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.
COVID-19 Vaccination and Assisted Reproduction Outcomes: A Systematic Review and Meta-Analysis

Dear Dr. Chamani:

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 06/16/2023, 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.

* Figures 1-3: Please name figures in the order in which they first appear (it appears that 2 and 3 should be switched). Please upload high resolution versions as individual figure files on Editorial Manager.
Reviewer #1: The authors present a systematic review and meta-analysis of the impact of coronavirus 19 vaccination on assisted reproductive outcomes. The primary outcome analyzed was clinical pregnancy rate. Literature search was completed January 2023 and included 25 original research studies. The authors performed overall analyses as well as subgroup analyses based upon country of origin and vaccine type. They analyzed heterogeneity and publication bias.

Line 9, Abstract: Please clarify that this study is evaluating "female" COVID 19 vaccination and outcomes.

Line 31, Abstract: Add one statement about the results of the subgroup analyses.

Line 162, Results: Recommend also including several other important characteristics of the studies such as number of vaccine doses, if they also compared before and after vaccination or just between vaccinated/unvaccinated, if they controlled for # embryos transferred, etc.

Lines 165-166, Results: Previously in the manuscript it was stated that a NOS of 6 was intermediate. Please correct this.

Lines 236-251, Discussion: There are potential physiological mechanisms behind recent vaccination and poorer reproductive outcomes. Please discuss these theories to present all possibilities.

Line 253, Discussion: Please also include and discuss the SR/MA by Huang published May 2023 (PMID 36702343).

Line 262, Discussion: Need to also include in the limitations discussion that this only accounted for female vaccination status, the variability of time course from vaccination, and the lack of information about natural infection/immunity.

Reviewer #2: This is a systematic review of fertility outcomes (pregnancy, oocyte retrieval, etc.) in patients with and without COVID vaccination who have undergone assisted reproductive technology.

Introduction: the authors outline clearly the risks of COVID in pregnancy (paragraph lines 59-63) and the recommendation for vaccination of patients seeking pregnancy (paragraph lines 52-57). The authors should consider a paragraph outlines the benefits of vaccination, particularly in pregnant patients (even if vaccinated patients get COVID, they have less severe illness, less likely to require hospitalization/intubation etc.).
Methods: please briefly describe the search terms used to identify articles (they are listed in detail in an appendix, but an overview is appropriate for the methods). How did the authors define assisted reproductive technology? (ovulation induction with timed intercourse, IUI, IVF?) How did the authors define vaccination (any vaccine, completed vaccine series)? There is a paragraph (lines 117-127) dedicated to describing the outcome of interest (pregnancy). There should be comparable description of how the exposure (COVID vaccination) was obtained.

Were the authors able to collect data from the studies about time from vaccination to pregnancy? This information would be of great interest to the general population. Line 241 leads me to believe that the authors have this information - if so, please share in the results.

What were the reasons that the 216 articles were excluded? Did not include data on pregnancy outcome? Did not include data on COVID vaccination? Other reasons?

Table 1 - consider adding a column with the total number of vaccinated and unvaccinated patients in each study.

Lines 209-210: This information is very important for public health officials. Consider including a graph/table/figure that illustrates this finding.

Lines 253-254: how many more studies are in this review compared to the Zace review?

Pro tip: consider "before" rather than "prior to" throughout. It helps with readability and decreases your word count.

STATISTICAL EDITOR COMMENTS:

Fig 2a, 2b: Should include, either in text or in a separate Table, the summary average # of retrieved oocytes and # mature oocytes for the vaccinated and unvaccinated cohorts.

Fig 2c, 2d, 2e and 2f: Should include, either in text or in a separate table, the summary average rates for the vaccinated and unvaccinated cohorts.

Fig 2g: This is actually a recapitulation of one study which overwhelmingly provided weight to the analysis. So it does not really represent a meta-analysis. Furthermore, since there were only two studies, once cannot estimate heterogeneity with any precision, so its calculation should be omitted.
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Sincerely,
Jason D. Wright, MD
Editor-in-Chief

The Editors of Obstetrics & Gynecology

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.
Dear Dr. Wright and the Editorial Board,

Thank you for considering our systematic review and meta-analysis titled “COVID-19 Vaccination and Assisted Reproduction Outcomes: A Systematic Review and Meta-Analysis” for publication in the Green Journal. We appreciate the time you took to review our work and the thoughtful and insightful edits. We reviewed the recommendations and incorporated them into the revised manuscript that is attached to this submission.

Below, please find a list of all the editors/reviewers comments and edits. Our responses are listed below each suggestion in italicized text. All changes that were made to the manuscript are highlighted in “tracked changes.”

We would like to reaffirm that our manuscript has not been published previously and is only under consideration at Obstetrics and Gynecology. We know of no conflicts of interest associated with the publication, and there has been no financial support for this work. All authors are responsible for the content of this manuscript and participated in the concept and design of this work, analysis and interpretation of the literature, drafting or revising, and have approved this manuscript as submitted. As the study did not involve human subjects, it was deemed exempt from IRB review. The study was conducted in accordance with the MOOSE guidelines. The systematic review was prospectively registered with PROSPERO (PROSPERO ID CRD42023400023). Dr. Mark A. Turrentine has been instrumental in the design and execution of this project and has permitted his acknowledgement in the manuscript.

Thank you very much for your consideration. We look forward to hearing from you.

Warmest Regards,

Isaac Chamani, MD
Baylor College of Medicine
Department of Obstetrics and Gynecology
Houston, TX 77030

Frederick Licciardi, MD
REI Fellowship Director
Professor of Obstetrics and Gynecology
NYU Langone Fertility Center

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.
  - Checklist reviewed and manuscript updated.

* Figures 1-3: Please name figures in the order in which they first appear (it appears that 2 and 3 should be switched). Please upload high resolution versions as individual figure files on Editorial Manager.
  - Figure names have been switched, thank you.

REVIEWER COMMENTS:

Reviewer #1: The authors present a systematic review and meta-analysis of the impact of coronavirus 19 vaccination on assisted reproductive outcomes. The primary outcome analyzed was clinical pregnancy rate. Literature search was completed January 2023 and included 25 original research studies. The authors performed overall analyses as well as subgroup analyses based upon country of origin and vaccine type. They analyzed heterogeneity and publication bias.

Line 9, Abstract: Please clarify that this study is evaluating "female" COVID 19 vaccination and outcomes.
  - Clarified, thank you.

Line 31, Abstract: Add one statement about the results of the subgroup analyses.
  - Added, thank you.

Line 162, Results: Recommend also including several other important characteristics of the studies such as number of vaccine doses, if they also compared before and after vaccination or just between vaccinated/unvaccinated, if they controlled for # embryos transferred, etc.
  - We added the information regarding the number of vaccine doses. Whether studies looked at before/after vaccination versus vaccinated/unvaccinated was already included in the table in the study design.

Lines 165-166, Results: Previously in the manuscript it was stated that a NOS of 6 was intermediate. Please correct this.
  - Corrected, thank you.

Lines 236-251, Discussion: There are potential physiological mechanisms behind recent vaccination and poorer reproductive outcomes. Please discuss these theories to present all possibilities.
  - We added this to the discussion. Thanks for the suggestion.

Line 253, Discussion: Please also include and discuss the SR/MA by Huang published May 2023 (PMID 36702343).
  - We cited and commented on the Huang study in our discussion. Thank you for this reference.

Line 262, Discussion: Need to also include in the limitations discussion that this only accounted for female vaccination status, the variability of time course from vaccination, and the lack of information about natural infection/immunity.
Reviewer #2: This is a systematic review of fertility outcomes (pregnancy, oocyte retrieval, etc.) in patients with and without COVID vaccination who have undergone assisted reproductive technology.

Introduction: the authors outline clearly the risks of COVID in pregnancy (paragraph lines 59-63) and the recommendation for vaccination of patients seeking pregnancy (paragraph lines 52-57). The authors should consider a paragraph outlines the benefits of vaccination, particularly in pregnant patients (even if vaccinated patients get COVID, they have less severe illness, less likely to require hospitalization/intubation etc.).
- included these details into the introduction. Thank you.

Methods: please briefly describe the search terms used to identify articles (they are listed indetail an appendix, but an overview is appropriate for the methods). How did the authors define assisted reproductive technology? (ovulation induction with timed intercourse, IUI, IVF?) How did the authors define vaccination (any vaccine, completed vaccine series)? There is a paragraph (lines 117-127) dedicated to describing the outcome of interest (pregnancy). There should be comparable description of how the exposure (covid vaccination) was obtained.
- Updated Methods to include search terms. Clarified assisted reproduction definition in Methods. Clarified vaccination status. Thank you.

Were the authors able to collect data from the studies about time from vaccination to pregnancy? This information would be of great interest to the general population. Line 241 leads me to believe that the authors have this information - if so, please share in the results.
- Time interval between vaccination and assisted reproduction has been included in Table 1 for the studies that supplied that information.

What were the reasons that the 216 articles were excluded? Did not include data on pregnancy outcome? Did not include data on COVID vaccination? Other reasons?
- They were excluded as they did not provide data on the study question: ART outcomes following COVID vaccination.

Table 1 - consider adding a column with the total number of vaccinated and unvaccinated patients in each study.
- This information is already depicted in Figure 3 in a more accurate manner – the number of vaccinated/unvaccinated patients included in the analysis for each outcome are depicted.

Lines 209-210: This information is very important for public health officials. Consider including a graph/table/figure that illustrates this finding.
- We felt that given that the outcomes did not change after conducting our sub-analysis, an additional table or figure would only be redundant and would make the manuscript’s message more cluttered.

Lines 253-254: how many more studies are in this review compared to the Zace review?
- 10 studies, clarified this in discussion.

Pro tip: consider "before" rather than "prior to" throughout. It helps with readability and decreases your word count.
- Thanks, changed this as well.

STATISTICAL EDITOR COMMENTS:

Fig 2a, 2b: Should include, either in text or in a separate Table, the summary average # of retrieved oocytes and # mature oocytes for the vaccinated and unvaccinated cohorts.
- Added mean of means for these results.

Fig 2c, 2d, 2e and 2f: Should include, either in text or in a separate table, the summary average rates for the vaccinated and unvaccinated cohorts.
- Added average rates for these outcomes.

Fig 2g: This is actually a recapitulation of one study which overwhelmingly provided weight to the analysis. So it does not really represent a meta-analysis. Furthermore, since there were only two studies, once cannot estimate heterogeneity with any precision, so its calculation should be omitted.
- Thank you for this insight. As per your recommendation, we removed the heterogeneity calculation from the figure. You raise an excellent point, the live birth data is still very scant, and we noted this in our discussion as a limitation to our study.