OBSTETRICS & GYNECOLOGY

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: Apr 02, 2021
To: "Naima Thavory Joseph" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-21-372

RE: Manuscript Number ONG-21-372

Maternal Antibody Response, Neutralizing Potency, and Placental Antibody Transfer following SARS-CoV-2 Infection

Dear Dr. Joseph:

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).

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 Apr 09, 2021, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

Thank you for the opportunity to review your work.

1. Intro. Is this research entirely novel, or is there anything published on this topic up to this study?
2. Lines 162-172. SPORE and EMPOWR. I was not sure from the methods section how enrollment took place. Can a flow chart be created to show how enrollment took place? For example, out of total women who delivered during study time, how many were tested, how many opted out, and out of those tested who many were positive, and out of those how many enrolled? Were there any incentives to enroll? How was enrollment set up-was there a research team member present on L+D 24/7 to capture all women, or was it more sporadic?
3. It seems to me that for the general audience not following COVID immunology science very closely, types of antibodies used as outcome remeasures (listed in table 2) is a bit difficult to follow. Would it be possible to put together a table that describes each antibody and its role in the evolution of the disease and how that is relevant to vaccines?
4. Not including a non-pregnant cohort for the comparison was a limitation as the authors pointed out. What was the reason for not doing so?

Reviewer #2:

Line 138-139: I assume you mean pediatric hospitalizations from COVID-19?

Line 153-156: It is unclear what you mean by "latency." Viral latency typically means period of time after initial infection in which viral genome is not eradicated and can become re-activated/shedding virus. Or do you mean clinical latency period which is typically the incubation period after infection is acquired but before the host is symptomatic? One weakness of this study is that you cannot be certain about "time of infection" unless your patient has a known exposure to COVID-19 infected individual. Important to not confuse time of infection and time of PCR positive "diagnosis." What is your hypothesis?

Line 162: Please clarify, were all pregnant women enrolled or only those with SARS

Lines 198-203: This is background and/or discussion, does not seem to belong in methods.

Results: In general, don't repeat results in the text that are listed in the table.

Line 301-303: Please clarify time frame between maternal blood sample collection and delivery. In the 53% of patients who endorsed one or more symptom (Line 281), were these tested at the time of presentation for delivery? Or at some other time earlier in the pregnancy, then delivered later? For those diagnosed earlier in pregnancy, were maternal samples collected both at the time of diagnosis and at the time of delivery?

Line 340-342: Why were patients grouped like this instead of just plotting antibody titer versus days from delivery? There does not seem to be enough patients in the middle group to draw any meaningful conclusions.

Line 365: Very difficult to use "time of infection"…. You can use "time of symptom onset" and " time of positive PCR" but the relationship between these and the actual time of infection is unclear. Did you collect data on time of known exposures?

Reviewer #3: In this manuscript, Dr. Joseph and colleagues sought to characterize the maternal adaptive immune response following naturally acquired symptomatic and asymptomatic SARS-CoV-2 infection. To do so they examined the maternal to fetal transfer of antibodies by examining levels of antibodies in maternal and cord blood. This study has a relatively small sample size but a strength is they analyzed paired maternal and fetal cord blood samples.

1. Results- Line 282-285 - The symptoms listed are referenced to be listed in Table 2, however in my review, I do not see this data in Table 2.
2. Results- Line 304 - maternal and cord serum samples are stated as analyzed, however, in the methods, plasma was collected and stored. Please clarify.
3. Results- Line 315 - add the number of cord blood samples with + RBD IgM.
4. Results - Lines 340 - 344. P=0.05 is technically not significant, consider rewording
5. Results - Line 353, Table 3 is referenced in this paragraph. Not sure if this table was accidently omitted or if they meant to reference Supplementary Table 1.
6. Discussion - Overall well written. Line 427 - likely a typo - change vaccinatable to vaccinable and Line 433 - delete last word.

Reviewer #4: ONG-21-372
This prospective cohort study by Joseph and colleagues describes maternal immune response and maternal-neonatal anti-SARS-CoV-2 antibody transfer in the setting of SARS-CoV-2 infection in pregnancy. Key findings include transfer of maternal anti-SARS-CoV-2 IgG to the cord at ratios < 1, and significantly lower neutralizing capacity of antibodies in the cord compared to maternal blood. IgM was detected in 3 cords and antigenemia in 1 cord.
The work is robust and the conclusions are important. The cohort is diverse and represents a relatively understudied population in SARS-CoV-2 in pregnancy research. Some aspects would benefit from reframing and the manuscript contains some typos/small errors such as sentences that are started and unfinished. A careful proofread is needed prior to resubmission.
Key concerns are indicated with a **

Comments for authors
Abstract:
-line91-92: IgA, IgM are not transferred across the placenta. This line should be deleted. IgG is selectively transferred across the placenta
-line 104: one example of typo referenced above: "and the nearly all" - will not highlight others but wanted to provide example.
-Results: would remove the colloquial language ("nearly all", "almost all", "a few") and just state the ns/%s to establish scientific tone.
-Given the IgM present in 3 cords, would be useful if authors stated whether any neonates were deemed infected at birth and by what method.
-The last sentence of results should be more precise. What was the mean or median cord:maternal ratio?
-Conclusion: delete colloquial language such as "almost uniformly" and describe conclusions definitively. End with a strong statement of the importance of the work rather than a vague call for future research. (Example, key points are the lower-than-expected efficiency of SARS-CoV-2 transplacental antibody transfer and the significant reduction in neutralization between maternal blood and cord blood). These results suggest that maternal infection does confer some degree of neonatal antibody protection, but the robustness and durability of protection require further study.)

Methods
-line 178: should this say a "trained medical abstractor"? If degree of concordance between abstractor and NTJ was evaluated, this should be stated here.
-line 213: were the ELISA assays validated for specificity by examination of performance in known SARS-CoV-2 negative participants and/or pre-pandemic serum? How were the thresholds of 0.2, 0.15 and 0.35 chosen? "clinically validated" in absence of a reference may not be sufficient description. Would be strongest design to define positivity threshold relative to known negatives.
-line 218- "developed by the Crawford and colleagues"
-line 251: "differences in presence of absence"
-335-336: 8 cord blood samples were said to have neutralizing antibody, but then only 3 asymptomatic and 4 symptomatic (7 total) are described? Also, with only 8 cord blood samples, likely not valid to compare neutralizing titers in symptomatic vs asymptomatic given substantially underpowered to see difference and comparison could be misleading.

Results
-line 309 on: antibody titers are stated to be reported as median[IQR] but no range is reported for IQR- are these mean [SD] values instead? Tables report what look like traditional IQRs so this is confusing.
-line 312: don't understand the comparison "there was no significant difference between overall cohort maternal RBD IgG and neutralizing titers"? what comparison was made and what is intended significance of the comparison/statement? The authors have already noted that neutralizing antibody was present in 30/32 maternal samples.
-Line 315: would again use more precise language "RBD was IgM was detected in the cord blood of 3 neonates". As none of the neonates were tested at birth, do the authors believe the IgM in 3 cord bloods reflect neonatal infection, or non-specificity of the assay?
-**Lines 322-329: The team should offer more analyses to prove that the higher antibody titers they are associating with maternal symptoms are not simply attributable to a longer time from infection. E.g. if they control for # days from symptom onset/infection, does the association between symptoms and maternal titer remain, given that those who are asymptomatic positives at delivery will have a less mature immune response/shorter latency.
-Why was < 7 rather than < 14 days selected as the cutpoint for titer analysis by time from infection? 14 days seems a more accepted cutoff for when a more mature antibody response could be expected.
- It seems odd that time from initial diagnosis to delivery was not associated with reduction in IgM titers. Was there delayed class switching or how do the authors interpret this finding? Would think IgM should decline with time from diagnosis as IgG response becomes dominant…
-The cord positive for IgA likely represents a false positive? Can the authors discuss this finding further?
-Was the umbilical cord with detectable antigen also one in which IgM was detected? This should be specified.

Discussion
-There should be some discussion of the limitations of evaluating only 1 anti-SARS-CoV-2 antibody (e.g. no evaluation of S, N).
-The discussion of the differences between saliva and blood IgA is confusing, and a reference for the statement in lines 390-393 should be provided (discussion about IgA duration as measured in saliva). Not sure how informative it is to make this comparison, and there are also studies about blood IgA response to SARS-CoV-2 which might be more informative.
-**The comparisons of pregnant immune vs non pregnant immune responses line lines 412-414 is a substantial overreach/overinterpretation of what this study can say. It's too simplistic/reductionist to simply say "detectable IgG" in comparable % of participants connotes "an immune response similar to non pregnant peers." Titers would need to be compared directly, run at the same time/in same batch, etc to be able to make pregnant to non-pregnant comparisons of the immune response to SARS-CoV-2. This whole aspect should be removed or substantially rephrased in a more conservative manner.
-More interpretation should be provided regarding why longer latency resulted in increased maternal RBD titers but not increased CB titers. Insufficient power? Inefficient transfer?
-Discussion should cite this paper and findings should be placed in context of this paper as well. DOI:https://doi.org/10.1016/j.ajog.2021.01.016
-426-428. Authors should make more explicit the connection between lower-than-expected placental transfer of SARS-CoV-2 RBD and Zika and the higher transfer efficiencies of pertussis and influenza. More discussion of a de novo antibody response versus a recall antibody response, and potential differences between titers generated after natural infection vs vaccination would make this part of the discussion stronger. Additionally, placing this discussion in context of what a de novo vaccine response vs a recall vaccine response might mean for NMR would make the results most relevant, as we have moved into a new/ =different phase of the pandemic.
-Lines 431-433: interpretation of Atyeo et al is incomplete. Study demonstrated that antibody glycosylation profile was key determinant of reduced transplacental antibody transfer seen only for SARS-CoV-2-specific antibodies. "Inherent pathophysiology of virus and its effects on syncytiotrophoblast cells of the placenta" is too vague of an interpretation. Study also showed importance of non-canonical FcRs (e.g. more than just neonatal FcRn) in facilitating transfer of SARS-CoV-2-specific antibodies. The next sentence (line 433) states, "Howevr" but there is no text that follows.
-Lines 443-444: should this read "nor are follow-up data available.."?
-Line 444-445: not sure what newborn antibody titers would add to the assessment if cord blood titers were assessed. Durability of antibodies at 1 month? Demonstration of IgM persistence in heelstick plasma to demonstrate the IgM is not a false + in the neonates? Additional detail should be provided re why this is viewed as a limitation.

Conclusions

-These read quite strong, with the exception of the lines 469-472: "Our data provides some evidence that as the natural immunogenicity is similar in pregnancy…"- again these data really cannot be used to support that statement and comparisons of immunogenicity between pregnant and non-pregnant simply on the basis of the % of participants in whom anti-RBD IgG is detectable are not robust. Would remove these statements from the paper and focus on other aspects that the paper can state, such as the reduced neutralizing capacity of cord blood vs maternal and that this finding will be important to follow up in larger studies and in vaccination as a correlate of neonatal protection (just one example of another aspect that should be included in the conclusions).

STATISTICAL EDITOR COMMENTS:

Lines 113-114: Need to clarify whether the p= 0.05 comparison was statistically significant, since the Methods section in text does not specify an inference threshold.

Fig 1: Need to include CIs for the proportions cited and also include results of stats comparison of the proportions/counts cited.

Fig 2: For the comparisons of cord blood IgM, IgA and neutralizing Ab, the results are statistically NS but also very underpowered, based on small numbers of (+) cord blood samples. Therefore, those comparisons cannot be generalized due to insufficient stats power.

Fig 3: The issue of low stats power is compounded in these analyses, since the subsets are even smaller, so all the NS findings cannot be generalized, this would require a much larger series. Again, need to clarify whether the overall difference in medians was statistically significant. Were any pair-wise comparisons significant? Judging from the graphs, it would appear not, but that is mostly based on the small sample sizes.

Fig 4: I think that there is too much information conveyed in each of these figures, with overlapping lines among the subsets, which makes it visually confusing for the reader. The supplemental Table is sufficient.

General: Need to include in limitations section that the comparisons of various subsets with low counts (ie. many of the cord blood titers for symptomatic vs asymptomatic mothers and for the various maternal subsets based on GA and time from infection to delivery) are underpowered and those NS conclusions therefore cannot be generalized from these data, even though they may be biologically plausible.

EDITOR COMMENTS:

1. Thank you for submitting this work to Obstetrics and Gynecology. If you opt to submit a revision, please make this as accessible as possible to clinicians. In particular, please try to really drill down on the clinical implications of this work, and how it relates to some of the published work around vaccine antibody response and transfer across the placenta. The majority of our readers are clinicians, and we want to make sure that the importance of this work is clear to them.

2. We would like to fast track the revision for on-line publication if accepted. We are, therefore, asking for a 7-day turn around on revisions. The editorial staff will then expedite publication as much as possible after a final decision is made on this manuscript.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase 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. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA). Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page. Each of your coauthors received an email from the system, titled "Please verify your authorship for a submission to Obstetrics & Gynecology." Each author should complete the eCTA if they have no yet done so.

3. 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.

4. All submissions that are considered for potential publication are run through CrossCheck for originality. The following lines of text match too closely to previously published works.

Please disclose meeting presentation of https://www.ajog.org/article/S0002-9378(20)32587-4/fulltext at AJOG if not already cited.

5. 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.

6. 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.

7. 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 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure

legends, and print appendixes) but exclude references.

8. 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]."

9. 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; Reviews is 300 words; Case Reports is 125 words; Current Commentary articles is 250 words; Executive Summaries, Consensus Statements, and Guidelines are 250 words; Clinical Practice and Quality is 300 words; Procedures and Instruments is 200 words. Please provide a word count.

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. ACOG is moving toward discontinuing the use of "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.

13. 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%").

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 reference you are citing is still current and available. If the reference you are citing has been updated (ie, 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 (exceptions could include manuscripts that address items of historical interest). All ACOG documents (eg, Committee Opinions and Practice Bulletins) may be found at the Clinical Guidance page at https://www.acog.org/clinical (click on "Clinical Guidance" at the top).

16. Figures 1-5: Please upload as individual figure files on Editorial Manager. Please consider moving some to supplemental digital content for article length.
Supplemental Figure 1: Please confirm that this is original to the manuscript. Does an illustrator need to be credited?

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.

17. Each supplemental file in your manuscript should be named an "Appendix," numbered, and ordered in the way they are first cited in the text. Do not order and number supplemental tables, figures, and text separately. References cited in appendixes should be added to a separate References list in the appendixes file.

18. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at http://links.lww.com/LWW-ES/A48. The cost for publishing an article as open access can be found at https://wkauthorservices.editage.com/open-access/hybrid.html.

Please note that 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.

You will be receiving 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.

***

If you choose to revise your manuscript, please submit your revision through Editorial Manager at http://ong.editorialmanager.com. Your manuscript should be uploaded in a word processing format such as Microsoft Word. 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 09, 2021, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Torri D. Metz, MD
Associate Editor, Obstetrics

2019 IMPACT FACTOR: 5.524
2019 IMPACT FACTOR RANKING: 6th out of 82 ob/gyn journals

_____

COVER LETTER

Dwight J. Rouse, MD, MSPH
Editor-in-Chief, *Obstetrics & Gynecology*

Torri Metz, MD
Associate Editor, *Obstetrics & Gynecology*

April 7, 2021

Dear Dr. Rouse, Dr. Metz, and the Editorial Board,

Please find attached our revised submission, **Maternal Antibody Response, Neutralizing Potency, and Placental Antibody Transfer following SARS-CoV-2 Infection**. Attached you will find the original document with tracked changes, a clean version, tables, figures, and supplemental data. A line by line response follows this letter. Thank you again for your consideration of our work.

Warm regards,

Naima Joseph, MD, MPH
[redacted]

RE: Manuscript Number ONG-21-372
Maternal Antibody Response, Neutralizing Potency, and Placental Antibody Transfer following SARS-CoV-2 Infection

Dear Dr. Joseph:

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).

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 Apr 09, 2021, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

Thank you for the opportunity to review your work.

1. Intro. Is this research entirely novel, or is there anything published on this topic up to this study?

Yes, there have been studies published on maternal immunity, which are cited in our paper, specifically

a. Edlow AG, Li JZ, Collier AY, Atyeo C, James KE, Boatin AA, et al. Assessment of Maternal and Neonatal SARS-CoV-2 Viral Load, Transplacental Antibody Transfer, and Placental Pathology in Pregnancies During the COVID-19 Pandemic. JAMA Netw Open. 2020;3(12):e2030455.
b. Flannery DD, Gouma S, Dhudasia MB, Mukhopadhyay S, Pfeifer MR, Woodford EC, et al. Assessment of Maternal and Neonatal Cord Blood SARS-CoV-2 Antibodies and Placental Transfer Ratios. JAMA Pediatr [Internet]. 2021 Jan 29; Available from: https://doi.org/10.1001/jamapediatrics.2021.0038
c. Kubiak JM, Murphy EA, Yee J, Cagino K, Friedlander RL, Glynn SM, et al. SARS-CoV-2 serology levels in pregnant women and their neonates. Am J Obstet Gynecol [Internet]. 2021; Available from: http://www.ncbi.nlm.nih.gov/pubmed/33497654

2. Lines 162-172. SPORE and EMPOWR. I was not sure from the methods section how enrollment took place. Can a flow chart be created to show how enrollment took place? For

example, out of total women who delivered during study time, how many were tested, how many opted out, and out of those tested who many were positive, and out of those how many enrolled? Were there any incentives to enroll? How was enrollment set up-was there a research team member present on L+D 24/7 to capture all women, or was it more sporadic?

Thank you for your comment. We have added this as a limitation of our study and included flow diagram of enrollment in the supplement. Enrollment was opportunistic at both locations. At Grady, patients who tested positive at any point during their pregnancy were offered enrollment into SPORE, and at Emory University Hospital Midtown (EUHM), SRS COV2 positive patients were offered enrollment into EMPOWR. . All clinicians were reminded periodically to refer SARS COV2 positive patients by sending the patient's name/MRN to involved study personnel through secure messaging in the electronic medical record. Any member of the study staff could enroll the patient, yet enrollment was done primarily by study authors NTJ, CMD, LSI, MLB, either in person, or using IRB Approved electronic consent in REDCap. We do not have information on how many patients declined testing, tested positive, were offered enrollment, and declined enrollment at both sites. However, previous data indicate a 1-2% test positive rate at EUHM and 7-9% test positive at Grady for patients admitted to L&D for delivery. We did publish our L&D screening protocol and results from opt out screening during admissions for delivery – please see Joseph NT, Stanhope KK, Badell ML, Horton JP, Boulet SL, Jamieson DJ. Sociodemographic Predictors of SARS-CoV-2 Infection in Obstetric Patients, Georgia, USA. Emerg Infect Dis. 2020;26(11):2787-2789 PMID: 33050982.

3. It seems to me that for the general audience not following COVID immunology science very closely, types of antibodies used as outcome remeasures (listed in table 2) is a bit difficult to follow. Would it be possible to put together a table that describes each antibody and its role in the evolution of the disease and how that is relevant to vaccines?

The text has been modified in its entirety to provide clarity on antibody findings and relevance to disease evolution and implications for vaccination

4. Not including a non-pregnant cohort for the comparison was a limitation as the authors pointed out. What was the reason for not doing so?

Unfortunately, we did not have access to a non-pregnant reproductive age cohort with viral illness for inclusion in the study

Reviewer #2:

Line 138-139: I assume you mean pediatric hospitalizations from COVID-19?

The text has been edited to specify COVID19 hospitalizations

Line 153-156: It is unclear what you mean by "latency." Viral latency typically means period of time after initial infection in which viral genome is not eradicated and can become re-activated/shedding virus. Or do you mean clinical latency period which is typically the incubation period after infection is acquired but before the host is symptomatic? One weakness of this study is that you cannot be certain about "time of infection" unless your patient has a known exposure to COVID-19 infected individual. Important to not confuse time of infection and time of PCR positive "diagnosis." What is your hypothesis?

The text has been edited to reflect time from PCR confirmation to delivery. The hypothesis is that prolonged duration from infection to delivery is associate with improved maternal antibody response and transfer.

Line 162: Please clarify, were all pregnant women enrolled or only those with SARS

Pregnant patients with positive SARS COV2 PCR and planning to deliver at either of the two hospitals were offered enrollment.

Lines 198-203: This is background and/or discussion, does not seem to belong in methods.

Thank you for this comment. This has been moved to discussion.

Line 301-303: Please clarify time frame between maternal blood sample collection and delivery.

*The section on Sample processing and Collection (Line 195) states "*Following enrollment, maternal venous blood was collected into EDTA tubes when patients presented for clinical blood draws and at delivery hospitalization.*" Maternal blood collection occurred during delivery hospitalization and for most parturients was within 24 hours of delivery.*

In the 53% of patients who endorsed one or more symptom (Line 281), were these tested at the time of presentation for delivery? Or at some other time earlier in the pregnancy, then delivered later?

As per our protocol, all patients undergoing SARS COV 2 nasopharyngeal swab testing undergo a symptom screen administered by a nurse and documented in the EMR. 47% tested positive after undergoing asymptomatic testing during delivery admission to L&D. The 53% who tested positive had symptoms at the time of positive PCR, which was either during delivery hospitalization or at other points in their pregnancy. Four of these women were tested in the first and second trimesters.

For those diagnosed earlier in pregnancy, were maternal samples collected both at the time of diagnosis and at the time of delivery?

*The section on Sample processing and Collection (Line 195) states "*Following enrollment, maternal venous blood was collected into EDTA tubes at when patients presented for clinical blood draws.*" Collection was opportunistic and occurred at points in prenatal care when labs were otherwise indicated (i.e. gestational diabetes screening). However for this study, we only paired samples (maternal and cord) obtained during delivery hospitalization.*

Line 340-342: Why were patients grouped like this instead of just plotting antibody titer versus days from delivery? There does not seem to be enough patients in the middle group to draw any meaningful conclusions.

Thank you for this comment. We performed this type of analysis to categorize patients with acute phase (i.e. < 7 days from PCR positive to delivery), intermediate phase (7 – 28 days), and convalescent phase immunity (> 28 days) given differences in immune response according to time. However, based on reviewer feedback we have instead modeled this as a continuous variable as well as binary categorization on 14 days based on evolved understanding and

recent publications demonstrating peak immune response 14 days from infection.

Line 365: Very difficult to use "time of infection"…. You can use "time of symptom onset" and " time of positive PCR" but the relationship between these and the actual time of infection is unclear. Did you collect data on time of known exposures?

Thank you for this comment. We have edited the text to reflect time from PCR test positive.

Reviewer #3:

In this manuscript, Dr. Joseph and colleagues sought to characterize the maternal adaptive immune response following naturally acquired symptomatic and asymptomatic SARS-CoV-2 infection. To do so they examined the maternal to fetal transfer of antibodies by examining levels of antibodies in maternal and cord blood. This study has a relatively small sample size but a strength is they analyzed paired maternal and fetal cord blood samples.

1. Results- Line 282-285 - The symptoms listed are referenced to be listed in Table 2, however in my review, I do not see this data in Table 2.

Thank you for noticing this oversight! The reference to Table 2 has been removed

2. Results- Line 304 - maternal and cord serum samples are stated as analyzed, however, in the methods, plasma was collected and stored. Please clarify.

Thank you for this comment – edited to reflect plasma was analyzed

3. Results- Line 315 - add the number of cord blood samples with + RBD IgM.

The number of cord blood samples with +RBD IgM was 3 or 9% and the text has been edited accordingly

4. Results - Lines 340 - 344. P=0.05 is technically not significant, consider rewording

Thank you. For this type of analysis, a p value less than or equal to 0.05 was considered statistically significant.

5. Results - Line 353, Table 3 is referenced in this paragraph. Not sure if this table was accidently omitted or if they meant to reference Supplementary Table.

Thank you. This was meant to reference Supplementary Table 1.

6. Discussion - Overall well written. Line 427 - likely a typo - change vaccinatable to vaccinable and Line 433 - delete last word.

Thank you for noting our many oversights. Vaccinatable changed to "vaccine preventable" and deleted "Howevr,"

Reviewer #4:

ONG-21-372
This prospective cohort study by Joseph and colleagues describes maternal immune response

and maternal-neonatal anti-SARS-CoV-2 antibody transfer in the setting of SARS-CoV-2 infection in pregnancy. Key findings include transfer of maternal anti-SARS-CoV-2 IgG to the cord at ratios < 1, and significantly lower neutralizing capacity of antibodies in the cord compared to maternal blood. IgM was detected in 3 cords and antigenemia in 1 cord.
The work is robust and the conclusions are important. The cohort is diverse and represents a relatively understudied population in SARS-CoV-2 in pregnancy research. Some aspects would benefit from reframing and the manuscript contains some typos/small errors such as sentences that are started and unfinished. A careful proofread is needed prior to resubmission.
Key concerns are indicated with a **

Comments for authors
Abstract:
-line91-92: IgA, IgM are not transferred across the placenta. This line should be deleted. IgG is selectively transferred across the placenta

Edited accordingly

-line 104: one example of typo referenced above: "and the nearly all" - will not highlight others but wanted to provide example.

Thank you and we apologize for these oversights

-Results: would remove the colloquial language ("nearly all", "almost all", "a few") and just state the ns/%s to establish scientific tone.

Edited accordingly

-Given the IgM present in 3 cords, would be useful if authors stated whether any neonates were deemed infected at birth and by what method.

Neonatal information provided in the results section

-The last sentence of results should be more precise. What was the mean or median cord: maternal ratio?

Edited accordingly

-Conclusion: delete colloquial language such as "almost uniformly" and describe conclusions definitively. End with a strong statement of the importance of the work rather than a vague call for future research. (Example, key points are the lower-than-expected efficiency of SARS-CoV-2 transplacental antibody transfer and the significant reduction in neutralization between maternal blood and cord blood). These results suggest that maternal infection does confer some degree of neonatal antibody protection, but the robustness and durability of protection require further study.)

Edited accordingly

Methods
-line 178: should this say a "trained medical abstractor"? If degree of concordance between abstractor and NTJ was evaluated, this should be stated here.

Yes, abstraction was changed to abstractor. Degree of concordance was not analyzed

-line 213: were the ELISA assays validated for specificity by examination of performance in known SARS-CoV-2 negative participants and/or pre-pandemic serum? How were the thresholds of 0.2, 0.15 and 0.35 chosen? "clinically validated" in absence of a reference may not be sufficient description. Would be strongest design to define positivity threshold relative to known negatives.

Text modified to reflect that lab thresholds relative to pre-pandemic negative controls as well as known clinical positives with convalescent plasma, as well as reference Supplemental Figure.

-line 218- "developed by the Crawford and colleagues"

Edited accordingly

-line 251: "differences in presence of absence"

*" differences in presence **or** absence"*

-335-336: 8 cord blood samples were said to have neutralizing antibody, but then only 3 asymptomatic and 4 symptomatic (7 total) are described?

Error, should have included 3 asymptomatic and 5 symptomatic. Text has been edited accordingly

Also, with only 8 cord blood samples, likely not valid to compare neutralizing titers in symptomatic vs asymptomatic given substantially underpowered to see difference and comparison could be misleading.

Removed this from analysis

Results
-line 309 on: antibody titers are stated to be reported as median[IQR] but no range is reported for IQR- are these mean [SD] values instead? Tables report what look like traditional IQRs so this is confusing.

Apologize, erroneously include range rather than first and 3rd quartiles. This has been appropriately fixed throughout text.

-line 312: don't understand the comparison "there was no significant difference between overall cohort maternal RBD IgG and neutralizing titers"? what comparison was made and what is intended significance of the comparison/statement? The authors have already noted that neutralizing antibody was present in 30/32 maternal samples.

Agree with reviewer comments. Initial comparison between maternal RBD and neutralizing b levels, however we have already noted raw data for each and statistical comparison is superfluous. This has been removed.

-Line 315: would again use more precise language "RBD was IgM was detected in the cord blood of 3 neonates". As none of the neonates were tested at birth, do the authors believe the IgM in 3 cord bloods reflect neonatal infection, or non-specificity of the assay?

In the discussion we write "Anti RBD IgM was also present in three cord blood samples. Although detectable anti RBD IgM can be secondary to known issues with laboratory assays (26) or rare transplacental transfer of IgM seen with increased disease severity (2), it is possible that some represent vertical infection, which is known to occur, albeit rarely.(27) Although a congenital virus syndrome has yet to be described, our data indicate that neonatal morbidity associated with infection is overall low. "

-**Lines 322-329: The team should offer more analyses to prove that the higher antibody titers they are associating with maternal symptoms are not simply attributable to a longer time from infection. E.g. if they control for # days from symptom onset/infection, does the association between symptoms and maternal titer remain, given that those who are asymptomatic positives at delivery will have a less mature immune response/shorter latency.

Thank you for this comment. We conducted additional analyses, which are included in the appendix. There was overlap between groups: among the 17 who were symptomatic, 13 delivered > 28 days from time of first positive PCR. Amongst the 15 who were asymptomatic, 11 delivered < 7 days from initial infection.
A linear regression model fitted to estimate the independent effect of maternal symptomatic infection and time between PCR positivity on maternal anti-RBD IgG failed to show statistical significance when both independent variables were included in the model and was likely underpowered to demonstrate an effect. We attempted to estimate differences in initial antibody response between symptomatic and asymptomatic infection, however only 6 symptomatic women provided multiple maternal plasma samples, and only 3 had provided a sample within 7 days from initial PCR based diagnosis. Therefore we have acknowledged the limitations of sample size in our limitations section and can use these data to inform sample size and power analyses in subsequent work.

-Why was < 7 rather than < 14 days selected as the cut point for titer analysis by time from infection? 14 days seems a more accepted cutoff for when a more mature antibody response could be expected.

We appreciate the reviewer comments. We initially chose the cutoffs to demonstrate differences in acute, intermediate, and convalescent phase immunity to infection, however given what is known regarding maternal seroconversion in COVID the data have been reanalyzed to estimate duration as a continuous exposure, as well as according to < 14 and > 14 days from infection.

- It seems odd that time from initial diagnosis to delivery was not associated with reduction in IgM titers. Was there delayed class switching or how do the authors interpret this finding? Would think IgM should decline with time from diagnosis as IgG response becomes dominant.

This is an interesting finding and not easily interpretable in our cohort. Although we attempted to collect periodic lab draws for all enrolled subjects, longitudinal data are only available for 6 of the delivered subjects of which 2 experienced increasing IgM, 2 demonstrated decreasing, and 2 demonstrated no change to IgM titers over time which did not correspond to change in IgG

levels. This likely represents nonuniformity in sample collection, as maternal blood was drawn in a convenience fashion (i.e. only when patient was obtaining blood for clinical indications) rather than pre-specified time intervals (i.e. at time of first documented infection, or at specified time points from first positive infection). This was in accordance with the protocol approved by our IRB.

-The cord positive for IgA likely represents a false positive? Can the authors discuss this finding further?

Current thought is that IgG is the only immunoglobulin actively transported across the placenta, while remaining immunoglobins transport rarely. IgA has been demonstrated in some natural infections or vaccine induced immunity to transport in small quantities (REF: Borte S, Janzi M, Pan-Hammarström Q, et al. Placental transfer of maternally-derived IgA precludes the use of guthrie card eluates as a screening tool for primary immunodeficiency diseases. PLoS One. 2012;7(8):e43419; Ben-Hur H, Gurevich P, Elhayany A, Avinoach I, Schneider DF, Zusman I. Transport of maternal immunoglobulins through the human placental barrier in normal pregnancy and during inflammation. Int J Mol Med. 2005 Sep;16(3):401-7. PMID: 16077946; Malek A, Sager R, Schneider H. Transport of proteins across the human placenta. Am J Reprod Immunol. 1998 Nov;40(5):347-51. PMID: 9870078.). Given small sample, we did not want to speculate on whether this represented true transfer or issues with laboratory assay, however have briefly included in discussion.

-Was the umbilical cord with detectable antigen also one in which IgM was detected? This should be specified.

Subject specific antibody titer and antigen results are included in the supplementary table, however this has been specified in the text.

Discussion

Thank you for thoughtful and detailed review of the manuscript and especially for comments directed toward improving the discussion section. This section has been rewritten in its entirety to address and include comments and suggested provided by the reviewer. A point-by-point response is enumerated following.

-There should be some discussion of the limitations of evaluating only 1 anti-SARS-CoV-2 antibody (e.g. no evaluation of S, N).

Added to limitations

-The discussion of the differences between saliva and blood IgA is confusing, and a reference for the statement in lines 390-393 should be provided (discussion about IgA duration as measured in saliva). Not sure how informative it is to make this comparison, and there are also studies about blood IgA response to SARS-CoV-2 which might be more informative.

This has been removed and IgA highlighted to discuss secretory response and implication for vaccination

-**The comparisons of pregnant immune vs non pregnant immune responses line lines 412-414 is a substantial overreach/overinterpretation of what this study can say. It's too simplistic/reductionist to simply say "detectable IgG" in comparable % of participants connotes "an immune response similar to non-pregnant peers." Titers would need to be compared directly, run at the same time/in same batch, etc. to be able to make pregnant to non-pregnant comparisons of the immune response to SARS-CoV-2. This whole aspect should be removed or substantially rephrased in a more conservative manner.

Agree and this entire section has been removed

-More interpretation should be provided regarding why longer latency resulted in increased maternal RBD titers but not increased CB titers. Insufficient power? Inefficient transfer?

This has been added to the discussion

-Discussion should cite this paper and findings should be placed in context of this paper as well. DOI:https://nam11.safelinks.protection.outlook.com/?url=https%3A%2F%2Fdoi.org%2F10.1016%2Fj.ajog.2021.01.016&data=04%7C01%7Cnaima.thavory.joseph%40emory.edu%7C638c3a5bd8ae47ad627408d8f5ed5025%7Ce004fb9cb0a4424fbcd0322606d5df38%7C0%7C0%7C637529747347031457%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=E4ssy4bJlf9tbYv83%2Fo8NbnB89swi%2FDhvBM0VU7i21c%3D&reserved=0

This has been added to the discussion

-426-428. Authors should make more explicit the connection between lower-than-expected placental transfer of SARS-CoV-2 RBD and Zika and the higher transfer efficiencies of pertussis and influenza. More discussion of a de novo antibody response versus a recall antibody response, and potential differences between titers generated after natural infection vs vaccination would make this part of the discussion stronger. Additionally, placing this discussion in context of what a de novo vaccine response vs a recall vaccine response might mean for NMR would make the results most relevant, as we have moved into a new/ =different phase of the pandemic.

This has been added to the discussion

-Lines 431-433: interpretation of Atyeo et al is incomplete. Study demonstrated that antibody glycosylation profile was key determinant of reduced transplacental antibody transfer seen only for SARS-CoV-2-specific antibodies. "Inherent pathophysiology of virus and its effects on syncytiotrophoblast cells of the placenta" is too vague of an interpretation. Study also showed importance of non-canonical FcRs (e.g. more than just neonatal FcRn) in facilitating transfer of SARS-CoV-2-specific antibodies. The next sentence (line 433) states, "Howevr" but there is no text that follows.

The text has been edited accordingly

-Lines 443-444: should this read "nor are follow-up data available.."?

This has been removed

-Line 444-445: not sure what newborn antibody titers would add to the assessment if cord blood titers were assessed. Durability of antibodies at 1 month? Demonstration of IgM persistence in heelstick plasma to demonstrate the IgM is not a false + in the neonates? Additional detail should be provided re why this is viewed as a limitation.

This has been removed

Conclusions
-These read quite strong, with the exception of the lines 469-472: "Our data provides some evidence that as the natural immunogenicity is similar in pregnancy…"- again these data really cannot be used to support that statement and comparisons of immunogenicity between pregnant and non-pregnant simply on the basis of the % of participants in whom anti-RBD IgG is detectable are not robust. Would remove these statements from the paper and focus on other aspects that the paper can state, such as the reduced neutralizing capacity of cord blood vs maternal and that this finding will be important to follow up in larger studies and in vaccination as a correlate of neonatal protection (just one example of another aspect that should be included in the conclusions).

The text has been edited accordingly

STATISTICAL EDITOR COMMENTS:

Lines 113-114: Need to clarify whether the p= 0.05 comparison was statistically significant, since the Methods section in text does not specify an inference threshold.

Thank you. The text has been edited accordingly

Fig 1: Need to include CIs for the proportions cited and also include results of stats comparison of the proportions/counts cited.

Thank you for this comment, however, there was no statistical analysis comparing raw percentages.

Fig 2: For the comparisons of cord blood IgM, IgA and neutralizing Ab, the results are statistically NS but also very underpowered, based on small numbers of (+) cord blood samples. Therefore, those comparisons cannot be generalized due to insufficient stats power.

Agree with statistical conclusion, however there is biologic plausibility as placenta transfer of IgM and IgA as measured through cord blood levels is known to be quite low.

Fig 3: The issue of low stats power is compounded in these analyses, since the subsets are even smaller, so all the NS findings cannot be generalized, this would require a much larger series. Again, need to clarify whether the overall difference in medians was statistically significant.

We determined a significant difference in maternal anti RBD IgG levels between the three groups, but no difference in maternal anti RBD IgA, IgM, or neutralizing response, nor in cord anti RBD IgG levels. This has also been stated in the text

Were any pair-wise comparisons significant? Judging from the graphs, it would appear not, but that is mostly based on the small sample sizes.

We did not perform pairwise comparisons given small sample size and concerns regarding type I and type II error.

Fig 4: I think that there is too much information conveyed in each of these figures, with overlapping lines among the subsets, which makes it visually confusing for the reader. The supplemental Table is sufficient.

Thank you for this comment. We utilized dot plot to demonstrate relative maternal to cord anti RBD IGG titers and overall convey reduced cord blood titers to maternal titers. This is the normative graphical representation for data of this type (for example: Edlow AG, Li JZ, Collier AY, Atyeo C, James KE, Boatin AA, et al. Assessment of Maternal and Neonatal SARS-CoV-2 Viral Load, Transplacental Antibody Transfer, and Placental Pathology in Pregnancies During the COVID-19 Pandemic. JAMA Netw Open. 2020;3(12):e2030455, Suthar MS, Zimmerman MG, Kauffman RC, Mantus G, Linderman SL, Hudson WH, et al. Rapid Generation of Neutralizing Antibody Responses in COVID-19 Patients. Cell Reports Med [Internet]. 2020;1(3):100040. Available from: https://doi.org/10.1016/j.xcrm.2020.100040; Atyeo C, Pullen KM, Bordt EA, Fischinger S, Burke J, Michell A, et al. Compromised SARS-CoV-2-specific placental antibody transfer. Cell [Internet]. 2021;184(3):628-642.e10. Available from: https://www.sciencedirect.com/science/article/pii/S0092867420317499)

Therefore we have opted to keep the figure as a main part of the text.

General: Need to include in limitations section that the comparisons of various subsets with low counts (i.e.. many of the cord blood titers for symptomatic vs asymptomatic mothers and for the various maternal subsets based on GA and time from infection to delivery) are underpowered and those NS conclusions therefore cannot be generalized from these data, even though they may be biologically plausible.

Thank you, the limitations section has been edited accordingly

EDITOR COMMENTS:

1. Thank you for submitting this work to Obstetrics and Gynecology. If you opt to submit a revision, please make this as accessible as possible to clinicians. In particular, please try to really drill down on the clinical implications of this work, and how it relates to some of the published work around vaccine antibody response and transfer across the placenta. The majority of our readers are clinicians, and we want to make sure that the importance of this work is clear to them.

Thank you for the comments and your thoughtful consideration of our manuscript. The text has been edited in its entirety to provide a version that targeted to a clinical audience.

2. We would like to fast track the revision for on-line publication if accepted. We are, therefore, asking for a 7-day turn around on revisions. The editorial staff will then expedite publication as much as possible after a final decision is made on this manuscript.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase 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.

OPT - IN

2. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA). Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page. Each of your coauthors received an email from the system, titled "Please verify your authorship for a submission to Obstetrics & Gynecology." Each author should complete the eCTA if they have not yet done so.

3. 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 (e.g., 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.

This has been done in accordance with journal standards.

4. All submissions that are considered for potential publication are run through CrossCheck for originality. The following lines of text match too closely to previously published works.

Please disclose meeting presentation of https://nam11.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.ajog.org%2Farti cle%2FS0002-9378&data=04%7C01%7Cnaima.thavory.joseph%40emory.edu%7C638c3a5bd8ae47ad627408d8f5ed5025%7Ce004fb9cb0a4424fbcd0322606d5df38%7C0%7C0%7C637529747347031457%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=ahuwm0iq1OepKA9Ibnadpf71GUJU0bRpNTvG5tNJB%2BY%3D&reserved=0(20)32587-4/fulltext at AJOG if not already cited.

Meeting presentation has been disclosed on title page

5. 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 (i.e., CONSORT), observational studies (i.e., STROBE), observational studies using ICD-10 data (i.e., RECORD), meta-analyses and systematic reviews of randomized controlled trials (i.e., PRISMA), harms in systematic reviews (i.e., PRISMA for harms), studies of diagnostic accuracy (i.e., STARD), meta-analyses and systematic reviews of observational studies (i.e., MOOSE), economic evaluations of health interventions (i.e., CHEERS), quality improvement in health care studies (i.e., 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 https://nam11.safelinks.protection.outlook.com/?url=http%3A%2F%2Fong.editorialmanager.com%2F&data=04%7C01%7Cnaima.thavory.joseph%40emory.edu%7C638c3a5bd8ae47ad627408d8f5ed5025%7Ce004fb9cb0a4424fbcd0322606d5df38%7C0%7C0%7C637529747347031457%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=CIdM4O%2Br5Tzu%2BRDHf5VrpvMq0cyUvUNJ2rcbqO5ikkY%3D&reserved=0. 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.

The reported work represents bench/laboratory research and does not apply to above named types of studies

6. 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://nam11.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.acog.org%2Fpractice-management%2Fhealth-it-and-clinical-informatics%2Frevitalize-obstetrics-data-definitions&data=04%7C01%7Cnaima.thavory.joseph%40emory.edu%7C638c3a5bd8ae47ad627408d8f5ed5025%7Ce004fb9cb0a4424fbcd0322606d5df38%7C0%7C0%7C637529747347031457%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=0b7UNLjxZzzjk8EPGd1QZTKlQS%2F0evz53V%2FQhBDREww%3D&reserved=0and the gynecology data definitions at https://nam11.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.acog.org%2Fpractice-management%2Fhealth-it-and-clinical-informatics%2Frevitalize-gynecology-data-definitions&data=04%7C01%7Cnaima.thavory.joseph%40emory.edu%7C638c3a5bd8ae47ad627408d8f5ed5025%7Ce004fb9cb0a4424fbcd0322606d5df38%7C0%7C0%7C637529747347031457%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=WpDrmkRKTvmgYIMAX9xpOTHnTab6X7%2F8J6HYhU1wtu4%3D&reserved=0. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

7. 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 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

8. 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]."

Appropriate edits included

9. 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; Reviews is 300 words; Case Reports is 125 words; Current Commentary articles is 250 words; Executive Summaries, Consensus Statements, and Guidelines are 250 words; Clinical Practice and Quality is 300 words; Procedures and Instruments is 200 words. Please provide a word count.

10. Only standard abbreviations and acronyms are allowed. A selected list is available online at https://nam11.safelinks.protection.outlook.com/?url=http%3A%2F%2Fedmgr.ovid.com%2Fong%2Faccounts%2Fabbreviations.pdf&data=04%7C01%7Cnaima.thavory.joseph%40emory.edu%7C638c3a5bd8ae47ad627408d8f5ed5025%7Ce004fb9cb0a4424fbcd0322606d5df38%7C0%7C0%7C637529747347031457%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=8mVmX8lZdFXxe%2B4LX6epYOWgjGG%2BTThIkRHNnnkb6mc%3D&reserved=0. 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. ACOG is moving toward discontinuing the use of "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.

13. 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%").

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: https://nam11.safelinks.protection.outlook.com/?url=http%3A%2F%2Fedmgr.ovid.com%2

Fong%2Faccounts%2Ftable_checklist.pdf&data=04%7C01%7Cnaima.thavory.joseph%40emory.edu%7C638c3a5bd8ae47ad627408d8f5ed5025%7Ce004fb9cb0a4424fbcd0322606d5df38%7C0%7C0%7C637529747347031457%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=tFDDoo5%2BpJoRXRdxzZrt61yiOeoDdx3ZrjXs59nUL2A%3D&reserved=0.

15. Please review examples of our current reference style at https://nam11.safelinks.protection.outlook.com/?url=http%3A%2F%2Fong.editorialmanager.com%2F&data=04%7C01%7Cnaima.thavory.joseph%40emory.edu%7C638c3a5bd8ae47ad627408d8f5ed5025%7Ce004fb9cb0a4424fbcd0322606d5df38%7C0%7C0%7C637529747347041452%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=zIyCl6k7iFPzfE7TlVafRVpJbRXsTeucoLI6303Qk6k%3D&reserved=0(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 reference you are citing is still current and available. If the reference you are citing has been updated (i.e., 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 (exceptions could include manuscripts that address items of historical interest). All ACOG documents (e.g., Committee Opinions and Practice Bulletins) may be found at the Clinical Guidance page at https://nam11.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.acog.org%2Fclinical&data=04%7C01%7Cnaima.thavory.joseph%40emory.edu%7C638c3a5bd8ae47ad627408d8f5ed5025%7Ce004fb9cb0a4424fbcd0322606d5df38%7C0%7C0%7C637529747347041452%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=mGmcubyVmvNIPt6MHrXRTGhy%2FMWCamdLS1aWjxoHpg8%3D&reserved=0(click on "Clinical Guidance" at the top).

16. Figures 1-5: Please upload as individual figure files on Editorial Manager. Please consider moving some to supplemental digital content for article length.
Supplemental Figure 1: Please confirm that this is original to the manuscript. Does an illustrator need to be credited?

Yes this is original to manuscript

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 (e.g., 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.

17. Each supplemental file in your manuscript should be named an "Appendix," numbered, and ordered in the way they are first cited in the text. Do not order and number supplemental tables, figures, and text separately. References cited in appendixes should be added to a separate References list in the appendixes file.

18. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at https://nam11.safelinks.protection.outlook.com/?url=http%3A%2F%2Flinks.lww.com%2FLWW-ES%2FA48&data=04%7C01%7Cnaima.thavory.joseph%40emory.edu%7C638c3a5bd8ae47ad627408d8f5ed5025%7Ce004fb9cb0a4424fbcd0322606d5df38%7C0%7C0%7C637529747347041452%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=wedMrI2E%2BDVRYhVHq5uOHNv%2F%2FEC9DMT7GHOcs%2F5l%2B20%3D&reserved=0. The cost for publishing an article as open access can be found at https://nam11.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwkauthorservices.editage.com%2Fopen-access%2Fhybrid.html&data=04%7C01%7Cnaima.thavory.joseph%40emory.edu%7C638c3a5bd8ae47ad627408d8f5ed5025%7Ce004fb9cb0a4424fbcd0322606d5df38%7C0%7C0%7C637529747347041452%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=QFNHeJbLG%2FjqIwXRzJDpbbDOwN5%2BwZb0LCj1XpbBDPU%3D&reserved=0.

Please note that 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.

You will be receiving 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.

***

If you choose to revise your manuscript, please submit your revision through Editorial Manager at https://nam11.safelinks.protection.outlook.com/?url=http%3A%2F%2Fong.editorialmanager.com%2F&data=04%7C01%7Cnaima.thavory.joseph%40emory.edu%7C638c3a5bd8ae47ad627408d8f5ed5025%7Ce004fb9cb0a4424fbcd0322606d5df38%7C0%7C0%7C637529747347041452%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=zIyCl6k7iFPzfE7TlVafRVpJbRXsTeucoLI6303Qk6k%3D&reserved=0. Your manuscript should be uploaded in a word processing format such as Microsoft Word. Your revision's cover letter should include the following:

* A confirmation that you have read the Instructions for Authors (https://nam11.safelinks.protection.outlook.com/?url=http%3A%2F%2Fedmgr.ovid.com%2Fong%2Faccounts%2Fauthors.pdf&data=04%7C01%7Cnaima.thavory.joseph%40emory.edu%7C638c3a5bd8ae47ad627408d8f5ed5025%7Ce004fb9cb0a4424fbcd0322606d5df38%7C0%7C0%7C637529747347041452%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=odQVTXBq1EsZHEi5j1OMShAyKx%2BpL9k1kTv3hOEm6SI%3D&reserved=0), 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 09, 2021, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Torri D. Metz, MD
Associate Editor, Obstetrics

2019 IMPACT FACTOR: 5.524
2019 IMPACT FACTOR RANKING: 6th out of 82 ob/gyn journals

PAoE%2BypILQ9lewuHlTwGT%2Frhqf876XBGJPwA%3D&reserved=0). Please contact the publication office if you have any questions.