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: Jul 15, 2020
To: "Antonio Saad" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-1937

RE: Manuscript Number ONG-20-1937

Corticosteroids in the Management of Pregnant Patients with COVID-19 Infection

Dear Dr. Saad:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. The Editors are 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 July 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: This is an excellent and timely commentary. I have concerns, some major.

1) The Recovery Trial has not been published in the peer reviewed literature. Peer reviewed COVID 19 papers from major journals have been retracted. Is this commentary therefore premature, and should it await the publication of the peer reviewed article?

2) The Recovery Trial was "open label" and "adaptive" and evaluated more than one treatment. Is it possible that there was interaction of steroids with those other treatments? And because it was open label, could other clinical treatments, biased by knowledge or treatment allocation, have influenced outcomes?

3) In the Recovery Trial, patients not on oxygen had a 17% mortality rate with steroids, versus a 13.2% mortality rate if they were not on steroids. This was not significant, but the RR was 1.22, and the P value 0.14 so maybe it was a power issue. And if this higher mortality were in fact true, the implications in pregnancy could be substantial, since, if I understand your algorithm, a pregnant patient qualifies if she has COVD and is receiving oxygen. Are you not concerned that pregnant women will receive oxygen at much higher frequency than patients not pregnant? That is, they will receive oxygen when not indicated, and may then experience outcomes like the no oxygen group in the Recovery Trial. At a minimum, you should specify the indications for oxygen in pregnancy and if they differ much from the trial criteria (that is, are much more liberal) is this not concerning?

4) Since all pregnant patients with COVID who are preterm are at risk for delivery in the next week, why not give them all dexamethasone for 48 hours and simplify the algorithm.

Minor issues:

Line 58: "Fewer" rather than "less";

Line 67: "suggest" not "suggests"

The "Steroid Therapy and ARDS section could be shortened by half;

Line 136: Here and in the algorithm, don't have to specify how to give insulin;

Line 77 and line 78: Don't need P values: Also, should data not be give for the no oxygen groups"

Lines 80-82: Exclusion details not necessary;

Lines 88-92: Don't really need.

Line 117: Where do you "summarize" it above?

Reviewer #2: The authors have submitted a timely commentary on important nuances to consider when treating pregnant women for severe COVID-19.

1 - The issues are adequately framed for further elaboration in the tightly-written Intro

2 - Debatable whether the summary statement (line 67-70) is necessary

3 - Repetition line 90 which has already been stated in Intro line 32

4 - Multiple times explaining 6 mg dex x 4 for pregnant women could be condensed.

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.

23.The précis is a single sentence of no more than 25 words, written in the present tense and stating 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. Precis should be the "hook" for people who scan the Table of Contents to see what to read. It shouldn't not include statements like "in this study" or "we found". Just state what you found.

You will need to submit an abstract.

30. Spell out all abbreviations (CDC) on firs use.

43. Please indicate that AI and BI are levels of evidence.

74. Describe the RECOVERY trial and please address one reviewer's concerns about reporting on this trial.

80 Can you state specifically if people with diabetes were excluded? Given that diabetes will likely be a common comorbidity in COVID-19 affected pregnant women, this should be explicitly stated.

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. Per WHO guidelines and journal style, “infection” should not be used with “COVID-19.” Similar to the differentiation between HIV and AIDS, SARS-CoV-2 infection can, but does not always, cause COVID-19, just as HIV infection can, but does not always, cause AIDS. Make sure your that paper indicates patients who are without symptoms do not have COVID-19.

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 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.

5. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Current Commentary articles should not exceed 12 typed, double-spaced pages (3,000 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. 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).

7. 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."

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 Current Commentary articles is 250 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. 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).

12. Figure 1 may be resubmitted with the revision.

13. 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.

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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

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

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In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: https://www.editorialmanager.com/ong/login.asp?a=r). Please contact the publication office if you have any questions.

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SCHOOL OF MEDICINE
DEPARTMENT OF MATERNAL FETAL MEDICINE

Antonio F Saad MD

[redacted]

July 20, 2020

Obstetrics & Gynecology

409 12th Street, SW,

Washington, DC 20024-2188

Dear Editors:

Please find attached our revised clinical practice manuscript entitled “Corticosteroids in the Management of Pregnant Patients with COVID-19 Infection.”

We provide responses to the reviewers’ comments on the following pages.

This article has not been previously published and is not currently under consideration for publication by any other journal. The authors will not submit it to another journal unless a final negative decision is made by the editors of Obstetrics & Gynecology.

Each of the authors made substantial contributions to the drafting of the manuscript, and each has confirmed they have no conflicts of interest.

For questions concerning this manuscript, please feel free to contact me.

Respectfully,

Antonio F Saad, MD

Manuscript Number ONG-20-1937

Corticosteroids in the Management of Pregnant Patients with COVID-19 Infection

Reviewer #1: This is an excellent and timely commentary. I have concerns, some major.

1) The Recovery Trial has not been published in the peer reviewed literature. Peer reviewed COVID 19 papers from major journals have been retracted. Is this commentary therefore premature, and should it await the publication of the peer reviewed article?

Response: The reviewer may be alluding to the studies regarding hydroxychloroquine. Unlike the RECOVERY trial, these studies were not randomized trial and were not performed by a national consortium with data coordinating center. The use of steroids in COVID patient is already standard of care now. The opinion is based on current knowledge and practice. It would be important to disseminate this knowledge now rather than wait until publication in print.

2) The Recovery Trial was "open label" and "adaptive" and evaluated more than one treatment. Is it possible that there was interaction of steroids with those other treatments? And because it was open label, could other clinical treatments, biased by knowledge or treatment allocation, have influenced outcomes?

Response: The RECOVERY trial was open label, with each patient allocated only one of a number of treatments on the adaptive platform. For the initial part of the trial, patients were allocated to one of dexamethasone (or equivalent corticosteroid for pregnant women), hydroxychloroquine, lopinavir-ritonavir, with azithromycin subsequently added in, or no treatment (with patients receiving usual clinical care) on a 1:1:1:1:2 basis. The only additional treatment more commonly used in combination with the allocated trial treatment was azithromycin, used for treatment of pneumonia by a very similar proportion in patients allocated to dexamethasone (23%) or usual care (24%). As the primary outcome was mortality within 28 days, we do not anticipate that this outcome is likely to have been biased by knowledge of treatment allocation.

3) In the Recovery Trial, patients not on oxygen had a 17% mortality rate with steroids, versus a 13.2% mortality rate if they were not on steroids. This was not significant, but the RR was 1.22, and the P value 0.14 so maybe it was a power issue. And if this higher mortality were in fact true, the implications in pregnancy could be substantial, since, if I understand your algorithm, a pregnant patient qualifies if she has COVD and is receiving oxygen. Are you not concerned that pregnant women will receive oxygen at much higher frequency than patients not pregnant? That is, they will receive oxygen when not indicated, and may then experience outcomes like the no oxygen group in the Recovery Trial. At a minimum, you should specify the indications for oxygen in pregnancy and if they differ much from the trial criteria (that is, are much more liberal) is this not concerning?

Response: We agree with the reviewer, we have recently published a commentary summarizing the basic initial respiratory support interventions and indications recommended for pregnant patients with infection with the severe acute respiratory syndrome coronavirus 2. (Pacheco LD, Saad AF, Saade G. Early

Acute Respiratory Support for Pregnant Patients With Coronavirus Disease 2019 (COVID-19) Infection. Obstet Gynecol. 2020;136(1):42-45. doi:10.1097/AOG.0000000000003929).

We have updated our algorithm (Figure 1) specifying to start oxygen therapy in pregnant patients when SpO2 values fall below 94%.

4) Since all pregnant patients with COVID who are preterm are at risk for delivery in the next week, why not give them all dexamethasone for 48 hours and simplify the algorithm.

Response: Thank you for the comment, we disagree with the reviewer since for the reasons that we give related to unnecessary use of dex. Surely clinicians should use their clinical judgement to assess risk of delivery in next 7 days as someone with mild symptoms is not at same risk of preterm delivery as someone requiring oxygen.
Minor issues:

Line 58: "Fewer" rather than "less";

Response: Changes made.

Line 67: "suggest" not "suggests"

Response: Changes made.

The "Steroid Therapy and ARDS section could be shortened by half;

Response: Section has been shortened.

Line 136: Here and in the algorithm, don't have to specify how to give insulin;

Response: Sentence was removed.

Line 77 and line 78: Don't need P values: Also, should data not be give for the no oxygen groups"

Response: We have removed the p values as suggested. And added the suggested data.

Lines 80-82: Exclusion details not necessary;

Response: Changes made as suggested.

Lines 88-92: Don't really need.

Response: Changes made.

Line 117: Where do you "summarize" it above?

Response: " As summarized above" was deleted.

Reviewer #2: The authors have submitted a timely commentary on important nuances to consider when treating pregnant women for severe COVID-19.

1 - The issues are adequately framed for further elaboration in the tightly-written Intro

Response: Thank you for the comment.

2 - Debatable whether the summary statement (line 67-70) is necessary

Response: Sentence removed as suggested.

3 - Repetition line 90 which has already been stated in Intro line 32

Response: Sentence removed as suggested.

4 - Multiple times explaining 6 mg dex x 4 for pregnant women could be condensed.

Response: We decreased the repetition.

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.

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Response: The précis has been changed as suggested.

You will need to submit an abstract.

Response: Abstract has been added.

30. Spell out all abbreviations (CDC) on firs use.

Response: Relevant changes have been made.

43. Please indicate that AI and BI are levels of evidence.

Response: Relevant changes have been made.

74. Describe the RECOVERY trial and please address one reviewer's concerns about reporting on this trial.

Response: Relevant changes have been made according to the editor's and reviewer 's concerns.

80 Can you state specifically if people with diabetes were excluded? Given that diabetes will likely be a common comorbidity in COVID-19 affected pregnant women, this should be explicitly stated.

Response: We have specified that patient with history of diabetes were not excluded (24% of the included patient population had diabetes).