OBSTETRICS & GYNECOLOGY

NOTICE: This document contains comments from the reviewers and editors generated during peer review of the initial manuscript submission and sent to the author via email.

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

Date: Apr 09, 2020
To: "Daniele De Luca" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-548

RE: Manuscript Number ONG-20-548

Low risk of SARS-CoV-2 vertical transmission in neonates born to mothers with COVID-19 pneumonia

Dear Dr. De Luca:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. Dr. Chescheir is interested in potentially publishing your revised manuscript in a timely manner. In order to have this considered quickly, we need to have your revision documents submitted to us as soon as you are able. I am tentatively setting your due date to April 13, 2020, but please let me know if you need additional time.

The standard revision letter text follows my signature.

Thank you,
Randi Zung
Interim Managing Editor
rzung@greenjournal.org
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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).

REVIEWER COMMENTS:

Reviewer #1:

This study presents the maternal and neonatal courses of eight patients with PCR confirmed COVID-19 pneumonia who delivered at term in Wuhan, China.

The study describes the epidemiology, symptoms, laboratory findings, time between symptoms and delivery, type of delivery, placenta, and antiviral treatment before delivery.

Seven of eight patients delivered by elective cesarean section before the onset of labor. The patient that delivered vaginally had an unaffected neonate based upon laboratory evaluation and clinical course. She was the lone patient to receive antiviral medication prior to delivery.

The lone neonate who had throat swabs positive at 36 and 72 hours of life had the shortest time between his mother's onset of symptoms and delivery (8 hours). His placenta was the only one that had abnormal pathologic findings.

The authors conclude that there is "a low chance of vertical transmission of SARS-CoV-2 from mothers affected by COVID-19 during the last days of pregnancy and the absence of perinatal consequences of SARS-COV-2 infection."

Comments

Line 51: Please distinguish between COVID-19 and SARS-CoV-2 which seem to be used interchangeably throughout the manuscript.

Line 64: Suggest that the sentence read "There seems to be a low chance of vertical transmission of SARS-CoV-2 from mothers affected by COVID-19 delivering by elective cesarean section during the last days of pregnancy."

Line 66: The sentence is somewhat incorrect because one infant did develop "clinical" evidence of COVID-19 with positive

throat swabs. The mother potentially was shedding high amounts of virus as she delivered within 8 hours of symptom onset. Her only symptom was fever.

Line 94: Please state the specificity for SARS-CoV-2 RT-PCR.

Line 133: The mother had a cough…Table 1 states that she did not have a cough.

Line 146 Case 6: I am not certain that this patient should be included in the study as RT-PCR of maternal throat swab specimen was negative. Authors should also state sensitivity for detection.

Line 175: Suggest expounding upon mechanism of viral attachment in adults.

Reviewer #2: In the manuscript under consideration, the authors describe a case series of eight pregnant women infected with SARS-CoV-2 with the focus on the risk of vertical transmission to their neonates.

PRECIS & ABSTRACT
-The authors state that the delivery must occur in isolation and that the neonates must be separated. I think this is a hard conclusion to draw from a case series. They can state that this was their practice which resulted in zero cases of vertical transmission, however, we do not know if the neonate was not separated if transmission would have occurred or not

TEACHING POINTS
-Again, I would make sure these are demonstrated as the author's experience.

CASES
-Line 93 states that RT-PCR was performed in maternal and fetal samples. These samples should be described here
-Line 115: were the neonates fed expressed milk from their mothers, donor milk, formula?
-In case 1, the authors describe the CT findings; in the remainder of the cases they only describe "findings typical of a viral pneumonia". This should be explicitly defined somewhere in this section.
-Case 3: Was there resolution of liver dysfunction? If so, when? Was this thought to be due to SARS-CoV-2?

DISCUSSION
-The authors planned on cesarean delivery for all of their cases and accomplished this in 7 of 8. The one vaginal delivery did not have vertical transmission. I think the authors have be careful with any claims that the cesarean was protective as we really do not know this based on this case series.
-The authors protocol was to separate the neonates, but it still remains unknown if there would be transmission from mom to baby after delivery if mom wears a mask, or if breastfeeding is protective, etc.
-The authors conclude with a strong statement about management. I think they can conclude that by separating mothers and infants they did not have any neonates develop infection.ac

Reviewer #3: Authors report a case series of 8 maternal-neonate pairing of mothers with COVID-19 viral pneumonia. RT-PCR testing confirmed COVID 19 pneumonia in 7/8 mothers; all neonates except 1 had negative testing for COVID 19: all amniotic fluid and breast milk samples tested negative.

This small case series adds to the current body of evidence based on 52 neonates born to COVID19 infected women who were investigated.

1. Authors need to update references to include data on 10 neonates reported by Zhu et al (Transl Pediatr 2020; 9(1):51-60 and the 33 neonates reported by Zeng et al (JAMA Pediatr doi :10.1001/jamapediatrics.2020.0878)

2. Lines 110-120: please clarify how testing was done on all neonates; daily from birth to 14 days (including sample sites) as described in case #1?

3. Lines 120-160 is redundant; table 2 should suffice

4. What do authors make of the neonate that tested positive in their series in light of Zeng's report of 3 infants with viral pneumonia despite isolation and negative RT-PCR testing of amniotic fluid, breast milk and cord blood? Yet, those authors stated vertical transmission cannot be ruled out. Please include in your discussions.

5. Table 3 has no added value.

Reviewer #4: Although it is encouraging that only 1 of 8 neonates was Covid-19(+), that proportion (12%) has 95% CIs of 0-70%, so it is difficult to generalize conclude from these data that vertical transmission would occur at a low rate. That is, the statement may be true, but one cannot use these data as definitive support for that conclusion. Similarly, although I understand the concern re: vertical transmission that led to cesarean delivery, the only Covid-19(+) occurred in one of the cesarean deliveries, while the one instance of a vaginal delivery did not result in transmission to the neonate.

Table 2: The minimum wgt during week 1 vs the birth weights have no apparent relationship to the % wgt loss. Need to clarify how the % wgt loss was calculated.

lines 193-195: What is the basis for isolation from the mother for 14 days vs after the mother has tested (-) for Covid-19?

EDITOR'S COMMENTS:

We no longer require that authors adhere to the Green Journal format with the first submission of their papers. However, any revisions must do so. I strongly encourage you to read the instructions for authors (the general bits as well as those specific to the feature-type you are submitting). The instructions provide guidance regarding formatting, word and reference limits, authorship issues ad other relevant topics. Adherence to these requirements with your revision will avoid delays during the revision process by avoiding re-revisions on your part in order to comply with formatting. Please format this as Research Letter when you revise your paper. We will allow additional tables beyond the limit described in the Instructions to Author. As you discussion will be much shorter, you can eliminate many of your references to be within this limits described.

Numbers below refer to line numbers.

45. As this is a case series, it is important not to overstate your conclusions. Some of this is noted by your reviewers. Please have your precis say something like “One of eight infants born to women with symptomatic Covid-19 infection tested positive for the infection and was asymptomatic”

55: as noted by reviewer, please clarify. In the manuscript you say the RT -PCR was positive at 36 and 72 hours. In table 2, its not clear either--

58: Again, avoid overstating. Something like “In this series of 8 neonates of women with symptomatic Covid-19 infection, 1 had a positive test at 36 hours and remained asymptomatic. Larger series of mother-infant pairs are necessary to understand transmission rates and interventions to prevent neonatal infection”. Use your own words of course but the content here is about the limit of what you can conclude.

Essentially none of these teaching points are acceptable for a case series. In your series you did not have perinatal consequences or sick babies, but other papers are being published that counter this. Please make teaching points limited to what you can say in your case series.

89. Please note that your study was conducted from date 1 to date 2, not between those dates. As written, it would exclude the dates given.

100. Table 1. Would you consider the following edits to paragraph starting on line 100:
“Clinical characteristics of the 8 pregnant women are reported in Table 1 and are summarized below. None had underlying disease and prior to the COVID-19 diagnosis, their pregnancies were uneventful. The clinical presentations included low grade fevers, 37.8-38.8 C, cough, and diarrhea: two were asymptomatic and were evaluated due to known exposures. Their clinical symptoms, if present, began 3-12 days prior to presentation to the obstetrics unit. Chest CT studies showed diffuse and patchy lung consolidation. [clarify that this is true]. Laboratory abnormalities, if present, included lymphopenia and mild transaminitis. No mother experienced clinical deterioration and there were no delivery-related complications. All mothers recovered from COVID-19.

According to regional guidelines, route of birth was planned as cesarean in all 8, although one spontaneously labored and delivered vaginally. Clinical characteristics of the neonates are summarized in Table 2. Infants were immediately isolated for 14 days.[Describe their nutrition: maternal breastmilk? Donor milk? Formula?] Again, according to protocol, neonatal RT=PCR throat swabs and blood, fecal and urine samples were tested [how often?]. Neonatal biochemical and complete blood count testing were done on the first and third day of life and these results are in table 3. Chest X-rays, brain ultrasounds were performed [how often? Routine or due to finding?] No neonate developed abnormal vital signs or respiratory distress. None of the neonates developed symptoms; all of the imaging studies and blood tests were normal. One infant had a positive throat swab at 36 and 72 hours hours of life [clarify: ; no other laboratory test was abnormal.

[With this summary and the tables, you can delete the individual case summaries, lines 120-160)

DISCUSSION—should be dramatically shortened.

163: In your discussion, please be very cautious about what you can conclude. You could say something like

In our case series of 8 mothers ill will Covid-19 in the hours to days prior to delivery, one asymptomatic neonate had a positive RT-PCR COVID-19 throat swab at 36 and 72 hours of life. The treatment protocols used in our center, based on guidance from the Wuhan government, included planned cesarean birth and neonatal isolation at birth with breast feeding of [breast milk, donor milk, formula]. This series includes results of protocol-based neonatal serial imaging, RT-PCR testing in multiple body compartments and clinical assessment.

It remains to be seen if this low rate of vertical transmission will be confirmed when more cases are described. If so, possible explanations include rapid maternal virus elimination and poor maternal-to-amniotic fluid transmission of virus. [please explain the logic for role of ACE receptors here].

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. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the 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.

3. Our journal requires that all evidence-based research submissions be accompanied by a transparency declaration statement from the manuscript's lead author. The statement is as follows: "The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained." *The manuscript's guarantor.

If you are the lead author, please include this statement in your cover letter. If the lead author is a different person, please ask him/her to submit the signed transparency declaration to you. This document may be uploaded with your submission in Editorial Manager.

4. To prevent confusion among our readers and reviewers, manuscripts submitted to the journal must be written in grammatically correct formal English. We recommend that you have a native English speaker read your revised manuscript before you submit it.

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 and gynecology data definitions at https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize. 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: 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.

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).

8. 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."

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 limits for different article types are as follows: Original Research articles, 300 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. 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%").

13. Line 82: Your claim about there only being one other case series article may have changed by the time you submit your revision. We recommend that you search this again and include your search strategy information (databases used, search terms, and search date ranges).

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.

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16. 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.

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.

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

2018 IMPACT FACTOR: 4.965
2018 IMPACT FACTOR RANKING: 7th out of 83 ob/gyn journals

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