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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.*

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

Date: Aug 04, 2022
To: "Kate Russell Woodworth"[redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-22-1203

RE: Manuscript Number ONG-22-1203

Characteristics, Testing, and Birth Outcomes among People with Hepatitis C in Pregnancy

Dear Dr. Woodworth:

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, STATISTICAL EDITOR COMMENTS (if applicable), and EDITORIAL OFFICE COMMENTS below. Your manuscript will be returned to you if a point-by-point response to each of these sections is not included.

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 21 days from the date of this letter. If we have not heard from you by Aug 25, 2022, we will assume you wish to withdraw the manuscript from further consideration.

EDITOR COMMENTS:

1. Thank you for submitting your work to Obstetrics & Gynecology. If you opt to submit a revision for consideration, please format as a Research Letter and focus on the descriptive data regarding the timing of testing rather than the perinatal outcome data for which there is no comparison group. The guidelines for Research Letters are available at https://journals.lww.com/greenjournal/Pages/InformationforAuthors.aspx.

2. Agree with the reviewers that Table 2 should be removed as the objective of this submission is not to compare people with and without substance use in pregnancy.

REVIEWER COMMENTS:

Reviewer #1: This is a surveillance cohort analysis of the association between substance use and adverse pregnancy outcomes. However the authors attempt to link Hepatitis C with adverse pregnancy outcomes without providing objective evidence of an association. Without this analysis, the conclusions are not supported by data. Additional comments follow with line numbers.

Abstract
12. The authors give the impression that the manuscript will assess the impact of HCV infection on maternal, pregnancy, and infant outcomes. However, this is not the case. Please revise this intro paragraph to reflect that the statistical analysis is of the association between adverse pregnancy outcomes associated with substance use disorders rather than hepatitis C.

38 please include a statistical test with confidence intervals to support the statement that "these are all higher than national baselines".

27. Primary outcome of what analysis? The impression is that the analysis will be of the strength of association between HCV and these outcomes.

Introduction
Line 51. Please add incidence numbers to this statement. What is the Hepatitis C incidence most recently estimated in the US?

Line 57-58. Is there more recent evidence on risk factors for perinatal or vertical transmission of Hepatitis C?

Line 84-85. How is this study proposed to be filling a gap in knowledge?

Methods are well described overall.

Are there a priori power calculations?

Line 131. If the primary objective is to evaluate the impact of HCV on adverse pregnancy outcomes as suggested in the abstract and in Line 76, then the reader would expect the investigators to include this analysis and attempt to adjust for confounders as best as possible, acknowledging limitations.

Results.
How many deliveries occurred in these 4 jurisdictions combined during the study period? What is the estimated prevalence of Hepatitis C in this population? How were these cases identified in each jurisdiction - what proportion from risk-factor based screening, and what proportion from universal screening in pregnancy or prior to pregnancy?

158. What was the mean viral load in the 47 who had first positive HCV RNA in the third trimester despite initiating care in the first trimester?

177. What proportion of the cohort had spontaneous preterm delivery or PROM compared to indicated preterm delivery? What were the indications for preterm delivery?

185. What are the protocols for NICU admission for observation or evaluation for NAS at the 4 jurisdictions participating?

186. What proportion of infants with NAS were born to people with opioid use disorder specifically? What about frequency of infants with NAS born to individuals on MAT? How was NAS diagnosed?

Discussion
193. It is clear from the data presented in this study that Hepatitis C and substance use appear to be closely linked, with almost 90% of individuals in the cohort reporting at least one substance used during pregnancy. However because the analysis does not include an analysis of the association between adverse pregnancy outcomes and Hepatitis C with adjustment for confounders, the data presented do not support the conclusion that screening for Hepatitis C prior or in pregnancy would reduce morbidity and mortality.

207-233. To provide context to this discussion paragraph, please include whether you were able to detect an association between Hepatitis C and preterm birth, SGA, or other adverse pregnancy outcomes.

Reviewer #2: In this descriptive study the authors report on the characteristics and outcomes of patients diagnosed with Hepatitis C in the peripartum period using data from a registry. This manuscript is well written and provides important demographic data regarding women in four US locations.

Introduction: Line 65: Consider removing "as clinical trials excluded pregnant people".

The most important finding from this study is the fact that 21 percent of women had known HCV infection prior to conception, which indeed highlights the missed opportunity to assist in curative treatment prior to conception.

Unfortunately, the risk factors and outcome findings from this study are not surprising and have been shown previously in similar studies including increased risk of preterm birth, SGA and NICU admission.

Reviewer #3: Thank you for the opportunity to review this manuscript entitled, "Characteristics, Testing, and Birth Outcomes among People with Hepatitis C in Pregnancy." This is a cross-sectional study of data from SET-NET that seeks to examine maternal characteristics, testing timing, and birth outcomes among patients with evidence of +HCV testing. This is a very important topic and with the increasing frequency of HCV infection, which will likely continue to rise with universal screening recommendations and increased substance use, and this is an excellent data source. However, I have several

concerns about study limitations that are not addressed in the manuscript, as described below:

-Lines 37-38 and Discussion: The authors state in the abstract and in the discussion that the frequencies of preterm birth, SGA, and birth defect are higher than national baseline frequencies, conveying the conclusion that HCV infection is associated with increased risk of these outcomes. However, to the average reader, this may be misinterpreted as a real association and potentially be very misleading. It is not appropriate to compare the frequencies in this limited cohort that only comes from 4 U.S. jurisdictions that are particularly high-risk jurisdictions including NYC, NY state, Allegheny County PA, and Tennessee in a high-risk population of patients who have HCV infection to national general population estimates and say that risks of adverse outcomes are higher.

-Lines 60-63, lines 92-93: As the authors state, universal HCV screening in the general population and pregnant population was recommended in 2020 and 2021, respectively. The study period for this manuscript is 1/1/2018-12/31/2021. Therefore, the pool of patients tested likely changed during the study period, and perhaps the characteristics of those who tested positive also changed during the study period. It would be important for the authors to acknowledge this possibility and would be nice if the authors could show if there are any time-related trends in testing timing and maternal characteristics.

-Lines 117-119: The authors discuss timing of HCV testing and include categorization by pregnancy trimester, however as discussed in the next point, gestational age is not reliably available for a significant portion of the cohort. This should at least be noted as a study limitation in the Discussion.

-Lines 127-131: A major concern I have is that 4/8 of the main study outcomes (preterm birth, late preterm, early preterm, and SGA) are dependent on gestational age determination. However, 13% of cases do not have available information on prenatal care, and of the 87% who do, 18% of them initiated care in the third trimester (when pregnancy dating is less accurate) or did not receive any prenatal care (lines 147-148). Therefore, there is a significant portion of patients who do not have reliable information to assess these GA-dependent outcomes. This is a major limitation of the study, and not mentioned when limitations are discussed.

-Lines 158-159: For the 47 individuals who had their first positive test during the 3rd trimester despite initiating prenatal care in the 1st trimester, did these patients have a negative test and then convert to a positive test during pregnancy. Or rather, did these patients miss the opportunity (for whatever reason) to be detected earlier in pregnancy? If the latter, are there any available data about how later diagnosis might have impacted pregnancy outcomes or care?

-Lines 178-179: Are there any available data on the indications for NICU admission among the 37% of newborns admitted to the NICU? Seems that NAS is a major reason, but what were the others?

-Lines 235-243: I recognize the known association between HCV infection and substance use, and it is very important to present the high frequency of substance use within the cohort. However, not sure that this study in particular highlights the "need for appropriate screening and care of substance use disorder." The study doesn't present any data about suboptimal screening and care of substance use in this population. This paragraph seems out of place.

STATISTICAL EDITOR COMMENTS:

Table 1: The large proportion of missing data for PROM ≥ 18hrs limits interpretation of that finding. Need units for age.

General: Useful as a descriptive series but lacks a cohort without HCV for comparison. That is, the patients herein have multiple risk factors for adverse outcomes besides HCV, so the reader cannot assess how much of the increased risk is associated with HCV vs the other risk factors (e.g., race, insurance, inadequate prenatal care, substance abuse.) Also, what were the criteria for HCV testing and was it uniform for all jurisdictions involved in the aggregated data? That is, how representative is this sample of all pregnant women with HCV?

EDITORIAL OFFICE COMMENTS:

1. If your article is accepted, the journal will publish a copy of this revision letter and your point-by-point responses as supplemental digital content to the published article online. You may opt out by writing separately to the Editorial Office at em@greenjournal.org, and only the revision letter will be posted.

2. When you submit your revised manuscript, please make the following edits to ensure your submission contains the required information that was previously omitted for the initial double-blind peer review:

* Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and at the end of the abstract. For industry-sponsored studies, describe on the title page how the funder was or was not involved in the study.
* Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable).
* Name the IRB or Ethics Committee institution in the Methods section (if applicable).
* Add any information about the specific location of the study (ie, city, state, or country), if necessary for context.

3. Obstetrics & Gynecology's Copyright Transfer Agreement (CTA) must be completed by all authors. When you uploaded your manuscript, each coauthor received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please ask your coauthor(s) to complete this form, and confirm the disclosures listed in their CTA are included on the manuscript's title page. If they did not receive the email, they should check their spam/junk folder. Requests to resend the CTA may be sent to em@greenjournal.org.

4. For studies that report on the topic of race or include it as a variable, 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, describe the reasons that race and ethnicity were assessed in the Methods section and/or in table footnotes. Race and ethnicity must have been collected in a formal or validated way. If it was not, it should be omitted. Authors must enumerate all missing data regarding race and ethnicity as in some cases missing data may comprise a high enough proportion that it compromises statistical precision and bias of analyses by race.

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

List racial and ethnic categories in tables in alphabetic order. Do not use "Other" as a category; use "None of the above" instead.

Please refer to "Reporting Race and Ethnicity in Obstetrics & Gynecology" at https://edmgr.ovid.com/ong/accounts/Race_and_Ethnicity.pdf.

5. ACOG uses person-first language. Please review your submission to make sure to center the person before anything else. Examples include: "People with disabilities" or "women with disabilities" instead of "disabled people" or "disabled women"; "patients with HIV" or "women with HIV" instead of "HIV-positive patients" or "HIV-positive women"; and "people who are blind" or "women who are blind" instead of "blind people" or "blind women."

6. The journal follows ACOG's Statement of Policy on Inclusive Language (https://www.acog.org/clinical-information/policy-and-position-statements/statements-of-policy/2022/inclusive-language). When possible, please avoid using gendered descriptors in your manuscript. Instead of "women" and "females," consider using the following: "individuals;" "patients;" "participants;" "people" (not "persons"); "women and transgender men;" "women and gender-expansive patients;" or "women and all those seeking gynecologic care."

7. Your submission indicates that one or more of the authors is employed by a pharmaceutical company, device company, or other commercial entity (Eagle Global Scientific, LLC). This must be included as a statement in the Financial Disclosure section on the title page.

8. Please add whether you received IRB or Ethics Committee approval or exemption to your Methods. Include the name of the IRB or Ethics Committee. If you received an exemption, explain why in this section.

9. 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.

10. Make sure your manuscript meets the following word limit. The word limit includes the manuscript body text only (for example, the Introduction through the Discussion in Original Research manuscripts), and excludes the title page, précis, abstract, tables, boxes, and figure legends, reference list, and supplemental digital content. Figures are not included in the word count.

Research Letters: 600 words (do not include more than two figures and/or tables [2 items total])

11. Specific rules govern the use of acknowledgments in the journal. Please review the following guidelines and edit your title page as needed:

* 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 or indicate whether the meeting was held virtually).
* If your manuscript was uploaded to a preprint server prior to submitting your manuscript to Obstetrics & Gynecology, add the following statement to your title page: "Before submission to Obstetrics & Gynecology, this article was posted to a preprint server at: [URL]."
* Do not use only authors' initials in the acknowledgement or Financial Disclosure; spell out their names the way they appear in the byline.

12. Provide a short title of no more than 45 characters, including spaces, for use as a running foot. Do not start the running title with an abbreviation.

13. 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.

14. The journal does not use the virgule symbol (/) in sentences with words, except with ratios. 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.

15. ACOG avoids using "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.

16. In your submission, 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.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001").

Express all percentages to one decimal place (for example, 11.1%"). Do not use whole numbers for percentages.

17. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available at http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

18. Please review examples of our current reference style at https://edmgr.ovid.com/ong/accounts/ifa_suppl_refstyle.pdf. Include the digital object identifier (DOI) with any journal article references and an accessed date with website references.

Unpublished data, in-press items, personal communications, letters to the editor, theses, package inserts, submissions, meeting presentations, and abstracts may be included in the text but not in the formal reference list. Please cite them on the line in parentheses.

If you cite ACOG documents in your manuscript, be sure the references you are citing are still current and available. Check the Clinical Guidance page at https://www.acog.org/clinical (click on "Clinical Guidance" at the top). If the reference is still available on the site and isn't listed as "Withdrawn," it's still a current document. In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript.

Please make sure your references are numbered in order of appearance in the text.

19. 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.

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 as a Microsoft Word document. Your revision's cover letter should include a point-by-point response to each of the received comments in this letter. Do not omit your responses to the EDITOR COMMENTS (if applicable), the REVIEWER COMMENTS, the STATISTICAL EDITOR COMMENTS (if applicable), or the EDITORIAL OFFICE COMMENTS.

If you submit a revision, we will assume that it has been developed in consultation with your coauthors and that each author has given approval to the final form of the revision.

Again, your manuscript will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Aug 25, 2022, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

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

_____

July 25, 2022

Obstetrics & Gynecology

Dear Editor(s),

Thank you very much for your review of our recent Original Research submission, entitled "*Characteristics, Testing, and Birth Outcomes among People with Hepatitis C in Pregnancy*". Based on the reviews we have revised the manuscript to be a Research Letter and are re-submitting this revised draft with all comments addressed. Below are the line by line responses to reviewer comments.

Also, I confirm that this article is not being submitted concurrently elsewhere. Some of the data from this report have been previously presented as an oral abstract at the 2021 Infectious Disease Society for Obstetrics and Gynecology conference. This manuscript was prepared as part of official duties at the Centers for Disease Control and Prevention and therefore will be in the public domain in the United States. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the funding agencies. All authors have contributed significantly to this work and have read the entire text, and table, agreed on its submission and are responsible for its content. In addition, authors do not have an association that might pose a conflict of interest.

Proposed category for the article: **Research letter.** The manuscript meets the requirements for the proposed category (598 words, and 1 table).

I will be the corresponding author and have full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Thank you for your consideration. We look forward to hearing from you soon.

Sincerely,

Kate R. Woodworth, MD, MPH

Centers for Disease Control and Prevention

[redacted]

EDITOR COMMENTS:

1. Thank you for submitting your work to Obstetrics & Gynecology. If you opt to submit a revision for consideration, please format as a Research Letter and focus on the descriptive data regarding the timing of testing rather than the perinatal outcome data for which there is no comparison group. The guidelines for Research Letters are available at https://journals.lww.com/greenjournal/Pages/InformationforAuthors.aspx.

Response: The manuscript has been reformatted as a research letter focusing on timing of testing.

2. Agree with the reviewers that Table 2 should be removed as the objective of this submission is not to compare people with and without substance use in pregnancy.

Response: Table 2 has been removed

REVIEWER COMMENTS:

Reviewer #1: This is a surveillance cohort analysis of the association between substance use and adverse pregnancy outcomes. However the authors attempt to link Hepatitis C with adverse pregnancy outcomes without providing objective evidence of an association. Without this analysis, the conclusions are not supported by data. Additional comments follow with line numbers.

Abstract
12. The authors give the impression that the manuscript will assess the impact of HCV infection on maternal, pregnancy, and infant outcomes. However, this is not the case. Please revise this intro paragraph to reflect that the statistical analysis is of the association between adverse pregnancy outcomes associated with substance use disorders rather than hepatitis C.

Response: The manuscript has been reworked to be a brief report focusing on timing of maternal HCV RNA testing

38 please include a statistical test with confidence intervals to support the statement that "these are all higher than national baselines".

Response: These results have been removed as manuscript has been reworked to be a brief report focusing on timing of maternal HCV RNA testing

27. Primary outcome of what analysis? The impression is that the analysis will be of the strength of association between HCV and these outcomes.

Response: These results have been removed as manuscript has been reworked to be a brief report focusing on timing of maternal HCV RNA testing

Introduction

Line 51. Please add incidence numbers to this statement. What is the Hepatitis C incidence most recently estimated in the US?

Response: These have been added to the introduction

Line 57-58. Is there more recent evidence on risk factors for perinatal or vertical transmission of Hepatitis C?

Response: This statement has been removed to format as a brief report

Line 84-85. How is this study proposed to be filling a gap in knowledge?

Response: The introduction has been reworked to focus on quantifying missed opportunities for treatment prior to pregnancy

Methods are well described overall.

Are there a priori power calculations?

Response: No, and these are no longer necessary since the pregnancy outcomes have been removed as a result

Line 131. If the primary objective is to evaluate the impact of HCV on adverse pregnancy outcomes as suggested in the abstract and in Line 76, then the reader would expect the investigators to include this analysis and attempt to adjust for confounders as best as possible, acknowledging limitations.

Response: These results have been removed as manuscript has been reworked to be a brief report focusing on timing of maternal HCV RNA testing

Results.

How many deliveries occurred in these 4 jurisdictions combined during the study period? What is the estimated prevalence of Hepatitis C in this population? How were these cases identified in each jurisdiction - what proportion from risk-factor based screening, and what proportion from universal screening in pregnancy or prior to pregnancy?

Response: Given the reformatting as a brief report we do not have room to include prevalence of HCV for each jurisdiction. Information on case ascertainment is included in the methods. Unfortunately we do not collect information on why the HCV RNA test was ordered (risk factor based vs. universal screening), nor to we have information on where the test was performed (prenatal care visit vs. substance use clinic vs. ED)

158. What was the mean viral load in the 47 who had first positive HCV RNA in the third trimester despite initiating care in the first trimester?

Response: These results regarding viral load were removed for simplicity in the research letter

177. What proportion of the cohort had spontaneous preterm delivery or PROM compared to indicated preterm delivery? What were the indications for preterm delivery?

Response: These results have been removed as manuscript has been reworked to be a brief report focusing on timing of maternal HCV RNA testing

185. What are the protocols for NICU admission for observation or evaluation for NAS at the 4 jurisdictions participating?

Response: These results have been removed as manuscript has been reworked to be a brief report focusing on timing of maternal HCV RNA testing

186. What proportion of infants with NAS were born to people with opioid use disorder specifically? What about frequency of infants with NAS born to individuals on MAT? How was NAS diagnosed?

Response: These results have been removed as manuscript has been reworked to be a brief report focusing on timing of maternal HCV RNA testing

Discussion

193. It is clear from the data presented in this study that Hepatitis C and substance use appear to be closely linked, with almost 90% of individuals in the cohort reporting at least one substance used during pregnancy. However because the analysis does not include an analysis of the association between adverse pregnancy outcomes and Hepatitis C with adjustment for confounders, the data presented do not support the conclusion that screening for Hepatitis C prior or in pregnancy would reduce morbidity and mortality.

207-233. To provide context to this discussion paragraph, please include whether you were able to detect an association between Hepatitis C and preterm birth, SGA, or other adverse pregnancy outcomes.

Response: These results have been removed as manuscript has been reworked to be a brief report focusing on timing of maternal HCV RNA testing

Reviewer #2: In this descriptive study the authors report on the characteristics and outcomes of patients diagnosed with Hepatitis C in the peripartum period using data from a registry. This manuscript is well written and provides important demographic data regarding women in four US locations.

Introduction: Line 65: Consider removing "as clinical trials excluded pregnant people".

The most important finding from this study is the fact that 21 percent of women had known HCV infection prior to conception, which indeed highlights the missed opportunity to assist in curative treatment prior to conception.

Unfortunately, the risk factors and outcome findings from this study are not surprising and have been shown previously in similar studies including increased risk of preterm birth, SGA and NICU admission.

Response: These results have been removed as manuscript has been reworked to be a brief report focusing on timing of maternal HCV RNA testing

Reviewer #3: Thank you for the opportunity to review this manuscript entitled, "Characteristics, Testing, and Birth Outcomes among People with Hepatitis C in Pregnancy." This is a cross-sectional study of data from SET-NET that seeks to examine maternal characteristics, testing timing, and birth outcomes among patients with evidence of +HCV testing. This is a very important topic and with the increasing frequency of HCV infection, which will likely continue to rise with universal screening recommendations and increased substance use, and this is an excellent data source. However, I have several concerns about study limitations that are not addressed in the manuscript, as described below:

-Lines 37-38 and Discussion: The authors state in the abstract and in the discussion that the frequencies of preterm birth, SGA, and birth defect are higher than national baseline frequencies, conveying the conclusion that HCV infection is associated with increased risk of these outcomes. However, to the average reader, this may be misinterpreted as a real association and potentially be very misleading. It is not appropriate to compare the frequencies in this limited cohort that only comes from 4 U.S. jurisdictions that are particularly high-risk jurisdictions including NYC, NY state, Allegheny County PA, and Tennessee in a high-risk population of patients who have HCV infection to national general population estimates and say that risks of adverse outcomes are higher.

Response: These results have been removed as manuscript has been reworked to be a brief report focusing on timing of maternal HCV RNA testing

-Lines 60-63, lines 92-93: As the authors state, universal HCV screening in the general population and pregnant population was recommended in 2020 and 2021, respectively. The study period for this manuscript is 1/1/2018-12/31/2021. Therefore, the pool of patients tested likely changed during the study period, and perhaps the characteristics of those who tested positive also changed during the study period. It would be important for the authors to acknowledge this possibility and would be nice if the authors could show if there are any time-related trends in testing timing and maternal characteristics.

Response: Now that this is being reformatted as a brief report we will not have room to discussing time-related trends but will plan to examine this in future analyses when additional jurisdictions have reported and we can feel confident about including the pandemic time period. We expect to have 3 additional jurisdictions reporting by early 2023.

-Lines 117-119: The authors discuss timing of HCV testing and include categorization by pregnancy trimester, however as discussed in the next point, gestational age is not reliably available for a significant portion of the cohort. This should at least be noted as a study limitation in the Discussion.

Response: This has been added as a limitation

-Lines 127-131: A major concern I have is that 4/8 of the main study outcomes (preterm birth, late preterm, early preterm, and SGA) are dependent on gestational age determination. However, 13% of cases do not have available information on prenatal care, and of the 87% who do, 18% of them initiated care in the third trimester (when pregnancy dating is less accurate) or did not receive any prenatal care (lines 147-148). Therefore, there is a significant portion of patients who do not have reliable information to assess these GA-dependent outcomes. This is a major limitation of the study, and not mentioned when limitations are discussed.

Response: This has been added as a general limitation related to classifying timing of testing. Pregnancy outcomes have been removed as a study objective.

-Lines 158-159: For the 47 individuals who had their first positive test during the 3rd trimester despite initiating prenatal care in the 1st trimester, did these patients have a negative test and then convert to a positive test during pregnancy. Or rather, did these patients miss the opportunity (for whatever reason) to be detected earlier in pregnancy? If the latter, are there any available data about how later diagnosis might have impacted pregnancy outcomes or care?

Response: Unfortunately, state and local health departments have limited ability to assess prior negative testing. For all pregnancies included in this report, this is the first positive test for each of the individuals, but may not have been the first test. We are unable to say with certainty when the pregnant person may have acquired the infection.

-Lines 178-179: Are there any available data on the indications for NICU admission among the 37% of newborns admitted to the NICU? Seems that NAS is a major reason, but what were the others?

Response: These results have been removed as manuscript has been reworked to be a brief report focusing on timing of maternal HCV RNA testing

-Lines 235-243: I recognize the known association between HCV infection and substance use, and it is very important to present the high frequency of substance use within the cohort. However, not sure that this study in particular highlights the "need for appropriate screening and care of substance use disorder." The study doesn't present any data about suboptimal screening and care of substance use in this population. This paragraph seems out of place.

Response: These statements have been removed as manuscript has been reworked to be a brief report focusing on timing of maternal HCV RNA testing

STATISTICAL EDITOR COMMENTS:

Table 1: The large proportion of missing data for PROM ≥ 18hrs limits interpretation of that finding. Need units for age.

Response: Age added to each row. Findings regarding PROM have been removed.

General: Useful as a descriptive series but lacks a cohort without HCV for comparison. That is, the patients herein have multiple risk factors for adverse outcomes besides HCV, so the reader cannot assess how much of the increased risk is associated with HCV vs the other risk factors (e.g., race, insurance, inadequate prenatal care, substance abuse.) Also, what were the criteria for HCV testing and was it uniform for all jurisdictions involved in the aggregated data? That is, how representative is this sample of all pregnant women with HCV?

Response: These results regarding pregnancy outcomes have been removed as manuscript has been reworked to be a brief report focusing on timing of maternal HCV RNA testing. While we do not collect information on reason for testing (e.g., maternal risk factor based screening or universal screening) this surveillance includes national notifiable reports of positive HCV testing linked with vital statistics, so includes population based estimates for women with HCV positive RNA testing during pregnancy, for those resulting in live births. We have excluded pregnancies ending in losses since these are not systematically captured. This is included in the limitations.

EDITORIAL OFFICE COMMENTS:

1. If your article is accepted, the journal will publish a copy of this revision letter and your point-by-point responses as supplemental digital content to the published article online. You may opt out by writing separately to the Editorial Office at em@greenjournal.org, and only the revision letter will be posted.

2. When you submit your revised manuscript, please make the following edits to ensure your submission contains the required information that was previously omitted for the initial double-blind peer review:

* Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and at the end of the abstract. For industry-sponsored studies, describe on the title page how the funder was or was not involved in the study.

  Response: Source of funding is included in the title page and has been added to the end of the abstract.

* Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable).

  Response: Not applicable

* Name the IRB or Ethics Committee institution in the Methods section (if applicable).

  Response: We have included the CDC required language that " This activity was deemed nonresearch and was conducted consistent with applicable federal law and policy. IRB review was not required."

* Add any information about the specific location of the study (ie, city, state, or country), if necessary for context.

  Response: States and counties included in the surveillance are described in the methods section

3. Obstetrics & Gynecology's Copyright Transfer Agreement (CTA) must be completed by all authors. When you uploaded your manuscript, each coauthor received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please ask your coauthor(s) to complete this form, and confirm the disclosures listed in their CTA are included on the manuscript's title page. If they did not receive the email, they should check their spam/junk folder. Requests to resend the CTA may be sent to em@greenjournal.org.

  Response: This work was performed as a part of official duties as a U.S. government employee. U.S. government policy is applicable if any of the authors are U.S. government employees who co-author the manuscript that was crafted as part of their official duties

4. For studies that report on the topic of race or include it as a variable, 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, describe the reasons that race and ethnicity were assessed in the Methods section and/or in table footnotes. Race and ethnicity must have been collected in a formal or validated way. If it was not, it should be omitted. Authors must enumerate all missing data regarding race and ethnicity as in some cases missing data may comprise a high enough proportion that it compromises statistical precision and bias of analyses by race.

  Response: This information is included in the table footnotes

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

Response: Done

List racial and ethnic categories in tables in alphabetic order. Do not use "Other" as a category; use "None of the above" instead.

Response: None of the above has been used for the table

Please refer to "Reporting Race and Ethnicity in Obstetrics & Gynecology" at https://edmgr.ovid.com/ong/accounts/Race_and_Ethnicity.pdf.

5. ACOG uses person-first language. Please review your submission to make sure to center the person before anything else. Examples include: "People with disabilities" or "women with disabilities" instead of "disabled people" or "disabled women"; "patients with HIV" or "women with HIV" instead of "HIV-positive patients" or "HIV-positive women"; and "people who are blind" or "women who are blind" instead of "blind people" or "blind women."

Response: Person first language has been used throughout wherever possible

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Response: Gender neutral language has been used throughout

7. Your submission indicates that one or more of the authors is employed by a pharmaceutical company, device company, or other commercial entity (Eagle Global Scientific, LLC). This must be included as a statement in the Financial Disclosure section on the title page.

Response: This has been added to the title page

8. Please add whether you received IRB or Ethics Committee approval or exemption to your Methods. Include the name of the IRB or Ethics Committee. If you received an exemption, explain why in this section.

Response: We have added additional information regarding “This activity was deemed not to be research as defined in 45 CFR 46.102(l) and IRB review was not required”

9. 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.

Response: We have used terminology consistent with the reVITALize definitions. However, it is important to note that we do not capture the method of ascertainment for EDD. We advise abstractors to use the hierarchy per reVITALize definitions.

10. Make sure your manuscript meets the following word limit. The word limit includes the manuscript body text only (for example, the Introduction through the Discussion in Original Research manuscripts), and excludes the title page, précis, abstract, tables, boxes, and figure legends, reference list, and supplemental digital content. Figures are not included in the word count.

Research Letters: 600 words (do not include more than two figures and/or tables [2 items total])

Response: The paper has been reformatted as a research letter with <600 words and 1 table.

11. Specific rules govern the use of acknowledgments in the journal. Please review the following guidelines and edit your title page as needed:

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Response: Acknowledgements are appropriately reported.

12. Provide a short title of no more than 45 characters, including spaces, for use as a running foot. Do not start the running title with an abbreviation.

Response: Short title has been added

13. 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.

Response: Abbreviations are spelled out

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Sincerely,

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