OBSTETRICS & GYNECOLOGY

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- 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: Apr 29, 2020
To: "Francesca Parisi" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-1026

RE: Manuscript Number ONG-20-1026

Clinical findings and disease severity in COVID-19 pregnant women

Dear Dr. Parisi:

Your manuscript has been rapidly reviewed by the Editors. We would like to pursue fast-track publication. If you can address the comments below and submit your revision quickly, the Editorial Office will start working on it as soon as possible. I am setting the due date to May 1, but we will start working on it whenever you can submit.

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 #2: The purpose of this manuscript is to "firstly, to present clinical features and evolution of confirmed maternal SARS-CoV-2 infection at different gestational ages; secondly, to investigate potential factors associated with severe maternal evolution, eventually leading to iatrogenic birth or pregnancy termination." This was a prospective cohort study.

1. The included patients had a "positive results on a reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay of a maternal nasopharyngeal swab specimen." As universal screening was not being practiced at the time, what was their protocol at the time of this study for obtaining the RT-PCR test on nasopharyngeal swab specimen? Do the authors know how many subjects under investigation they screened with the RT-PCR and were negative?

2. Could the authors supply more information about which RT-PCR assays were used in their hospitals? What is the sensitivity, specificity, positive predictive value and negative predictive value of the RT-PCR? What is the false-negative rate? How long did it take for the test result to return for clinical use?

3. The authors note that they performed "radiological chest assessment". What type of radiological chest assessment was performed? Was it an PA and Lateral Chest X-Ray? Or did they perform Chest CT? In the discussion could they discuss the benefits/risks of these 2 methods of radiological assessment?

4. The authors note that the data was recorded on a customized data collection form. Was the data transferred to an electronic database? Did the 2 study investigators independently record the data in the electronic database and confirm accuracy?

5. The authors note that anticoagulant prophylaxis was administered to 38.6% of their cases, including all severe cases. Did they have a protocol at the time for starting anticoagulant prophylaxis, or was the decision made by the independent attending physician? What was the dose?

6. In discussion could the authors discuss the patients who underwent "maternal respiratory-indicated urgent delivery"? How well did their oxygenation and respiratory status improve after delivery? What were the criteria for "maternal respiratory-indicated urgent delivery"? I assume in Table 3, that "Maternal indication to delivery" was Maternal respiratory-indicated urgent delivery? Please clarify in Table 3. How did they decide to proceed with induction and vaginal delivery or cesarean section in this group?

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Reviewer #3: The authors present a series of 77 pregnant women with sars-cov-2 admitted to 12 Italian maternity hospitals from february 23 - march 28, 2020. This is relevant and important data. However, I do have concerns that the data was collected from hospitalized women only, which will overestimate overall risk, yet the authors do not make this clear in the title and abstract and many readers might misinterpret their findings and think the risk of severe disease is 20% in all pregnant women with Covid, which is not justified from the results of this particular study. specific comments on this are below.

-From the Results, it appears that 65 of the 77 women were admitted to the hospital specifically for Covid symptoms and only 12 were identified semi-incidentally as they were tested on admission for labor due to a known sick contact. As such, the large majority of this cohort are pregnant women with Covid requiring admission, not simply pregnant women with Covid. Therefore, the title and abstract need to be reworded to clarify that the percentages, risks, and risk factors are only relevant to this subset of women with Covid-19, and not to the rest of the pregnant women with Covid who presumably stayed at home.
-Perhaps a title "Clinical findings and disease severity in COVID-19 pregnant women requiring admission", or something to that effect.
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ASSOCIATE EDITOR
Please address this additional comment from an ad hoc reviewer:
One thing I would like them to address is the post delivery deterioriation of their patient they sectioned for respiratory reasons who ended up on ECMO.

Seems these sections are being done by some (not necessarily these authors) to improve maternal respiratory status. This case illustrates that the result is not always achieved.

EDITOR 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. 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.

4. 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.

5. 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).

6. 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 Original Research articles are 300 words. Please provide a word count.

7. 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%").

8. Regarding reviewer 3's comment about line 304: "The authors should avoid stating their series is the "largest" without supporting data":

We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If on the other hand, it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

9. 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.

10. When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

Figure 1: Please provide at a higher resolution. The map should be crisp when you zoom in.

Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce.

11. 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.

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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,

The Editors of Obstetrics & Gynecology

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

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Obstetrics & Gynecology

Nancy C. Chescheir, MD, *Editor-in-Chief*

Obstetrics & Gynecology

409 12th Street, SW

Washington, DC 20024-2188

Milan, 30/04/2020

Dear Editor,

Thank you for the opportunity to revise our manuscript entitled "**Prospective evaluation of clinical findings and disease severity in hospitalized COVID-19 pregnant women**" as original research paper by Savasi et al. for *Obstetrics & Gynecology.*

Enclosed is the revised version of the manuscript with highlighted changes and a point-by-point response to the editor' and reviewers' suggestions and comments, which further improved the manuscript. I confirm that I have read the Instructions for Authors

The content of the manuscript has not been previously published and all authors approved the final version for submission. The protocol has been approved by the local medical ethics committee and all women signed a written informed consent form before participation. We thank you for reconsidering our manuscript for publication.

On behalf of all authors,

Yours sincerely,

ASST Fatebenefratelli Sacco

[redacted]

REVIEWER COMMENTS:

Reviewer #2: The purpose of this manuscript is to "firstly, to present clinical features and evolution of confirmed maternal SARS-CoV-2 infection at different gestational ages; secondly, to investigate potential factors associated with severe maternal evolution, eventually leading to iatrogenic birth or pregnancy termination." This was a prospective cohort study.

1. The included patients had a "positive results on a reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay of a maternal nasopharyngeal swab specimen." As universal screening was not being practiced at the time, what was their protocol at the time of this study for obtaining the RT-PCR test on nasopharyngeal swab specimen? Do the authors know how many subjects under investigation they screened with the RT-PCR and were negative?

We thank the reviewer for this comment. According to the Italian guidelines, only patients with symptoms or known contact with suspected/confirmed COVID-19 patients were tested during the study period. Despite the required information on negative results is not available for all the participating centers, even because some participating hub units were reference centers only for confirmed COVID-19 patients, we could assume a percentage of negative results of 75% on the tested population in smaller centers. The M&M and Result sections have been modified as suggested.

2. Could the authors supply more information about which RT-PCR assays were used in their hospitals? What is the sensitivity, specificity, positive predictive value and negative predictive value of the RT-PCR? What is the false-negative rate? How long did it take for the test result to return for clinical use?

The swab samples were processed by using RealTime PCR testing SARS-CoV-2 with the automated ELITe InGenius® system and the GeneFinder™ COVID-19 Plus RealAmp Kit assay (ELITechGroup, France), according to manufacturer's instruction; the assay enables to detect three target genes: RNA-dependent RNA polymerase (RdRP), Nucleocapsid protein (N) and Envelope membrane protein (E), with high reported specificity. The result was obtained within 24 hours. A low sensitivity has been suggested, but it is not precisely known. As a positive result to the swab was the inclusion criterion, this excludes the false negative results. The M&M section has been modified according to this comment.

3. The authors note that they performed "radiological chest assessment". What type of radiological chest assessment was performed? Was it an PA and Lateral Chest X-Ray? Or did they perform Chest CT? In the discussion could they discuss the benefits/risks of these 2 methods of radiological assessment?

The radiological chest assessment has been always performed through PA and Lateral Chest X-Ray in the antepartum period. A postpartum chest CT was performed in three patients of the total study population because of a strong clinical suspicion with a negative Chest X-Ray. This information has been added to the Result section (lines 162-166). Guidelines for diagnostic imaging during pregnancy indicate that, in addition to ultrasound or MRI, CT scanning should not be withheld in a pregnant patient if necessary. However, concerns about the impact of in utero radiation exposure on the development of fatal

childhood cancer may indeed favor the choice of less invasive diagnostic techniques, unless first-line assessments are not conclusive (ACOG Committee Opinion October 2017, volume 130. Diagnostic Imaging during pregnancy and lactation)

4. The authors note that the data was recorded on a customized data collection form. Was the data transferred to an electronic database? Did the 2 study investigators independently record the data in the electronic database and confirm accuracy?

The data collection form was transferred to an electronic database by Francesca Parisi. Valeria Savasi and Francesca Parisi subsequently and independently verified the data accuracy by comparing the electronic database and the paper forms. Any discrepancy or unclear information was then verified with the specific participating center. We clarified this procedure in the M&M section.

5. The authors note that anticoagulant prophylaxis was administered to 38.6% of their cases, including all severe cases. Did they have a protocol at the time for starting anticoagulant prophylaxis, or was the decision made by the independent attending physician? What was the dose?

We thank the reviewer for this important comment. Unfortunately, we do not have a common protocol for the therapeutic management of COVID-19 pregnant patients, both in the antepartum and in the postpartum period. This is true for antiviral and antibiotic therapy, as well as for anticoagulant prophylaxis. The final decision was made by the independent physician/equipe of the participating unit, mainly based on the severity of clinical manifestations and prolonged bed sitting. *The result section has been modified accordingly.*

6. In discussion could the authors discuss the patients who underwent "maternal respiratory-indicated urgent delivery"? How well did their oxygenation and respiratory status improve after delivery? What were the criteria for "maternal respiratory-indicated urgent delivery"? I assume in Table 3, that "Maternal indication to delivery" was Maternal respiratory-indicated urgent delivery? Please clarify in Table 3. How did they decide to proceed with induction and vaginal delivery or cesarean section in this group?

We appreciate the reviewer comment. Table 3 has been modified accordingly.
In the severe subgroup, maternal respiratory indication to urgent delivery was mostly related to the worsening of symptoms (dyspnea) and vital signs, with no response to oxygen support. A cesarean section was performed in nine cases out of 11, as the maternal respiratory distress did not allow to coping with labor and vaginal delivery. A significant improvement of maternal clinical conditions was detected among six severe patients on the second postpartum day (4 from cesarean section, 2 from vaginal delivery). Five patients were admitted to ICU after urgent cesarean section performed at 25 (n=1), 28 (n=1) and 37 (n=3) gestational weeks. These results support the idea that pregnancy interruption leads to a clinical improvement of maternal condition in about 55% of cases, whereas 45% of severe patients undergoing maternal-indicated cesarean section requires ICU. In line with recent reports of a 12 times higher maternal mortality from C-section than vaginal delivery and despite vaginal delivery is mostly contraindicated by maternal respiratory distress in severely affected COVID-19 patients, we cannot exclude that

performing a surgical delivery could aggravate the inflammatory and endothelial antepartum dysfunction in these subgroups, thus leading to a postpartum deterioration of clinical conditions requiring ICU admission (Donati et al., Acta obstet Gynecol Scand 2018). The Results and Discussion sections have been modified according to this comment.

7. Line 144: Figure 1. Should this be Figure 2?

The text is actually correct, as figure 1 shows the total study population of 77 patients divided into 12 participating centers, whereas figure 2 shows the severe subgroup clinical evolution.

8. Line 188: "support 10 l)." please spell out l.

The sentence has been modified accordingly

9. Line 284: " and 11 out of 13 available dosages showed D-dimer higher than 500 (data not shown)." ?available dosages?

The available dosages are 13, just a small subgroup of the total study population, thus explaining our decision to not include this marker in the analysis. We have specified this information in the Discussion section.

10. In the Title could the authors include the type of study?

We have modified the title according to the reviewers' comments as follows: Prospective evaluation of clinical findings and disease severity in hospitalized COVID-19 pregnant women

11. Figure 2: Please clarify exactly what mean by non-invasive mechanical ventilation.

We clarified CPAP in the figure legend.

12. In Table 1. Did any subjects VAPE? Is Vaping a common occurrence in Italy?

We do not have this information, but it is definitely not common in Italy among pregnant women.

Reviewer #3: The authors present a series of 77 pregnant women with sars-cov-2 admitted to 12 Italian maternity hospitals from february 23 - march 28, 2020. This is relevant and important data. However, I do have concerns that the data was collected from hospitalized women only, which will overestimate overall risk, yet the authors do not make this clear in the title and abstract and many readers might misinterpret their findings and think the risk of severe disease is 20% in all pregnant women with Covid, which is not justified from the results of this particular study. specific comments on this are below.

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-The authors may even want to split their data between the 65 women admitted due to Covid and the 12 diagnosed at the time of admission.

We very much appreciate the reviewer's comment and modified the title and abstract accordingly to her/his suggestion.

-The methods state that severe and non-severe cases were compared, but the tables seem to compare severe vs the entire study population. The authors should clarify.

The comparison has been always performed between severe and non-severe cases, as specified in the tables footnotes by the asterisks and the corresponding numbers of patients compared.

-line 304. The authors should avoid stating their series is the "largest" without supporting data.

We definitely agree with the reviewer and modified the sentence accordingly.

ASSOCIATE EDITOR
Please address this additional comment from an ad hoc reviewer:
One thing I would like them to address is the post delivery deterioriation of their patient they sectioned for respiratory reasons who ended up on ECMO.

Seems these sections are being done by some (not necessarily these authors) to improve maternal respiratory status. This case illustrates that the result is not always achieved.

We very much appreciate this comment and tried to improve the Discussion section by arguing the topic of pregnancy termination in order to improve maternal outcome, also in agreement with previous reviewer's comment.

EDITOR 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.

OPT-IN

All Editor comments (points 2-11) have been addressed.