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: 01/30/2023
To: "Stephanie L Gaw" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-23-104

RE: Manuscript Number ONG-23-104

Patient experience with nirmatrelvir/ritonavir (paxlovid) for mild COVID-19 in pregnancy and lactation

Dear Dr. Gaw:

Thank you for sending us your work for consideration for publication in Obstetrics & Gynecology. Your manuscript has been reviewed by the Editorial Board and by special expert referees. The Editors would like to invite you to submit a revised version for further consideration.

If you wish to revise your manuscript, please read the following comments submitted by the reviewers and Editors. Each point raised requires a response, by either revising your manuscript or making a clear argument as to why no revision is needed in the cover letter.

To facilitate our review, we prefer that the cover letter you submit with your revised manuscript include each reviewer and Editor comment below, followed by your response. That is, a point-by-point response is required to each of the EDITOR COMMENTS (if applicable), REVIEWER COMMENTS, and STATISTICAL EDITOR COMMENTS (if applicable) below.

The revised manuscript should indicate the position of all changes made. Please use the "track changes" feature in your document (do not use strikethrough or underline formatting).

Your submission will be maintained in active status for 14 days from the date of this letter. If we have not heard from you by 02/13/2023, we will assume you wish to withdraw the manuscript from further consideration.

EDITOR COMMENTS:

Please note the following:

* Help us reduce the number of queries we add to your manuscript after it is revised by reading the Revision Checklist at https://journals.lww.com/greenjournal/Documents/RevisionChecklist_Authors.pdf and making the applicable edits to your manuscript.

* Please break figure into two figures (A and B/C)
* Figure C needs to be cited in the manuscript text

REVIEWER COMMENTS:

Reviewer #1:

Lines 46-70: The sample is too small to generalize findings, especially re: rates of rebound or any adverse outcomes. No need to include CIs, but had they been included, the CIs of %s would be very wide.

Discussion: Needs to emphasize further that this is a descriptive series, not all eligible women participated, and the samples are small. Therefore, it should be looked as descriptive, not generalizable from these data. This includes lines 91-92, since the samples do not allow sufficient evidence to give reassurance of no adverse clinical outcomes. For having 0/12 adverse outcomes in this series, the resulting 95% CI has an upper bound of 30%, so not particularly reassuring on that basis.

Reviewer #2:

In this research letter, the authors describe a survey of 64 patients with COVID in the study period. Of these asked to participate in the survey less than 2/3 responded. Of the 40 respondents (35 pregnancy and 5 lactating), only 18 pregnancies and 3 lactating individuals received a paxlovid rx of whom even a smaller group took the medication.

This limited sample size is the major weakness of the study. There is a significant problem with bias given the respondent size. It is hard to make any inference about safety with this small a sample size. In addition, regarding side effects, many can be associated with pregnancy itself, making it hard to draw conclusions about increased side effect profile (i.e. abdominal pain, altered taste). While the letter is well-written and an important topic, with such a small sample of individuals is hard to draw any sustainable conclusions.

Reviewer #3:

In this 'prospective' cohort study, the authors surveyed a cohort of vaccinated pregnant and lactating persons with breakthrough COVID-19 who were administered nirmatrelvir/ritonavir, and concluded that nirmatrelvir/ritonavir was well tolerated in pregnancy and lactation, with mild side effects and rebound being common. Great early work on the safety and tolerability of nirmatrelvir/ritonavir in pregnant persons. A number of issues need to be addressed prior to publication of this work:

General comments:

1. The kind of study design the authors used is important. Among a cohort of participants who were vaccinated against COVID-19 and developed a breakthrough infection in the parent study, the investigators used a REDCap-based approach to survey participants about their experience with nirmatrelvir/ritonavir. This is a cross-sectional design and not a prospective cohort study.

2. The sample size of this study is very limited to make inferences on nirmatrelvir/ritonavir safety.

3. Did the authors extract data on how many days nirmatrelvir/ritonavir was administered, as well as nirmatrelvir/ritonavir adherence data in pregnant and lactating persons with mild COVID-19 infection? There is evidence to suggest that if nirmatrelvir/ritonavir is administered for <5 days, symptoms are usually mild compared to a complete 5-day course of therapy.

4. Why did the authors limit their research to pregnant persons with mild COVID-19? nirmatrelvir/ritonavir is FDA licensed for both mild-and/or-moderate COVID-19.

Lines 4-5: The authors refer to the adverse effects from use of nirmatrelvir/ritonavir as mild. What does mild mean? The use of mild in this sentence can mean anything, as it seems very subjective. What classification system for adverse effects (mild versus moderate versus severe) was used - DAIDS? World Health Organization? 'Mild' needs to be better qualified.

Line 9: Please replace 'side effects' with 'adverse effects' here and throughout the manuscript. Adverse effects is the preferred terminology in Clinical Pharmacology.

Line 10: Why did the investigators limit their data collection to pregnant and lactating persons with breakthrough COVID-19 infection during pregnancy?

Lines 10-12: The adverse effects presented here are very similar to those experienced by non-pregnant persons. How does this differ from those of non-pregnant persons?

Lines 13-14: The authors describe "there were no significant adverse outcomes in either group". What groups are the authors referring to? Pregnant and lactating persons? This need to be qualified.

Line 14: Unknown medication risk is also the commonest reason for declining medications even in non-pregnant settings. Why is this particularly important in pregnant and lactating persons?

Line 22-23: The authors state that "patient experience, such as side effects and incidence of rebound symptoms, has not been reported in these groups". How is this information important in pregnant persons, differently from non-pregnant individuals?

Lines 32-33: How did the authors identify participants who used nirmatrelvir/ritonavir? Via medical record review or via survey? Not stated in this report. So did the authors first identify participants who developed SARS-CoV-2 infection between January - December 2022 through a review of their medical records, and then called them on the phone to survey them? Or did the participants complete a questionnaire? The description of the methods section is not clear and need to be clarified.

Line 81: The reviewer recommend that the authors state the features of nirmatrelvir/ritonavir that participants were uncertain about. Fear about severe adverse effects? Teratogenicity?

Line 82-83: Why do the authors think that the rate of medication adverse effects was higher in their study than those cited in nirmatrelvir/ritonavir clinical trials? Due to the effect of pregnancy on nirmatrelvir/ritonavir or the effect of nirmatrelvir/ritonavir on pregnancy? Efficacy versus effectiveness of nirmatrelvir/ritonavir in the context of a clinical trial versus real world? Bias?. Would be nice to give some plausible explanations.

This statement is not correct. Nirmatrelvir's safety has been reported in pregnant and lactating persons and not just animal models. The author should review the paper with PubMed ID: 36445705. Please revise this statement.

Line 87: What do the authors mean by 'confidence'?. Needs to be clarified.

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Sincerely,

Torri D. Metz, MD, MS
Deputy Editor, Obstetrics

The Editors of Obstetrics & Gynecology

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February 1, 2023

Dear Dr. Metz,

We are respectfully submitting the revisions for our research letter entitled "**Patient experience with nirmatrelvir/ritonavir (paxlovid) for mild COVID-19 in pregnancy and lactation**" by Lin et al, for consideration by *Obstetrics & Gynecology*. We thank the editors and reviewers for the thoughtful comments, and for the opportunity to improve the manuscript through these revisions.

We believe we have addressed all comments. We include the following in our resubmission:

1. Detailed response to each of the comments below
2. Tracked changes version of the revised manuscript.
3. Clean version of the figures.

Please do not hesitate to contact me with any questions and we look forward to your response.

Sincerely,

Stephanie Gaw, MD, PhD

Editor Comments:
* Help us reduce the number of queries we add to your manuscript after it is revised by reading the Revision Checklist

Done

* Please break figure into two figures (A and B/C)

Done. These are now entitled Figure 1 and Figure 2 (A&B). Citations in the manuscript text have been updated (lines 68, 74, 77).

* Figure C needs to be cited in the manuscript text

Citation added to line 77.

REVIEWER COMMENTS:

Reviewer #1:

1. Lines 46-70: The sample is too small to generalize findings, especially re: rates of rebound or any adverse outcomes. No need to include CIs, but had they been included, the CIs of %s would be very wide.

We agree that this is a small study, and that robust data needs to be generated from larger prospective trials in pregnant and lactating individuals. However, due to a higher risk of adverse outcomes of COVID-19 in pregnancy in the setting of an ongoing pandemic, and common prescribing practices of paxlovid by clinicians despite a lack of currently available data in this population — we do feel that this early data in this vulnerable population is important until data from larger clinical trial studies are available.

2. Discussion: Needs to emphasize further that this is a descriptive series, not all eligible women participated, and the samples are small. Therefore, it should be looked as descriptive, not generalizable from these data. This includes lines 91-92, since the samples do not allow sufficient evidence to give reassurance of no adverse clinical outcomes. For having 0/12 adverse outcomes in this series, the resulting 95% CI has an upper bound of 30%, so not particularly reassuring on that basis.

We agree and have softened the language throughout to emphasize that we are reporting on a small series of participants.

Reviewer #2:

In this research letter, the authors describe a survey of 64 patients with COVID in the study period. Of these asked to participate in the survey less than 2/3 responded. Of the 40 respondents (35 pregnancy and 5 lactating), only 18 pregnancies and 3 lactating individuals received a

paxlovid rx of whom even a smaller group took the medication.

1. This limited sample size is the major weakness of the study. There is a significant problem with bias given the respondent size.

We agree and have added text to address this (see Reviewer 3 comment 2 below)

2. It is hard to make any inference about safety with this small a sample size.

See Reviewer 3, comment 2 below.

3. In addition, regarding side effects, many can be associated with pregnancy itself, making it hard to draw conclusions about increased side effect profile (i.e. abdominal pain, altered taste). While the letter is well-written and an important topic, with such a small sample of individuals is hard to draw any sustainable conclusions.

The goal of this study was to understand the patient experience with NMV/r during pregnancy. We agree with the reviewer that outside of a randomized controlled trial it is incredibly difficult to pinpoint whether side effects are specifically from the medication or from the condition being treated, or other coexisting conditions, similar to many other medications administered in pregnancy and lactation. However, pregnant and lactating individuals are being prescribed paxlovid by clinicians due to the higher risk of COVID-19 outcomes in pregnancy in line with leading professional society recommendations. Additionally, to our knowledge, we are unaware of any current ongoing randomized trials of paxlovid in pregnant individuals, as there are currently no RCTs registered for paxlovid in pregnancy on clinicaltrials.gov. Understanding the pregnant person's experience is an important component of medication counseling and can guide clinician prescribing practices. While we cannot draw definitive conclusions, we believe this data is of value to many providers and patients, especially on a topic where there is almost no real-world data to date.

Reviewer #3:

In this 'prospective' cohort study, the authors surveyed a cohort of vaccinated pregnant and lactating persons with breakthrough COVID-19 who were administered nirmatrelvir/ritonavir, and concluded that nirmatrelvir/ritonavir was well tolerated in pregnancy and lactation, with mild side effects and rebound being common. Great early work on the safety and tolerability of nirmatrelvir/ritonavir in pregnant persons. A number of issues need to be addressed prior to publication of this work:

General comments:

1. The kind of study design the authors used is important. Among a cohort of participants who were vaccinated against COVID-19 and developed a breakthrough infection in the parent study, the investigators used a REDCap-based approach to survey participants about their experience with nirmatrelvir/ritonavir. This is a cross-sectional design and not a prospective cohort study.

We thank the reviewer for this correction. We have corrected this in line 35 of the manuscript.

2. The sample size of this study is very limited to make inferences on nirmatrelvir/ritonavir safety.

We agree that the sample size of the study is too small to make safety inferences and hope that our revisions throughout the letter clarify this limitation to the study.

We have added the following to lines 181-183:

"While our study size was too small to infer true medication safety data, until clinical trials are completed, this study provides early data on NMV/r experience in this population."

3. Did the authors extract data on how many days nirmatrelvir/ritonavir was administered, as well as nirmatrelvir/ritonavir adherence data in pregnant and lactating persons with mild COVID-19 infection? There is evidence to suggest that if nirmatrelvir/ritonavir is administered for <5 days, symptoms are usually mild compared to a complete 5-day course of therapy.

All participants in our study took a 5-day course. We have added the following line clarify. (line 71-72):

"Of pregnant respondents, 18 (51.4%) received an NMV/r prescription, of whom 66.7% opted to take the full 5-day course."

4. Why did the authors limit their research to pregnant persons with mild COVID-19? nirmatrelvir/ritonavir is FDA licensed for both mild-and/or-moderate COVID-19.

Thank you for this important point. Of those in the parent study with a breakthrough COVID-19 infection, all were mild. No cases meet criteria for moderate COVID-19. We added the following to line 67-68 to clarify:

"All cases were mild."

5. Lines 4-5: The authors refer to the adverse effects from use of nirmatrelvir/ritonavir as mild. What does mild mean? The use of mild in this sentence can mean anything, as it seems very subjective. What classification system for adverse effects (mild versus moderate versus severe) was used – DAIDS? World Health Organization? 'Mild' needs to be better qualified.

Thank you for this comment. We have added the following line to our Methods section:

"Adverse effect severity was graded according to DAIDS criteria."

6. Line 9: Please replace 'side effects' with 'adverse effects' here and throughout the manuscript. Adverse effects is the preferred terminology in Clinical Pharmacology.

This change has been made throughout the document, except in the survey to stay true to the wording in the survey that the patients received.

7. Line 10: Why did the investigators limit their data collection to pregnant and lactating persons with breakthrough COVID-19 infection during pregnancy?

We limited our data collection to pregnant and lactating persons with breakthrough COVID-19 due to the nature of our parent study cohort, all of whom have completed their primary COVID-19 vaccine series. We thought that this was an important group to focus on given that to date, approximately 70% of pregnant persons in the U.S. have completed their primary COVID-19 vaccine series according to CDC data. This makes our findings pertinent to many pregnant and lactating individuals to date.

8. Lines 10-12: The adverse effects presented here are very similar to those experienced by non-pregnant persons. How does this differ from those of non-pregnant persons?

Though the adverse effects themselves were similar to those experienced by non-pregnant persons, we found a higher incidence, particularly of dysgeusia, than was reported in clinical trials in non-pregnant persons.

9. Lines 13-14: The authors describe "there were no significant adverse outcomes in either group". What groups are the authors referring to? Pregnant and lactating persons? This need to be qualified.

Thank you for this comment; we have clarified line 15-16 to read:

"There were no significant adverse outcomes in pregnant or lactating persons."

10. Line 14: Unknown medication risk is also the commonest reason for declining medications even in non-pregnant settings. Why is this particularly important in pregnant and lactating persons?

Pregnant and lactating persons have unique concerns about medication effects on their offspring, including teratogenicity and infant exposure to medications through milk feeding. As such, medication counseling in pregnant and lactating persons must address concerns in these populations.

11. Line 22-23: The authors state that "patient experience, such as side effects and incidence of rebound symptoms, has not been reported in these groups". How is this information important in pregnant persons, differently from non-pregnant individuals?

Thank you for this question. We believe that pregnant and lactating individuals have unique concerns about taking medications due to potential exposure to their offspring (as mentioned in the comment above), as well as sharing the same concerns that non-pregnant populations have. Information on patient experience, such as side effects and incidence of

rebound symptoms, is important because without it, we do not know if they are the same as in non-pregnant/lactating groups. This information is crucial in informing patient expectations and provider counseling.

12. Lines 32-33: How did the authors identify participants who used nirmatrelvir/ritonavir? Via medical record review or via survey? Not stated in this report. So did the authors first identify participants who developed SARS-CoV-2 infection between January – December 2022 through a review of their medical records, and then called them on the phone to survey them? Or did the participants complete a questionnaire? The description of the methods section is not clear and need to be clarified.

We have updated the methods section to clarify how participants were identified. As a part of the parent study, surveys are sent out periodically for participant updates. As boosters were becoming available, we sent surveys to assess breakthrough infection and booster intentions. Those who reported an infection received a survey about NMV/r.

Line 37-40 now reads:

"Enrollees receive periodic questionnaires to assess for breakthrough infections and other changes in their health. SARS-CoV-2 infection (confirmed by medical record review) between January – December 2022 received an additional survey about their experience with NMV/r."

13. Line 81: The reviewer recommend that the authors state the features of nirmatrelvir/ritonavir that participants were uncertain about. Fear about severe adverse effects? Teratogenicity?

This is an important point; we have included the patient comments in Appendix 2, which outline respondents' concerns. We also included two additional comments in Appendix 2 that were inadvertently omitted in our first draft. Unfortunately, our survey does not provide further detail about specific uncertainties. This is a topic that merits further study through future qualitative studies.

14. Line 82-83: Why do the authors think that the rate of medication adverse effects was higher in their study than those cited in nirmatrelvir/ritonavir clinical trials? Due to the effect of pregnancy on nirmatrelvir/ritonavir or the effect of nirmatrelvir/ritonavir on pregnancy? Efficacy versus effectiveness of nirmatrelvir/ritonavir in the context of a clinical trial versus real world? Bias?. Would be nice to give some plausible explanations.

Thank you for this point. Our study is too small to generalize, as pointed out by the reviewers. We have edited line 160-161:

"There may be bias in survey reporting in this small sample size; larger trials are needed."

This statement is not correct. Nirmatrelvir's safety has been reported in pregnant and lactating persons and not just animal models. The author should review the paper with PubMed ID: 36445705. Please revise this statement.

Thank you for pointing this out. While we had cited Garneau, et al's paper, we agree that this line was misleading. Lines 177-178 now reads:

"Ritonavir is well-studied and widely used in pregnancy/lactation, but nirmatrelvir's safety is largely based on animal models6, and one series of 46 pregnancies.5"

Line 87: What do the authors mean by 'confidence'?. Needs to be clarified.

We agree that this was unclear and have deleted this line.