

OBSTETRICS & GYNECOLOGY



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

Date: Sep 10, 2021
To: "Angela Rose Seasey" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-21-1802

RE: Manuscript Number ONG-21-1802

Maternal and perinatal outcomes associated with the rise in the SARS-CoV-2 delta variant

Dear Dr. Seasey:

Thank you for your submission to Obstetrics & Gynecology. Given the timeliness and importance of your findings, the Editors are considering your manuscript for rapid dissemination and publication if you can address the comments raised by the peer reviewers. If you can submit your revision to us quickly, the Editorial Office will prioritize processing the submission.

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 7 days from the date of this letter. If we have not heard from you by Sep 17, 2021, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: This research letter describes maternal and perinatal outcomes during two different COVID pandemic periods - prior to widespread circulation of Delta vs. period when Delta variant predominates.

Line 2-4: The paper cited here compares asymptomatic pregnant women vs. pregnant women with severe disease. It would make more sense to cite a paper that compared pregnant women with and without COVID here.

Line 10: Please define the study population here. Are these all pregnant women admitted to the hospital during this time period who tested positive for COVID? Does this include asymptomatic women who were admitted for labor? How many of these women were admitted for labor/delivery vs. admitted for COVID? Were all pregnant women during this time period tested for COVID?

Line 15: Please specify how pre-delta and delta time periods were defined. Were these time periods based on sequencing from your specific institution or from national trends?

Line 21-22: From this I assume that all pregnant women were tested upon admission?

Line 24: A short description of the breakthrough cases would be helpful. Were these patients sick, asymptomatic, admitted for labor vs. COVID?

Line 25: What is meant by "ICU transfers"? How does this relate to "ICU admissions"?

Line 34: What criteria were used to define "COVID positive neonates"? Were these in utero transmissions, intrapartum transmissions, or postnatal transmissions?

Line 41: Please clarify what is meant by "downstream long-term negative impacts".

Reviewer #2: This was an interesting research letter. There are two general issues that I'd like addressed:

1) Given the short format of the research letter, the discussion was relatively long with some inferences that are intuitive (public health importance of vaccination) and others not related to the data (neonatal outcomes). In comparison, there are many important details that are not included in the methods section. I would recommend editing the discussion down and using the additional word count for clearer, more detailed methods.

2) The type of hospital this is could have an effect on the findings; if there was a large 'n' of delta infections in the community (compared to prior waves) and severe cases were transferred or directed to this hospital it could overestimate the proportion of severe disease. You could get around this by simply demonstrating 'n' of COVID cases detected on universal screening for labor admission although likely the sample would be too small. Alternately, the potential effect of this being a referral center on risk estimates secondary to increased shunting of high risk/morbid cases should be acknowledged as a limitation. I presume this is a referral center given that they offer ECMO.

Introduction

Lines 1-4 - Would contextualize data. That is, would describe that it is the MFMU data or large multi-center cohort data. As presented the reader doesn't know without looking at the citation that it is MFMU. Could be CDC data, meta-analysis data, etc.

Methods

There are a few questions that I have related to the methods:

One has to do with ascertainment: did this hospital have universal screening of all hospitalizations for the entire study period? Or was it only symptomatic or exposed patients? If the screening policy changed over the study period it could bias towards greater or lesser severity (symptom-based screening more severe, universal less severe).

Also, was genotyping performed for all patients? Or is this just a sample from the general hospital population? If general hospital population would describe in methods how the 85% then 95% predominance was determined.

Also, by August 2021 some patients would have been vaccinated. Does this figure into the analysis?

Was critical illness defined using same criteria as MFMU?

Unclear on models. Was the analysis performed using delta as the exposure and alpha as the reference?

One question I have is related to transfers - is this a referral hospital where patients are being transferred in with COVID? That is, outcomes could have appeared worse with delta because delta causes more severe infections. Or it could be because delta is more infectious leading to a greater number of infections in the community with the most severe cases being transferred to the study hospital. To what degree was this patient population community patients who received their prenatal care at affiliated hospital sites versus women transferred/referred in/brought in by ambulance because of COVID infection without having received care at practices/clinics affiliated with this hospital?

Results

OK, some of my questions related to methods are answered in results section. Would be better to have this info in methodology section.

For Table 1, there are a lot of comparisons; if you performed some sort of adjustment for multiple comparisons the significance of asthma may fall out.

Table 2. Is respiratory support supplemental oxygen?

I think letter format allows for 2 tables and/or figures and there are 3. I think you could get rid of Table 1 noting that demographic differences were non-significant except for asthma.

I don't know that adjusting for asthma adds much and given you only have 2 delta patients with asthma I'm not sure it's appropriate statistically.

Discussion

Lines 40-42 Since you didn't look at neonatal outcomes I wouldn't speculate on neonatal outcomes.

Line 42. 'COVID-19 vaccinations were made available to the public in 4/2021 yet all cases of COVID-19 in pregnant women admitted to the hospital since occurred in unvaccinated women. When considering the low (23%) vaccination rates in pregnant women together with the overall low vaccination rates of some southern states (as low as 37-38%), this sudden increase in COVID-morbidity is expected to have a negative impact on statewide efforts to reduce maternal mortality.'

OK, but didn't the directive SMFM/ACOG recommendations come at the end of July? Before that vaccination recommendations were more equivocal, right?

Given sampling issues I don't know from your data that you can say that delta itself causes worse infections (i.e. is more morbid) versus is more infectious and causes more cases and would hedge a little. You can say that delta is causing serious morbidity in the obstetric population however.

Reviewer #3: The authors present a research letter evaluating the adverse perinatal outcomes in the early COVID-19 pandemic versus the more recent delta variant surge. They conclude that the delta variant is associated with higher rates of ICU admissions, respiratory support, intubation and pharmacologic treatment. This highlights the concern for the increasing rates of transmission of the delta variant and provides further support to encourage vaccination among pregnant women.

Line 5- please include june 2021

Line 10- is this an urban, rural, referral center?

Line 13- if room permits can you include a small amount of data regarding testing protocols in the hospital as this may influence asymptomatic rates, did this change?

Also were any patients tested specifically for the delta variant?

Where was testing obtained from, inpatients or all clinic patients or simply patient report?

Line 34- The increased rate of positive neonates is interesting. What was the time frame for positivity? At birth or within the first month of life?

Line 44- Please include reference for these percentages

STATISTICAL EDITOR COMMENTS:

The Statistical Editor makes the following points that need to be addressed:

General and Fig 1: In order to compare the 3/22/2020-5/31/2021 period with the 7/1/2021-8/18/2021 period, one needs to assure the reader that ascertainment of Covid-19 was uniformly applied during those time periods. Early in the pandemic, testing was not widely available and often had eligibility criteria (exposure, symptoms etc), rather than being universally available later on. Need to provide (either in present Table or in supplemental), the number of deliveries each month from 3/20 to 8/21, the number tested, then the counts of + tests and ICU admissions. Simply comparing the counts of Covid+ and ICU admits in each month lacks sufficient context.

Table 1: Need units for age, BMI. Many of the %s are low (fortunately), but that means that the stats power is very limited. Therefore, cannot generalize those NS findings. Suggest formatting as n(%), rather than %s alone.

Table 2: Again, suggest formatting as n(%), rather than as %s alone. The comparisons are predicated on previous general comments, ie, that the groups were similarly, completely ascertained for Covid-19. The adjustment for an additional variable (asthma) results in an over fitted model for the following comparisons: maternal death, VTE, ECMO. Those comparisons are also underpowered.

Table 2: Section "Patients who required delivery": Need units for GA at delivery. Again, suggest formatting as n(%), rather than as %s alone. Many of the comparisons (aRRs) are both overfitted and underpowered as well as NS: pre-eclampsia, abruption, PPH, IUFD, transfusion, Neonatal covid (+), (which has a calculable Fisher's $p = 0.24$). Were all neonates tested during pre-delta period?

EDITOR 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. Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), observational studies using ICD-10 data (ie, RECORD), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), quality improvement in health care studies (ie, SQUIRE 2.0), and studies reporting results of Internet e-surveys (CHERRIES). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at <http://ong.editorialmanager.com>. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, RECORD, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

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: Research Letters should not exceed 600 words and may include no more than two figures and/or tables (2 items total). 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. Provide a short title of no more than 45 characters, including spaces, for use as a running foot.

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

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

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

12. In your submission, 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. 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.

14. 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.

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15. Figure 1: Add a label to the y-axis and upload the figure to Editorial Manager as a Figure file.

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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 7 days from the date of this letter. If we have not heard from you by Sep 17, 2021, we will assume you wish to withdraw the manuscript from further consideration.

Best,
Jason D. Wright, MD
Editor-in-Chief

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

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