericarditis, central venous sinus thrombosis (CVST), venous thromboembolism (VTE), and thrombosis with thrombocytopenia syndrome (TTS). Please see the Figure for a full list of outcomes evaluated. The Figure footnote includes outcomes we included in the evaluation for which there were no cases in the source population.

Methods:

5. Lines 36-37. How did the authors treat participants who received only 1 dose of the COVID-19 vaccination? Were these pregnant participants excluded from the analysis? Did any participants receive the Janssen (Johnson & Johnson) monovalent Novavax booster dose iCOVID-19 Vaccine? If yes, was one dose of J&J vaccine considered as 'complete'?
    a. Our group previously published an initial evaluation of acute safety outcomes following COVID-19 vaccination pregnancy (citation: DeSilva M, Haapala J, Vazquez-Benitez G, et al. Evaluation of Acute Adverse Events after Covid-19 Vaccination during Pregnancy. *N Engl J Med.* 2022;387(2):187-189.). In that report, we evaluated the primary series. This is a study of the safety of mRNA COVID-19 booster doses administered during pregnancy. We are not focusing on other COVID-19 vaccine types for this analysis. From the manuscript, "'Booster dose' was defined as an mRNA monovalent COVID-19 vaccine received during September 23, 2021–June 30, 2022 and ≥2 months after completion of the 2-dose mRNA primary series."

HealthPartners Institute
8170 33rd Avenue So.MS21112R
Bloomington, MN 55425

healthpartnersinstitute.org

Mailing Address:
Mailstop 21112R, PO Box 1524
Minneapolis, MN 55440-1524

6. Line 41 - Please describe in a little bit more detail how matching was done, since matching is the bedrock of case-controlled studies.
    a. As above, this is not a case-control study, rather it is a cohort study. From the manuscript, "Pregnant people receiving a booster dose during pregnancy or within 28 days of their last menstrual period (LMP) were matched 1:1 to pregnant people who did not receive a COVID-19 vaccine during pregnancy or within 28 days of LMP ("unexposed") using a greedy matching algorithm. Unexposed pregnant persons either received no COVID-19 vaccines or may have received COVID-19 vaccines before or after pregnancy or the study period."

7. Lines 56-58: I understand the rationale for analysis using Poisson regression. However, conditional logistic regression is usually the traditional regression method used in analyses of case-controlled studies. Why did the authors choose Poisson regression instead?
    a. We chose to use Poisson regression in this cohort study because we are analyzing incidence rates of outcomes that are uncommon.

8. Lines 21-61: Did the authors conduct analysis by subgroup based on the type of vaccine received - Moderna versus Pfizer versus Johnson & Johnson?
    a. We focused on mRNA vaccines for this analysis. In our previous manuscript we did report results based on vaccine product, but did not in this evaluation as overall results were not significantly different between products (see supplemental appendix, Figure S4 from DeSilva M, Haapala J, Vazquez-Benitez G, et al. Evaluation of Acute Adverse Events after Covid-19 Vaccination during Pregnancy. *N Engl J Med.* 2022;387(2):187-189.) and we have very few J&J booster doses in our population.

9. Description of the source population - Since the authors conducted a case-controlled study, a detailed description of 'the source population' is very essential.
    a. Please see answer to #1 above.

10. Selection of cases and controls: Detailed description of how controls were selected was not adequately described. There was no description of incidence density sampling, the goal standard sampling technique in case-controlled studies. In incidence density sampling, each case is matched on variables, e.g. sex and age group, with controls per case by the use of an incidence density sampling strategy.
    a. Please see answer to #2 above.

11. Analytical approach - Provide a good justification for the use of Poisson regression analyses rather than conditional logistic regression analyses.
    a. Please see answer to #7 above.

12. Results and discussion - The results and discussion sections of these manuscript was adequately discussed and described.
    a. Thank you.

HealthPartners Institute
8170 33rd Avenue So.MS21112R
Bloomington, MN 55425

healthpartnersinstitute.org

Mailing Address:
Mailstop 21112R, PO Box 1524
Minneapolis, MN 55440-1524

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STATISTICAL EDITOR COMMENTS:

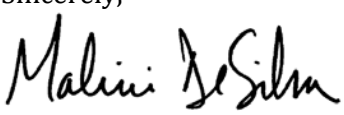
13. General: Should include (in supplemental material) a version of Figure 1 in Table format that includes the rates of events per 10,000 along with 95% CIs for those rates for both the vaccinated and unvaccinated groups.
    a. We have created a supplemental table 2 which includes the details from Figure 1 along with rates of events per 10,000 along with 95% CIs for both the vaccinated and unvaccinated groups.

14. Also, since several of the adverse events of interest occur rarely (e.g., VTE, PE, myocarditis), the counts in those instances range from 0-2, thus the CIs are wide, the stats power is low to generalize the NS finding in terms of expression as aRR. Should include in limitations and make reference to the new Table in supplemental that includes CIs for the rates.
    a. We have revised lines 88 – 89, this sentence now reads, "No increased risks for other assessed adverse events following vaccination were detected, although for many outcomes with low incidence power was limited resulting in wide confidence intervals for the associated rate ratios."

This manuscript has not been submitted to any other journal and it has not been previously published, either in whole or in part, nor have the findings been posted online. We will not submit the manuscript elsewhere unless a final negative decision is made by the Editors of Obstetrics & Gynecology. This study was approved by institutional review boards of all participating healthcare organization sites with a waiver of informed consent and was conducted consistent with federal law and CDC policy. §§ See e.g., 45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq. As the corresponding author, I had full access to all aspects of the research and writing process and take final responsibility for the paper.

Please contact me with any further questions or concerns.

Sincerely,



Malini DeSilva, MD, MPH
[redacted]