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: May 12, 2020
To: "Benjamin Huntley" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-1163

RE: Manuscript Number ONG-20-1163

COVID-19 in pregnancy: a systematic review of reports with at least ten cases

Dear Dr. Huntley:

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 May 20, 2020, but please let me know if you need additional time.

The standard revision letter text follows.

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: The authors have submitted a very timely paper on COVID-19 pregnancy outcomes. The Precis is startling. The Abstract is straightforward although the data could be better displayed in Results. The Conclusion seems misplaced as no one is expecting droves of maternal or neonatal deaths and the 82%(!) c-section rate is glossed over as if it is a trivial finding.

Intro
1 - Concise, yet effective background is provided to justify the need for this study.

Methods
2 - Importantly, journal guidelines were rigidly followed (line 87, 92)
3 - The limitations of identifying 'clean' data are highlighted (line 97-103) and though with mixed results, the transparency of the process is easy to follow and refreshing.

Results
4 - 14 studies included which is quite a lot, yet a flow chart here would be helpful to understand how 91 got whittled to 14
5 - The 82% c-section rate is mentioned line 150, but the 'may have been due' opinion is best moved to the Discussion (where it is repeated line 160). It's going to raise the point though of how this applies to the US. Can the authors break it down by country? I cannot imagine the rates in Italy and US are in that ballpark. The rate of PTL, C-section and NICU deserve more attention in the Discussion than just a dismissal statement suggesting the authors have no idea why yet seeming to still claim that COVID-19 is associated with an increase in pregnancy complications (line 164)

Discussion
6 - This section is sloppily written and would benefit from re-reading and fixing grammatical mistakes or missing words.
7 - The concluding paragraph (line 185-190) is unnecessary in suggesting here that COVID-19 somehow led to more PTL and c-sections when earlier the authors largely blew this off as just regional panic or some such reason.
8 - It would be helpful to address the possible data problems as limitations when they did not get responses from the 3 authors in China and therefore cannot vouch for those as independent data sets

Table 1 is necessary

Table 2 can be moved to SDC

Table 3, 4 and 5 have a lot of missing data and also can be triaged to SDC

Reviewer #2: Important aggregation of data.

Major issues:
Inconsistently in ordering and reporting what were declared to be primary outcomes. This starts with the Precis and extends to the Abstract and text (the focus on cesarean delivery and prematurity is understandable but those really are not your specific main outcomes).

I don't think you need all of the Tables.

Minor issues:Line 26: would drop the first "the"

Line 35: very garbled especially with the awkward "dyad" business

Could be much crisper

STATISTICAL EDITOR COMMENTS:

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

General: The descriptive statistics of n(%) and pooled proportions with 95% CIs are arithmetically accurate, but have to be interpreted with caution. For instance, although it is obvious that only Covid-19 pregnancies were eligible for inclusion into the analysis, that criterion depends on whether only symptomatic women vs all pregnant women were tested. That is included in Table 2 and needs emphasis in the discussion. Clearly the test criteria could influence the proportion of comorbidities in Table 1, for example. Also, the pooled data is heavily weighted towards the 4 largest cohorts out of 14 studied (n = 118, 89, 65 and 43), which total = 315, or 55% of the women.

Table 2: As seen in this Table, most (~ 82%) were identified by selective screening, thus biasing the results if one were to include asymptomatic Covid-19 (+) women.

Table 3: Due to heterogeneity among the individual studies, many maternal characteristics were reported in small proportions of the women (eg, myalgia, headache, lymphopenia or abn hepatic enzymes). Thus those estimates may be biased for this N = 569, in
addition to being non-representative of all covid-19(+) pregnant women.

Table 4: Again, the arithmetic is correct, but the proportion with mild disease represents a selected group and asymptomatic women are
likely under represented.

Table 5: The incomplete reporting and selected groups makes these outcome proportions difficult to generalize.

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 and 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.

Numbers below refer to line numbers.

PRESENTATION OF STATS INFORMATION (P Values vs Effect Size and Confidence Intervals)
While P values are a central part of inference testing in statistics, when cited alone, often the strength of the conclusion can be misunderstood. Whenever possible, 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.
This is true for the abstract as well as the manuscript, tables and figures.

Please provide absolute values for variables, in addition to assessment of statistical significance.

We ask that you provide crude OR's followed by adjusted OR's for all relevant variables.

Please limit p values to 3 decimal places.

Please spell out all abbreviations on first use in the abstract and in the manuscript.

Dr. Fox's paper was not accepted and those patients will need to be excluded. Not all of them were microbiologically confirmed.

45. were these the only definitions of morbidity? Why not use a standard definition like the CDC definition?

51. Why/how did you include deliveries without outcomes? Given that your objective was complications and disease severity of the maternal-neonatal dyad, its unclear how your inclusion criteria included pregnancies without delivery outcomes.

Quality of studies must be very poor if you don't have available information on comorbidities in almost half of patients. Also, how could the # of women with critical disease be about half the number admitted to ICU? Generally, severely ill people are admitted to ICU. To clarify, please define terms in your methods (ie, what constitutes severe disease, etc).

Delete "with" before "95% CI " throughout manuscript and abstract, tables.

Conclusion seems like it should include limitation of what is likely (Based on what I've read so far) poor quality data.

68: saying they "provided" bronchoalveolar lavage samples sounds like they just walked into the hospital with a sterile cup and donated it. Perhaps they "underwent bronchoalvealar lavage"?

72. Delete "that"

73. "associated "with the novel virus"…

79. You've stated here that your objectives related to maternal-neonatal dyads. As such, your included cases should be limited to outcomes for both. In your methods, please be clearer about how you selected papers. Did they require microbiologic diagnosis for all patients? When did you accept a paper without a delivery outcome or neonatal outcome description, for instance. How did you define comorbidities? Please state in your methods that you did not require microbiologically confirmation.

85. I don't know what you mean by "a protocol designed preemptively". (definition: taken as a measure against something possible, anticipated, or feared; preventive;)

Somewhere in the results section, please tell us the # of included patients from China, the US, Italy and other. This is relevant given the CS rate of 82% as practice patterns really differ across these sites. It may also inform peoples' thinking a bit about the results.

144: This sentence is incomplete. Wouldn't some values be elevated, as well as depressed? Perhaps just say something like "Laboratory result reporting varied widely, precluding useful analysis". Perhaps say something like "In reporting cases, lymphopenia was found in xx% (# with lymphopenia/Total with report of lymphocyte value) of women

How many patients had microbiologic confirmation?

147. You should describe the Wu criteria in the methods section.

150. Can you report how many were spontaneous preterm birth v iatrogenic? Or at least how many of CS were preterm vs term? Can you provide EGA at birth? How many cases did not result in a birth, and the EGA of these cases . This may be irrelevant if you exclude the non-birthing patients to align with your objective. Can you report these date (preterm birth, CS, NICU admits) by country?

169> Another strength is that you tried to eliminate duplicates.

174. what is the relevance of the sentence starting with "it is possible…". You are not studying outcomes of people not infected and you've provided no data on it.

178: Missing a word "how TO manage"

182: “threatened” should be “threaten”.

Starting around 173 would you consider adding some verbiage about there being no data as yet to support such a high cesarean rate and nor, if known, the iatrogenic prematurity rate. We don’t know which sick Covid patients need to get delivered in order to improve their ventilatory status, for instance. Maybe all of them, may be only a few. The results of your study are a snap shot of what has happened to date in a rapidly changing pandemic, across 3 continents primarily with wildly different OB practice patterns in some cases to begin with. The results may be telling us what sort of questions need to be asked, but we should be careful about suggesting that the results show us how we should be caring for these patients.

173. Did any papers have a control group?

181: who I making these projections?

186: these adverse outcomes may all be preventable…may not be indicated.
As far as neonatal transmission, please provide additional informatin about these were tested for in the results. Were the neonates adequately tested?

Table 1: Give unit for age; do you have a mean gestational age for the different studies? The number with deliveries?

Since you have to remove Fox’s data and redo your analysis, it may be worth it to see if there are any more studies that fit your inclusion that have published since you submitted. We are about to publish a paper from Italy with 77 women included. The paper will publish ahead of print on May 18 (at www.greenjournal.org) and if you would like, I can put you in touch with the authors.

MANUSCRIPT EDITOR'S COMMENTS:

1. Would you provide a title that is more specific? One suggestion is, “Pregnancies Complicated by Coronavirus Disease 2019 (COVID-19), Rates of Maternal and Perinatal Mortality, and Vertical Transmission: A Systematic Review.” Please do not use “with at least 10 Cases” in the subtitle.

2. Provide a running title of about 45 characters.

3. Please ask Erin Huntley to complete the Copyright Transfer Agreement. A link to it was sent to her email on 5/11.

4. Please make sure your manuscript’s headings conform to the ones for a Systematic Review in our Instructions for Authors:

a. In the abstract: Objective: Statement of purpose of the review; Data Sources: Sources searched, including dates, terms, and constraints; Methods of Study Selection: Number of studies reviewed and selection criteria, as well as any software used to assist with the review process; Tabulation, Integration, and Results: Guidelines for extracting data, methods of correlating, and results of review.

b. In the body text: Introduction: Indicates why the topic is important and states the specific bjective(s) of the review; Sources: Identifies what was searched and how; if a computerized system was used, specify the dates searched, the language(s) covered, and the search terms used; Study Selection: Identifies the number and nature of reports reviewed, the basis of any selection (ie, exclusion and inclusion criteria), and the reports in the final tabulation; Results: Describes how observations across studies were tabulated and integrated into a cohesive whole; Discussion: Includes what can be concluded from the review, along with clinical implications and need for additional research.

5. Provide more detail about reference 28. If it will continue to be in press within the next two weeks, remove it from your reference list and cite it in the text only. Renumber your subsequent references, both in the body text and References list.

6. Make sure all abbreviations used in the tables are defined in each table footnote. In Table 2, what does "NM" mean in the "Reported COVID-19 symptoms at presentation" column (5th row)?

7. Questions about your supplemental table:

a. The table cites Murad as reference 15, but the only Murad article cited in the References list is reference 20. Would you clarify which reference the table came from?

b. If the table was from "Methodological quality and synthesis of case series and case reports" by Murad et al, how did you use the article to create your table?

c. Please cite the supplemental table as “Appendix 1” in your article. Change the title of the supplemental table from

"Supplemental Table 1" to "Appendix 1."

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). 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. 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.

5. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Review articles should not exceed 25 typed, double-spaced pages (6,250 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.

6. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.

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. 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 Reviews is 300 words. Please provide a word count.

9. 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.

10. 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.

11. 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%").

12. 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.

13. 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.

14. 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 http://edmgr.ovid.com/acd/accounts/ifauth.htm.

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.

***

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