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: Sep 03, 2020
To: "Yalda Afshar" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-2355

RE: Manuscript Number ONG-20-2355

Clinical Presentation of Coronavirus 2019 (CoVID-19) in Pregnancy and Puerperium

Dear Dr. Afshar:

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 September 10, 2020, but please let me know if you need additional time.

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 Sep 10, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

The authors describe their prospective cohort study on the clinical presentation of COVID-19 in pregnancy.

1. Line 119: perhaps you should have a list as an appendix of what means you used to recruit participants and through what sources. And, when you focused on minority groups, how did you know if there was overlap with some of your other sources? How were records checked for duplicate enrollments?
2. Given that questionnaires were filled out, is literacy is necessary for enrollment for all patients?
3. How long after symptoms or testing were patients still allowed to enroll?
4. Line 189: do you think that the majority of patients were from the northeast because that is where the largest national impact of COVID occurred during your timeframe?
5. Since the largest group studied were healthcare workers, is this less of an evaluation of the general population? And, wouldn't they be most likely to give accurate histories?
6. Did the cases you checked for accuracy include healthcare workers who would be more likely to provide accurate results?
7. Given that patients on ventilators enrolled by proxy, was there follow up on these cases?
8. In Table 1 >20% were unsure of the number of gestations they were carrying? Do you have an explanation for this result?
9. In table 1, alcohol use should be blank and not to the number of the entire cohort in each column: it seems as if 100% of the population are using alcohol during pregnancy.
10. I think you could have a stronger assessment of your limitations. Although you do state that a large percentage were healthcare workers, your very varied enrollment, likely requirement of literacy, ascertainment bias of those who choose to enroll affects your results and observations.
11. Were there any maternal or neonatal deaths or stillbirths?
12. How does knowing that COVID-19 symptoms and presentations that you provide change care now? What new information is really provided here?

Reviewer #2:

The authors present the result of a prospective observational study of pregnant women with suspected COVID-19. I have several questions for the authors:

ABSTRACT
1. In the abstract conclusion, the authors state that "symptomatology is similar between those who test positive and negative". however, in the results most symptoms were significantly higher in the test-positive group.
2. it is unclear what the authors mean by "given that, universal screening approaches may be justified". is the assumption that those who tested negative are all true negatives, despite having all those symptoms in the middle of a pandemic? one could look at their data and make the exact opposite conclusion: since testing likely has so many false negatives, universal screening approaches may be unhelpful. more on this below.
3. the "objective" as written is really background, not an objective.

INTRODUCTION
4. line 89. would not state there "are no data" without supporting evidence. (like a pubmed search)
5. the objective in the Introduction and the Objective in the Abstract are not the same. was the objective of the study to compare those who test positive to those who test negative or to just report outcomes in those who are suspected to have COVID? (or both)

METHODS
6. according to the clinicaltrials.gov registration, the planned enrollment was 2000 women in 12 months. as neither of those were reached, what was the reason this analysis was performed at this time? were results "hidden" until it was run? is this a preliminary analysis? if so, that needs to be stated clearly.
7. although it is understandable why the authors chose to enroll patients from anywhere, it does limit the ability to make conclusions about percentages. for example, women with milder symptoms may be more likely to enroll than women who are sicker (or the opposite)
8. the authors do not have data on the reliability of the tests done, as they were from many different labs and there was no standardization of sampling, processing, nor reporting. therefore, they dont know the likelihood that women who tested negative were true negatives and the women who tested positive were true positives. given the symptoms in the population in the middle of a pandemic, i would guess there were more false negatives than false positives)

RESULTS
9. for point percentages, it would be helpful to include 95% confidence intervals
10. also related to the false negative comment above, looking at figure 2a and 2b, it appears that those who tested negative had an increase of symptoms then a decrease, as opposed to the group that tested positive who only had decreasing symptoms. this would indicate to me that the ones who tested negative were just earlier on in the course and may have tested positive a few weeks later when symptoms were peaking.

DISCUSSION
11. similar to comment 2 above, the authors need to discuss the possibility that their conclusions rely on the assumption that testing in this population had a 100% sensitivity (low false negative rate). i would argue their data does not show this, nor has anyone proven this to be the case before. the brief mention of this in lines 302-305 is not really enough as all their conclusions rely on this.
12. another limitation that should be mentioned is the difficult to define population studied, as they were people from all over the country who chose to sign up online,

overall, this is a nice prospective cohort, and the authors should be commended for doing this, but the conclusions are not justified from the data presented. the authors assume nobody had a false negative test, despite the fact that there was no way to standardize testing, from sampling all the way through reporting results. i do think the data are quite valuable, but mostly to be descriptive, and not to compare the groups. i certainly would not conclude that these data indicate we need universal testing. maybe we do and maybe we dont, but that cant be concluded from these data due to the limitations of this study.

STATISTICAL EDITOR COMMENTS:

Table 1: Gravidity and parity can only have integer values, so should be cited as median(IQR) or as categories

Table 2: The time period of this study (March-July 2020) includes different protocols for testing, which were based on travel history, contacts, and an evolving protocol of symptoms. Thus the symptom profile of those tested would reflect the symptoms in the protocol that enabled testing to be done. In other words, the distributions cited are likely biased and not representative generally of pregnant women who were SARS-CoV-2 (+) or a PUI.

Table 3: Similarly, this table of the clinical course, although based on a large series, is likely biased. Also, many of the columns have totals < 100, so the %s in those columns should be rounded to nearest integer %, not cited to nearest 0.1% precision.

Fig 2E: Although the median times differ significantly, should report the log-rank for these two curves. I suspect it would be NS, since the curves cross one another.

General: Table 3 and FIg 2 A-D: It is not clear whether these are serial evaluations of patients, or reports of symptoms by different patients at each time point, although it appears to be the latter. If so, then one cannot portray the data as representing serial changes. That is, this does not appear to represent serial changes in symptoms vs time, but rather observations at several time points of variable samples of the entire population of SARS-CoV-2 (+) and (-) women. If so, then comparison of medians is not representative of each population, in addition to the issues of overall selection bias.

EDITOR'S COMMENTS:

We are very happy to have received your manuscript. We are, however, asking for the following revisions:

1)That you drop the comparison group and provide descriptive data only (with appropriate 95% confidence intervals) for the following group only:

Women who underwent testing because they had symptoms suggestive of Sars-CoV-2 infection and were found to be positive. That is, please remove data from the manuscript on women who were asymptomatic at the time of testing and all those who tested negative.

Other issues:

2)Please remove the suggestion for universal testing as this suggestion does not really follow from your data.

3)Please provide a Precis that describes you findings.

4)Although your Abstract Objective may have been correct at the start of the pandemic, it no longer is and needs to be reworded.

5) The rows in Table 2 seem to be ordered alphabetically. Please reorder by frequency of symptoms.

6) The column numbers in Table 3 if added way exceed your cohort number. Please indicate that some patients are included more than once (if this is indeed true).

7) Please explain why 364 did not meet eligibility criteria.

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. For studies that report on the topic of race, authors must provide an explanation in the manuscript of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, the reasons that race/ethnicity were assessed in the study also should be described (eg, in the

Methods section and/or in table footnotes).

Use "Black" and "White" (capitalized) when used to refer to racial categories.

The category of "Other" is a grouping/label that should be avoided, unless it was a prespecified formal category in a database or research instrument. If you use "Other" in your study, please add detail to the manuscript to describe which patients were included in that category.

4. All studies should follow the principles set forth in the Helsinki Declaration of 1975, as revised in 2013, and manuscripts should be approved by the necessary authority before submission. Applicable original research studies should be reviewed by an institutional review board (IRB) or ethics committee. This review should be documented in your cover letter as well in the Methods section of the body text, with an explanation if the study was considered exempt. If your research is based on a publicly available data set approved by your IRB for exemption, please provide documentation of this in your cover letter by submitting the URL of the IRB website outlining the exempt data sets or a letter from a representative of the IRB. In addition, insert a sentence in the Methods section stating that the study was approved or exempt from approval. In all cases, the complete name of the IRB should be provided in the manuscript.

5. Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for observational studies (ie, STROBE), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), and studies reporting results of Internet e-surveys (CHERRIES). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at http://ong.editorialmanager.com. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, RECORD, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

6. 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.

7. 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.

8. 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).

9.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 Original Research articles is 300 words. Please provide a word count.

10. 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.

11. 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.

12. 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.

13. 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%").

14. Your manuscript contains a priority claim. 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 it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

15. 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.

16. Figures 1-2: Please upload as figure files on Editorial Manager. 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.

When you submit your revision, art saved in a digital format should accompany it. Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file).

If the figures were created using a statistical program (eg, STATA, SPSS, SAS), please submit PDF or EPS files generated directly from the statistical program.

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.

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

17. 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.

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 Sep 10, 2020, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Dwight J. Rouse, MD
Associate Editor, Obstetrics

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

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Dear Editorial Board,

Thank you for your insightful comments and suggestions for our manuscript (ONG-20-2355) entitled ***"Clinical Presentation of Coronavirus 2019 (CoVID-19) in Pregnancy and Puerperium"***

Please find enclosed ***our revised manuscript*** *with suggestions from the reviewers that have been incorporated into the new revision for submission to Obstetrics and Gynecology.*

We have submitted a revised manuscript through the portal and responded to the comments below in order to expedite processing of the revised manuscript. Reviewer and Editorial comments are bolded and our responses are in Italics in blue:

Sincerely,
Yalda Afshar on behalf of all co-authors

REVIEWER COMMENTS:

Reviewer #1: The authors describe their prospective cohort study on the clinical presentation of COVID-19 in pregnancy.

1. Line 119: perhaps you should have a list as an appendix of what means you used to recruit participants and through what sources. And, when you focused on minority groups, how did you know if there was overlap with some of your other sources? How were records checked for duplicate enrollments?

Thank you for this suggestion. We have included a supplemental file which includes links to all our recruitment material including fliers, social media posts, and websites. We recruited for PRIORITY through advertisements on social medial platforms and announcements in professional society communications. We also partnered with 20 community organizations and the 21 members of the PRIORITY Community Advisory Council to support recruitment of Black, Indigenous, and People of Color (BIPOC). We do not know if there was overlap in recruitment material seen by the study participants.

To avoid duplicate enrollment, we set an automated duplicate check in the data collection system on a unique identifying variable collected at the time of screening for study eligibility. Any duplicate record is flagged at this screening step to avoid consent or enrollment of duplicate participants.

2. Given that questionnaires were filled out, is literacy is necessary for enrollment for all patients?

Thank you for raising this point that we have clarified in the body of the manuscript. Literacy is not an inclusion criterion for the PRIORITY registry. Consent can be completed verbally and all questionnaires can be read to participants by phone with verbal responses. We have added clarifying language in the methods section: "Literacy was not necessary as participants can complete consent and all questionnaires verbally by phone with a trained research coordinator".

3. How long after symptoms or testing were patients still allowed to enroll?

The inclusion criteria is unrelated to their symptoms. Rather we included participants diagnosed with COVID-19; or being evaluated for COVID-19 ("patient under investigation") since January 1, 2020. This language is in our inclusion criteria in methods: "Eligible women included those 13 years of age or older, who were pregnant or who had been pregnant within the last 6 weeks, were diagnosed with CoVID-19 infection or being evaluated for CoVID-19 ("person under investigation (PUI)") at any time since January 1, 2020, and were able and willing to give informed consent."

4. Line 189: do you think that the majority of patients were from the northeast because that is where the largest national impact of COVID occurred during your timeframe?

This is very likely. During this pandemic we have watched the demographic shift from the northeast, to west, to south and have been able to capture this through our real-time infographic and dashboard available online: https://priority.ucsf.edu/dashboard

5. Since the largest group studied were healthcare workers, is this less of an evaluation of the general population? And, wouldn't they be most likely to give accurate histories?

In the early days of the COVID-19 pandemic when PRIORITY began recruiting, there was widespread concern that healthcare workers were at increased risk of infection and subsequent adverse pregnancy outcomes. Therefore, healthcare workers, in particular nurses, were highly engaged in participating in PRIORITY and represent 28% of the overall study population in this interim analysis. We agree with the reviewer that the study population may over-represent the proportion of healthcare workers in the general population of pregnant women with COVID-19. However, healthcare workers are not the "largest group studied"; 72% of study participants are not employed in healthcare. In addition, we targeted recruitment to the general population and aimed to enroll a diverse study cohort in all regards including race/ethnicity, geography, and employment status. The PRIORITY Reproductive Health Equity and Birth Justice Core was formed with the goal of assuring enrollment of Black, Indigenous, and People of Color (BIPOC) populations.

To our knowledge, there are no studies that compare the accuracy of self-reported medical history among healthcare workers compared with people not employed in healthcare. As discussed in response to question #6, we did not observe any differences between healthcare workers and other study participants in the accuracy of self-report for COVID-19 diagnosis when adjudicated with the medical record. In another PRIORITY manuscript, we adjudicated self-report of NICU admission and similarly did not see any differences in accuracy between healthcare workers and other study participants.

6. Did the cases you checked for accuracy include healthcare workers who would be more likely to provide accurate results?

In the cases reviewed to adjudicate self-report of COVID-19 diagnosis, 55% were healthcare workers. As described in the manuscript, there was 99% overall accuracy in this self-report. With this high rate of concordance between self-report and the medical record, there were no differences in reporting accuracy between healthcare workers and other participants.

7. Given that patients on ventilators enrolled by proxy, was there follow up on these cases?

Thank you for this question. We have clarifying language in the methods to this point. "Pregnant patients with COVID-19 in the intensive care unit on respiratory ventilators are eligible to enroll through proxy consent by the designated medical decision-maker. If enrolled is by a medical proxy, the participant is re-consented once she gains capacity."

8. In Table 1 >20% were unsure of the number of gestations they were carrying? Do you have an explanation for this result?

One likely reason may have been the modification in how prenatal care was being delivered during the pandemic. Namely, there was a significant modification in prenatal care in that the first trimester ultrasound was deferred to minimize interaction with the healthcare system and replaced by virtual visits. Augmented by that, may be the 13% of participants that enrolled in the first trimester before a dating scan. These may be reasons to account for this result.

9. In table 1, alcohol use should be blank and not to the number of the entire cohort in each column: it seems as if 100% of the population are using alcohol during pregnancy.

Thank you for pointing this issue out. We have removed the Ns from the start of the row but retained N at the top of the column to clarify the presentation of this data.

10. I think you could have a stronger assessment of your limitations. Although you do state that a large percentage were healthcare workers, your very varied enrollment, likely requirement of literacy, ascertainment bias of those who choose to enroll affects your results and observations.

The aim of PRIORITY is to enroll a nationally representative sample of pregnant women with known or suspected COVID-19. The study design is a volunteer registry with national recruitment efforts to enroll a sample that accurately represents the population of infected pregnant women across the country. As with any cohort study, there may be volunteer bias in which individuals who agree to participate in research have different characteristics than the general population (generally that they may be healthier). We added a sentence on the possibility of volunteer bias in the paragraph on limitations: "An additional limitation is the possibility of volunteer bias in which participants may have a better baseline health status than the general population that does not volunteer to enroll in a research study". However, literacy was not a requirement for enrollment and we do believe that there is any ascertainment bias in PRIORITY. We consider ascertainment bias to occur when the exposed group, in this case those who are COVID-19 positive, may have more intense surveillance or screening for the outcome of interest. In these analyses, the outcome is self-report of duration of symptoms which would not be impacted by ascertainment bias.

11. Were there any maternal or neonatal deaths or stillbirths?

Thank you for raising this point. Maternal and neonatal mortality are outcomes of interest to the PRIORITY registry. This manuscript focuses on maternal disease presentation. We have other manuscripts in press and planning that will review in detail mortality outcomes.

12. How does knowing that COVID-19 symptoms and presentations that you provide change care now? What new information is really provided here?

Thank you for this comment. We have expanded our discussion to include this point. We describe heterogeneity of symptoms in COVID-19 and that this is further complicated by

overlapping symptoms of normal pregnancy, including nausea, fatigue, congestion, among others. The symptoms appear to be non-specific and disparate. The data presented here suggests that solely relying on symptom-based strategies as a predictor of SARS-CoV-2 status and risk stratification is ineffective for this population of pregnant and postpartum women.

We believe our study adds new information to the literature because, to our knowledge, this analysis is the only nationwide prospective cohort study in the United States with longitudinal follow-up from the time of diagnosis to >8 weeks after symptom onset. This study design affords us the opportunity to present information on disease presentation and course of disease including time to recovery that has not yet been published in a sample enrolled from every region of the country.

Reviewer #2: The authors present the result of a prospective observational study of pregnant women with suspected COVID-19. I have several questions for the authors:

ABSTRACT

1. In the abstract conclusion, the authors state that "symptomatology is similar between those who test positive and negative". however, in the results most symptoms were significantly higher in the test-positive group.

Since the original submission, we have removed the symptomatic but SARS-CoV-2 negative cohort from the primary analysis at the request of the editor and focused on the SARS-CoV-2 positive symptomatic cohort. As such, we removed this sentence from the abstract.

2. it is unclear what the authors mean by "given that, universal screening approaches may be justified". is the assumption that those who tested negative are all true negatives, despite having all those symptoms in the middle of a pandemic? one could look at their data and make the exact opposite conclusion: since testing likely has so many false negatives, universal screening approaches may be unhelpful. more on this below.

Thank you for this point. We have expanded the limitations to include the discussion of the false negatives that we expect with this cohort and have made significant modifications to the manuscript text that includes removal of strong recommendation for universal testing.

3. the "objective" as written is really background, not an objective.

This has been modified. New objective reads: "To describe the clinical presentation, symptomology, and disease course of coronavirus disease 2019 (CoVID-19) in pregnancy".

INTRODUCTION

4. line 89. would not state there "are no data" without supporting evidence. (like a pubmed search)

Thank you for pointing this out. We have clarified this language in the introduction and modified the language specific to the limited data on longitudinal changes in symptoms over time in pregnant population. We think this is much more precise than original written.

5. the objective in the Introduction and the Objective in the Abstract are not the same. was the objective of the study to compare those who test positive to those who

test negative or to just report outcomes in those who are suspected to have COVID? (or both)

We have modified the objective in the abstract to match the appropriate objective in the introduction and since we have removed the symptomatic but SARS-CoV-2 negative group form the analysis, we have modified the objective as descriptive of the symptomatology over time of the SARS-Co-V-2 positive group.

METHODS

6. according to the clinicaltrials.gov registration, the planned enrollment was 2000 women in 12 months. as neither of those were reached, what was the reason this analysis was performed at this time? were results "hidden" until it was run? is this a preliminary analysis? if so, that needs to be stated clearly.

Thank you for this comment. We have clarified this point in the methods section. The PRIORITY study opened at a time when the anticipated incidence of COVID-19 among pregnant women was unknown. We projected 2,000 for the study as an estimation of plausible sample size. We have now revised the sample size to approximately 1,400 based on more precise estimations of required sample size for key outcomes, as well as available study funding and resources. This is a preliminary analysis completed because we believe that the unique data provided from the only nationwide prospective cohort study warranted publication during the pandemic prior to completing enrollment of the full cohort. All data is kept confidential and locked by the coordinating center until planned analyses are conducted.

7. although it is understandable why the authors chose to enroll patients from anywhere, it does limit the ability to make conclusions about percentages. for example, women with milder symptoms may be more likely to enroll than women who are sicker (or the opposite)

We agree with the reviewer that a strength of PRIORITY is our nationwide enrollment, irrespective of where participants receive pregnancy care. We also acknowledge that, similar to all clinical research studies, study volunteers may overall be somewhat healthier than people who do not volunteer for studies (ie volunteer bias). We have addressed this potential for volunteer bias as a possible limitation in question 10 of Reviewer 1 above and also in the manuscript discussion section. Despite this possibility of volunteer bias, we were able to enroll hospitalized and critically ill patients through physician referral. In the study population, ~50% were self-referred and ~50% were physician referral with 5% hospitalized and 2% in ICU at the time of study enrollment.

8. the authors do not have data on the reliability of the tests done, as they were from many different labs and there was no standardization of sampling, processing, nor reporting. therefore, they dont know the likelihood that women who tested negative were true negatives and the women who tested positive were true positives. given the symptoms in the population in the middle of a pandemic, i would guess there were more false negatives than false positives)

We agree with the reviewer that we do not have data on the reliability of the test that was done. We include only those with NP RT-PCR results; however, there are differences in FP and FN rates based on testing, which we are aware. We have added language to limitations: "Categorization by SARS-CoV-2 status solely depends on the test results and some of the

overlap in first symptoms in the two groups may result from false negative tests which include the assay, type, and quality of specimen (34). Furthermore, timing of PCR in relation to symptom onset must be considered in both cases of short and long latency from symptom onset and testing (35). . . Other limitations include changes in testing availability over time based on the participants location and access of the women during the study period, timing of testing relative to symptoms, and accuracy of testing, as discussed above."

RESULTS

9. for point percentages, it would be helpful to include 95% confidence intervals

Done. We have added 95% CI to Table 1.

10. also related to the false negative comment above, looking at figure 2a and 2b, it appears that those who tested negative had an increase of symptoms then a decrease, as opposed to the group that tested positive who only had decreasing symptoms. this would indicate to me that the ones who tested negative were just earlier on in the course and may have tested positive a few weeks later when symptoms were peaking.

As per the Editor's recommendation, we have removed the symptomatic but SARS-CoV-2 negative cohort from these figures in the primary analyses. However, we include these figures in the Supplemental materials as reference. Please note that the figures match the groups in terms of onset of symptoms. Therefore, the SARS-CoV-2 negative group would not be further out from start of symptoms compared with the SARS-CoV-2 positive group. We agree that the cohort of SARS CoV-2 negative could include those with false negative test results, and/or those with other viral illnesses. We keep the group available as a supplement because they represent the real world experience of pregnant women during the pandemic with symptoms of COVID-19 and subsequent negative test results. We believe this is an important and clinically informative group of pregnant women that we care for in our practice.

DISCUSSION

11. similar to comment 2 above, the authors need to discuss the possibility that their conclusions rely on the assumption that testing in this population had a 100% sensitivity (low false negative rate). i would argue their data does not show this, nor has anyone proven this to be the case before. the brief mention of this in lines 302-305 is not really enough as all their conclusions rely on this.

Thank you for highlighting this issue. As discussed above, per the editor's request, we have modified the paper to focus on the SARS-CoV-2 positive cohort and describe the symptomology over time (versus compare to a control group of symptomatic SARS-CoV-2 negative).. Therefore, we have removed this recommendation and attenuated the discussion around this point. However, we kept the discussion of false negatives and relationship to timing in the discussion section as it remains relevant for categorization of study participants. "Categorization by SARS-CoV-2 status solely depends on the test results and some of the overlap in first symptoms in the two groups may result from false negative tests which include the assay, type, and quality of specimen (34). Furthermore, timing of PCR in relation to symptom onset must be 305 considered in both cases of short and long latency from symptom onset and testing (35).'

12. another limitation that should be mentioned is the difficult to define population studied, as they were people from all over the country who chose to sign up online,

We believe that the recruitment efforts to enroll participants from across the country is a strength of the study, rather than a limitation. Every region of the country is represented in PRIORITY which increases the generalizability of study results. The population is well defined with extensive assessment of baseline demographic and clinical characteristics. Participants were not enrolled online. Rather, a study website was used to advertise the study and potential participants contacted the study team through a link on the website to learn more about study participation.

overall, this is a nice prospective cohort, and the authors should be commended for doing this, but the conclusions are not justified from the data presented. the authors assume nobody had a false negative test, despite the fact that there was no way to standardize testing, from sampling all the way through reporting results. i do think the data are quite valuable, but mostly to be descriptive, and not to compare the groups. i certainly would not conclude that these data indicate we need universal testing. maybe we do and maybe we don't, but that can't be concluded from these data due to the limitations of this study.

Thank you for this comment and suggestion which is consistent with the Editors comment below. Because of this recommendation we have removed the symptomatic but SARS-CoV-2 negative group from the primary analysis and focus on the descriptive nature of the SARS-CoV-2 positive group. We maintain the SARS-CoV-2 negative cohort as data available in the Supplemental files as we believe this was central to our study design and recruitment and want to provide transparency to readers and researchers regarding this group. As discussed above, we believe data on the symptomatic SARS-CoV negative group is clinically informative because it represents the real-world experience of pregnant women during the pandemic. In addition, for future PRIORITY analyses, such as obstetric and neonatal outcomes, we believe that the SARS CoV negative group is a stronger comparison group that an asymptomatic pregnant population because they had morbidities such as fever that are associated with adverse pregnant outcomes; therefore, using this control group will likely decrease the effect of known and unknown confounding on future analyses. However, at the request of reviewers we do not focus on this group in the revised primary analyses.

STATISTICAL EDITOR COMMENTS:

Table 1: Gravidity and parity can only have integer values, so should be cited as median(IQR) or as categories

We have corrected this. Thank you for pointing that out.

Table 2: The time period of this study (March-July 2020) includes different protocols for testing, which were based on travel history, contacts, and an evolving protocol of symptoms. Thus the symptom profile of those tested would reflect the symptoms in the protocol that enabled testing to be done. In other words, the distributions cited are likely biased and not representative generally of pregnant women who were SARS-CoV-2 (+) or a PUI.

We completely agree with the statistical editor that who has access to testing can be biased by multiple reasons – protocol based testing as the editor implies, access to care, structural biases in healthcare delivery, among others. We acknowledge that the protocol for testing by symptom presentation and risk factors has been changing over time during the pandemic and that will manifest in who is enrolled in the SARS CoV-2 positive cohort in PRIORITY. However, we do

not make any assertions in the manuscript that the distribution of estimates for positive or negative test results represent the distribution of test results in the general population. Rather, we describe that the study design enrolled only pregnant women with known or suspected COVID-19. Therefore, by design, we are not aiming to create population estimates for disease incidence. We do believe our estimates for the distribution of symptoms is appropriate because this represents the self-reported clinical manifestations in women who were tested during real-world circumstances of the pandemic, which, by definition, accounts for changes in testing protocols. Additionally, we have removed the symptomatic but SARS-CoV-2 negative group from the primary analyses, as the Editor has requested.

Table 3: Similarly, this table of the clinical course, although based on a large series, is likely biased. Also, many of the columns have totals < 100, so the %s in those columns should be rounded to nearest integer %, not cited to nearest 0.1% precision.

Done. Thank you for this suggestion.

Fig 2E: Although the median times differ significantly, should report the log-rank for these two curves. I suspect it would be NS, since the curves cross one another.

Since we have removed the comparison group – symptomatic but SARS-CoV-2 negative, we have also removed the curve related to this cohort.

General: Table 3 and Flg 2 A-D: It is not clear whether these are serial evaluations of patients, or reports of symptoms by different patients at each time point, although it appears to be the latter.

Table 3 and Figure 2A (and Supplemental Figure 5A) do not explicitly consider the serial nature of the data and are cross-sectional at each time point (with time zero being symptom onset). However, Figure 2B and Supplemental Figure 5B do account for the serial nature of the data by using Kaplan Meier time-to-event analysis for the elapsed time from symptom onset to symptom resolution or end-of-follow-up (censoring).

If so, then one cannot portray the data as representing serial changes. That is, this does not appear to represent serial changes in symptoms vs time, but rather observations at several time points of variable samples of the entire population of SARS-CoV-2 (+) and (-) women.

Thank you for this comment. Our paper aims to be largely descriptive and we have generally avoided complex statistical modeling of the longitudinal data. We are presenting both simple cross-sectional (T3, F2A, Supp5A) and time-to-event/serial analysis (F2B, Supp5B). A more detailed longitudinal analysis of the repeated multivariate symptom indicators is beyond the scope of this paper.

If so, then comparison of medians is not representative of each population, in addition to the issues of overall selection bias.

We are computing median time from symptom onset to symptom resolution, through the use of Kaplan-Meier time to event analysis.

EDITOR'S COMMENTS: We are very happy to have received your manuscript. We are, however, asking for the following revisions:

1) That you drop the comparison group and provide descriptive data only (with appropriate 95% confidence intervals) for the following group only:
Women who underwent testing because they had symptoms suggestive of Sars-CoV-2 infection and were found to be positive.
That is, please remove data from the manuscript on women who were asymptomatic at the time of testing and all those who tested negative.

Thank you for this comment and the follow up emails regarding the point of removing the cohort of symptomatic but SARS-CoV-2 negative participants. As requested we have completely removed the SARS-CoV-2 negative cohort from the primary analyses, abstract, and all primary tables and figures. The focus now is a descriptive paper of the SARS-CoV-2 positive group that includes the 95% CIs in the tables. In the initial submission, we excluded women who were asymptomatic at time of testing from the figures and Table 3. However, in the revised manuscript, we also remove all asymptomatic women from Table 1 and Table 2. ***This changed the N for analyses and therefore all data in Table 1 and 2.***
We included data on the symptomatic SARS-CoV-2 negative group as supplemental material because this control group is central to our study design, recruitment, and enrollment. We are concerned that excluding this cohort entirely from the first PRIORITY publication on maternal infection may confuse readers about the overall design and approach of PRIORITY, particularly providers across the country who have referred PUI with negative test results to enroll in PRIORITY. In addition, as previously described, we believe this control group of symptomatic, but test negative participants is critical for future analyses of obstetric and neonatal outcomes. This control group will more effectively reduce confounding compared with selecting a control group of asymptomatic healthy pregnant women.. Thank you for the opportunity to modify and share what we still believe is clinically useful data, re: longitudinal symptomology in a SARS-CoV-2 pregnant population.

Other issues:
2)Please remove the suggestion for universal testing as this suggestion does not really follow from your data.

Done.

3)Please provide a Precis that describes you findings.

Done. Thank you.

4)Although your Abstract Objective may have been correct at the start of the pandemic, it no longer is and needs to be reworded.

Thank you. We have reworded the objective.

5) The rows in Table 2 seem to be ordered alphabetically. Please reorder by frequency of symptoms.

Done.

6) The column numbers in Table 3 if added way exceed your cohort number. Please indicate that some patients are included more than once (if this is indeed true).

We have clarified that patients could choose more than one symptom so that the column numbers would exceed the cohort total. Thank you for pointing this out.

7) Please explain why 364 did not meet eligibility criteria.

The vast majority (91%) were excluded as they were not PUIs or diagnosed with SARS-CoV-2, 2% were not pregnant or recently pregnant within 6-weeks of pregnancy. The other 7% included persons not residing in the United States or were incarcerated.