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: May 04, 2020
To: "Keith A. Hansen" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-1079

RE: Manuscript Number ONG-20-1079

To Operate, or Not To Operate: Ectopic Pregnancy during COVID-19

Dear Dr. Hansen:

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 11, 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 present a Clinical Conundrum regarding a woman with an ectopic pregnancy who is also Covid-19 positive. I have a few comments/questions for the authors:

1. I would suggest adding more clinical data to the vignette. Specifically, how/why was she diagnosed with Covid-19 (routine screening, exposure, illness, and if so, how severe). Also, I would add a sentence that clarifies that she is stable from an ectopic perspective (vitals, exam, for example).

2. in "What is a reasonable course of action" is the statement that methotrexate is contraindicated an opinion of the authors or a true contraindication? obviously, it makes sense, but they should clarify if they have a source for this or not.

3. the authors list the testing required prior to methotrexate, but since they recommend surgery for this patient, they should clarify what preoperative testing they would want in a Covid-19 positive patient undergoing surgery for ectopic. It would likely be more expansive than a non-covid patient about to undergo surgery. they mention the CXR, but nothing else specifically.

4. how would the authors handle anticoagulation, if any, postoperatively? there is a lot of talk about increased risk of thromboembolism with covid-19 patients.

5. from my read, the main point of this CC is to state that MTX isnt an option in patients who are Covid-19 positive. As such, I think this manuscript would be improved if the authors gave more details on this recommendation. for example, are there any circumstances when the authors would consider MTX in a covid-19 positive patient? what if she has no symptoms and it was picked up on routine screen? how long after a positive test would they consider her immunosuppressed? what if covid-19 is suspected but testing isnt available?

Reviewer #2: This is an tough clinical scenario and likely the most significant gynecologic emergency we will face during this pandemic.

1) The part subtitled:
"What is the evidence to counsel your patient?" needs a different subtitle or to be arranged differently - after this subtitle, there is a discussion of the science, dosage, indication for treatment with methotrexate, so perhaps the subtitle should be

"When to use Methotrexate and how does it work?" The information given is more information for the doctor and not counseling the patient. There should be a separate discussion of risks and actual counseling of patient. Furthermore, there is a discussion of transmission of COVID-19 in this section with explanation of respiratory droplets and aerosolization which does not fit under this subtitle and should be organized separately.

2) There is a statement that laparoscopy has increased risk over laparotomy yet there are no citations to substantiate this. Is this proven? If so, there should be a citation. Is this just theoretical based on understanding the surgery? One may think that given that laparoscopy is more contained, there would be less risk. There needs to be some discussion of what this statement is based on or it would seem that people may be encouraged to proceed with laparotomy.

3) The last sentence in this same section states that laparotomy should be done if increased risk of bowel injury seems not complete. Laparotomy should be done on anyone if it is deemed the safest route due to adhesions, patient status, etc, so perhaps a broader statement that one should always proceed with the safest route is most appropriate.

4) What is a reasonable course of action? In this section it states that Methotrexate is contraindicated in COVID-19 patients due to the risk of myelosuppression. While MTX would definitely be of concern given this risk, is there direct evidence of absolute contraindication and if so it should be cited. Otherwise, perhaps this statement should be softened - "it is a relative contraindication" or "should be used with caution" just to protect from this statement legally exposing someone who might have treated an ectopic with MTX to avoid surgery given limitations and fear/little evidence early on in this pandemic.

5) It seems incongruous that the recommendation is for laparoscopy after a discussion above that laparoscopy has more risk of spread of virus. These pieces of information need to be brought together -
"despite the theoretical risk of increased transmission of COVID with laparoscopy, this approach can be modified to decrease this risk . . . this is still the preferred route of surgery when done appropriately." Or some such statement.

There has to be a transition from when you state that it is the bigger risk of transmission but then the recommended route of treatment - why is it still recommended? Is there proof that the modifications helps or just theoretical assumptions?

Just afraid to imply that 1 treatment is the best route without evidence or with the risk of jeopardizing someone to have done something "wrong" with treatment if there is not strong evidence to support that.

CONSULTANT EDITOR COMMENTS:

The editor conference call had some important suggestions for you to consider. The reviewers thought there may not have been evidence to completely remove MTX as an option; however, a suggestion was made to make the clinical vignette more challenging. I am including an edited MS Word version of your submission. Randi Zung will send it to you by email.

EDITORIAL OFFICE COMMENTS:

1. Please confirm that the "patient" case you are presenting in your submission is hypothetical. Or, please confirm that you have obtained written consent from the patient to potentially publish their case.

2. 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.

3. 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.

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: Clinical Conundrums articles should not exceed 6 pages (1,500 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.

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 short title of no more than 45 characters, including spaces, for use as a running foot.

8. 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.

9. 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.

10. 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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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,

Mark A. Turrentine, MD
Consultant Editor for Clinical Conundrums

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

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.

Mark A. Turrentine, MD

Consultant Editor, Clinical Conundrums

409 12th Street SW

Washington, DC 20024

Dear Dr Turrentine,

We are submitting the revision of our manuscript ONG-20-1079 titled “To Operate, or Not To Operate: Ectopic Pregnancy during COVID-19”as a potential Clinical Conundrums article. The revised version is saved as a Word file using the “track changes” feature of word to demonstrate the position of changes made in the manuscript.

We would like to thank the reviewers and the editors for the comments to improve our manuscript. Below you will see responses to reviewers and editors.

Reviewer #1: The authors present a Clinical Conundrum regarding a woman with an ectopic pregnancy who is also Covid-19 positive. I have a few comments/questions for the authors:

1. I would suggest adding more clinical data to the vignette. Specifically, how/why was she diagnosed with Covid-19 (routine screening, exposure, illness, and if so, how severe). Also, I would add a sentence that clarifies that she is stable from an ectopic perspective (vitals, exam, for example).

We have expanded the data within the clinical vignette to include that she was diagnosed with COVID-19 due to exposure and that she is stable from a clinical standpoint.

2. in "What is a reasonable course of action" is the statement that methotrexate is contraindicated an opinion of the authors or a true contraindication? obviously, it makes sense, but they should clarify if they have a source for this or not.

This was an opinion of the authors. With the revised version we have removed that MTX is a contraindication and discuss the importance of balancing benefits and risks of all potential therapies in a COVID-19 positive patient. We also discuss that one wants to carefully consider the risk of potential myelosuppession and immunodeficiency with MTX in someone who is COVID-19 positive.

3. the authors list the testing required prior to methotrexate, but since they recommend surgery for this patient, they should clarify what preoperative testing they would want in a Covid-19 positive patient undergoing surgery for ectopic. It would likely be more expansive than a non-covid patient about to undergo surgery. they mention the CXR, but nothing else specifically.

We have expanded the area of testing, to include suggested testing for patients with mild to moderate COVID-19 and those with more severe disease.

4. how would the authors handle anticoagulation, if any, postoperatively? there is a lot of talk about increased risk of thromboembolism with covid-19 patients.

This is an important addition to the manuscript as COVID-19 patients may have a higher risk of both arterial and venous thromboembolism. The WHO suggests anticoagulation in hospitalized COVID-19 patients. In this asymptomatic, obese, pregnant, COVID-19 positive patient it would make sense to prophylactically anticoagulated prior to surgery.

5. from my read, the main point of this CC is to state that MTX isnt an option in patients who are Covid-19 positive. As such, I think this manuscript would be improved if the authors gave more details on this recommendation. for example, are there any circumstances when the authors would consider MTX in a covid-19 positive patient? what if she has no symptoms and it was picked up on routine screen? how long after a positive test would they consider her immunosuppressed? what if covid-19 is suspected but testing isnt available?

These are interesting, thought provoking questions, but with the change in our clinical vignette and the “softening” of our stance on MTX use they are no longer necessary for this discussion.

Reviewer #2: This is an tough clinical scenario and likely the most significant gynecologic emergency we will face during this pandemic.

1) The part subtitled:
"What is the evidence to counsel your patient?" needs a different subtitle or to be arranged differently - after this subtitle, there is a discussion of the science, dosage, indication for treatment with methotrexate, so perhaps the subtitle should be "When to use Methotrexate and how does it work?" The information given is more information for the doctor and not counseling the patient. There should be a separate discussion of risks and actual counseling of patient. Furthermore, there is a discussion of transmission of COVID-19 in this section with explanation of respiratory droplets and aerosolization which does not fit under this subtitle and should be organized separately.

The subtitle “What is the evidence to counsel your patient” has been changed into two sections; Methotrexate and how it works and COVID-19 transmission and surgery.

2) There is a statement that laparoscopy has increased risk over laparotomy yet there are no citations to substantiate this. Is this proven? If so, there should be a citation. Is this just theoretical based on understanding the surgery? One may think that given that laparoscopy is

more contained, there would be less risk. There needs to be some discussion of what this statement is based on or it would seem that people may be encouraged to proceed with laparotomy.

This section has been re-written to more fully discuss the benefits and risks of laparotomy or laparoscopy in this patient, and the advantages of a minimally invasive approach even in a COVID-19 positive patient. Most of this discussion is theoretical for COVID-19 based on other viruses and understanding of the surgical techniques.

3) The last sentence in this same section states that laparotomy should be done if increased risk of bowel injury seems not complete. Laparotomy should be done on anyone if it is deemed the safest route due to adhesions, patient status, etc, so perhaps a broader statement that one should always proceed with the safest route is most appropriate.

Absolutely agree. This segment has been modified to discuss the importance of balancing benefits and risks and selecting the safest surgical approach for the patient.

4) What is a reasonable course of action? In this section it states that Methotrexate is contraindicated in COVID-19 patients due to the risk of myelosuppression. While MTX would definitely be of concern given this risk, is there direct evidence of absolute contraindication and if so it should be cited. Otherwise, perhaps this statement should be softened - "it is a relative contraindication" or "should be used with caution" just to protect from this statement legally exposing someone who might have treated an ectopic with MTX to avoid surgery given limitations and fear/little evidence early on in this pandemic.

Thank you for this insight and the statements have been softened throughout the manuscript .

5) It seems incongruous that the recommendation is for laparoscopy after a discussion above that laparoscopy has more risk of spread of virus. These pieces of information need to be brought together -
"despite the theoretical risk of increased transmission of COVID with laparoscopy, this approach can be modified to decrease this risk . . . this is still the preferred route of surgery when done appropriately." Or some such statement.

We have attempted to bring this information together through the manuscript and noting that “Laparoscopy, with appropriate surgical techniques and PPE to reduce the theoretical risk of viral transmission from the surgical smoke plume, remains a reasonable mini*m*ally invasive approach for treating an ectopic pregnancy in a COVID-19 positive patient.”

There has to be a transition from when you state that it is the bigger risk of transmission but then the recommended route of treatment - why is it still recommended? Is there proof that the modifications helps or just theoretical assumptions?

We have clarified the theoretical concerns for spread of the virus and technique that one can use in surgery to reduce the potential risk of transmission.

Just afraid to imply that 1 treatment is the best route without evidence or with the risk of jeopardizing someone to have done something "wrong" with treatment if there is not strong evidence to support that.

Editorial Comments.

1. Please confirm that the "patient" case you are presenting in your submission is hypothetical. Or, please confirm that you have obtained written consent from the patient to potentially publish their case. Yes, this was a hypothetical patient.

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The manuscript has been reduced to 1487 words (without the references) and the references have been reduced to 14.

4. A Short title has been added to the title page.

5. There was no financial support for this manuscript and the authors do not have conflict of interest with this manuscript.

Thank you for this opportunity to submit the revision to our manuscript.