

OBSTETRICS & GYNECOLOGY



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

Date: Oct 30, 2020
To: "Chitra Gotluru" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-2682

RE: Manuscript Number ONG-20-2682

COVID-19: Clinical Commentary on Interplay of Sex, Hormones And Immune Functions

Dear Dr. Gotluru:

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 21 days from the date of this letter. If we have not heard from you by Nov 20, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

This is a review of the literature and a set of hypothesis about how the female cis-gender and certain female-specific hormonal states, such as pregnancy, menopause, or PCOS may affect susceptibility to the SARS-CoV-2 virus. This is a very intriguing commentary; I learned a lot reading it and appreciate the chance to review this for inclusion in our journal.

Strengths:

- * The commentary is well-written and well-structured, and appropriate literature is cited where necessary/available.
- * The commentary keeps the knowledge base of its comments at the right level for readers, not assuming that they are not experts in the virology of SARS-CoV-2, but physicians with high medical comprehension to understand these concepts.
- * This reviews several female-individual states that are relevant to our reading audience, such as the reasoning behind pregnancy and gynecologic-related illnesses like PCOS being susceptible states.

Limitations:

- * Certain statements can only be based on supposition, as evidence regarding the sub-population being discussed is sorely limited, and potential for evidence emerging on it is limited, such as the statement that rapid progesterone withdrawal in the postpartum state may lead to more susceptibility to the SARS-CoV-2 virus. The authors, however, do mention when statements or hypothesis are just suppositions.
- * Some odd use of commas, both in lack of them and inappropriate placement of them, throughout the document. As the document has many longer and multi-clause sentences, a copy-writer should review this thoroughly before publication.

Reviewer #2:

Thank you for the opportunity to review "COVID-19: Clinical Commentary on Interplay of Sex, Hormones And Immune Functions" by Gotluru et al.

This manuscript posits that "certain female populations, including pregnant and menopausal women and possibly polycystic ovary syndrome (PCOS) patients, are more susceptible to COVID-19 related morbidity."

This is an interesting commentary positing hypotheses relating hormonal states of pregnancy, menopause and PCOS to

increased susceptibility to COVID-19.

These hypotheses are all associative. It is true that pregnancy, and post menopause have increased risk of COVID-19 infection and hospitalization compared to reproductive age non-pregnant women.

The authors make a leap to suggest that the hormonal and inflammatory state of PCOS may increase the risk of COVID-19 among women with PCOS although they present no data demonstrating the increased risk.

The role of sex steroids estrogen, progesterone, and androgens are posited by the authors to have a role in susceptibility to COVID-19 infection. They hypothesize that the post partum drop in progesterone may increase the risk of COVID19 and that providing progesterone or progestins may mitigate that increased risk. They support the hypothesis with evidence of apparent mild disease while pregnant becoming more acute in postpartum patients.

Similarly they cite the increased risk of severe COVID morbidity and mortality that begins in women after the age of menopause. And suggest that loss of sex steroids may be part of the the reason for this increased risk.

A recent preprint from a group in the UK the "COVID Symptom Study" (<https://doi.org/10.1101/2020.07.30.20164921>) found that oral contraceptive use appeared to be protective for women of reproductive age but that among post-menopausal women HRT increased the risk of infection. The above findings should be noted in this commentary.

The relationship of sex steroids to ACE-2 expression is dealt with in somewhat more depth in another recent review (Groban, L., Wang, H., Sun, X. et al. Is Sex a Determinant of COVID-19 Infection? Truth or Myth?. Curr Hypertens Rep 22, 62 (2020). <https://doi.org/10.1007/s11906-020-01073>). This too should be cited.

It's still too early to dismiss any hypothesis regarding COVID-19. This commentary is thought provoking and well written.

Reviewer #3:

This manuscript presents a good summary of the possible role of hormones and COVID-19. The writing is at times clunky and would benefit from a good editor. A few thoughts for consideration are as follows:

1. Running Title: Change to "Commentary on COVID-19 and Sex" . . . you can't have an interplay on one subject
2. Authors: Include degrees for the first and second authors as well as the city, state of the author affiliation
3. Precis: Use people first language throughout, such as "people with PCOS."
4. Make the manuscript more concise through a careful edit, such as the following:
 - a. Abstract: " . . . the virus that causes COVID-19, utilizes . . . " (delete "is a virus that"), " . . . females and males, which may explain a mechanism . . . (add comma, delete extra space, delete possible), the last sentence of the abstract is cumbersome
 - b. Missing hyphen in COVID-19 on line 33
 - c. E
5. Add a sentence in the manuscript about people who are neither female nor male.
6. The sentence structure throughout is very simple. In order to engage the reader, I suggest some variation. In addition, the paragraphs are overly short and frequently do not clearly link to one another.
7. Introduction: I would start with your third paragraph . . . make the case for why this matter before you present the background information. The epidemiology paragraph should also include information that supports the claim of increased disease severity among males.
8. The entire foundation of your paper is that people who are pregnant, menopausal, and have PCOS have higher COVID-19-related morbidity, but this statement does not appear in the introduction. I would argue that this commentary's main goal is to establish this foundational claim and also posit some theories as to why this might be.
9. I recommend that the paper topic order of pregnancy, menopause, and PCOS matches the presented order in the abstract and the introduction.
10. The discussion of the possible role of progesterone contraceptives should very much reinforced as a theoretical idea. The sentence about breast milk production is inappropriate in this context and should be removed - the decision between a progesterone-only and combined hormonal agent is much more complicated than presented.
11. Figure 1 is excellent.

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.
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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. In order for an administrative database study to be considered for publication in Obstetrics & Gynecology, the database used must be shown to be reliable and validated. In your response, please tell us who entered the data and how the accuracy of the database was validated. This same information should be included in the Materials and Methods section of the manuscript.

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5. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric data definitions at <https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions> and the gynecology data definitions at <https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions>. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

6. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: 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.

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 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. 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.

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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.

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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).

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- * 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 Nov 20, 2020, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

John O. Schorge, MD
Associate Editor, Gynecology

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

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