

OBSTETRICS & GYNECOLOGY



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

Date: Sep 19, 2019
To: "Robert M Rossi" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-1571

RE: Manuscript Number ONG-19-1571

Prevalence of Maternal Hepatitis C Virus in the United States

Dear Dr. Rossi:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. Although it is judged not acceptable for publication in Obstetrics & Gynecology in its present form, we would be willing to give further consideration to a revised version.

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 Oct 10, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

REVIEWER #1:

Overall:

This is a population -based retrospective cohort study all live births in the United States over a 9-year period (2009-2017). Data was obtained from the livebirth records provided by the National Center for Health Statistics (NCHS). The primary objective was to evaluate the trend in reported maternal HCV over the 9-year period (2009-2017). Secondary objectives were to identify maternal characteristics and obstetric outcomes associated with maternal HCV in the U.S. utilizing a contemporary subgroup of the cohort (2014-2017).

The prevalence of reported maternal HCV increased 161% from 1.8 to 4.7 cases per 1,000 livebirths (RR 2.7, CI 2.6-2.8) from 2009 to 2017. Maternal HCV was associated with non-Hispanic White race (aRR 2.8, CI 2.7-2.8), cigarette smoking (aRR 11.1, CI 10.9-11.3), residential county population size < 100,000, Medicaid insurance, and not receiving any prenatal care prior to delivery. Maternal HCV was also associated with cesarean delivery, preterm birth, SGA birthweight, maternal ICU admission, and blood transfusion, NICU admission, assisted ventilation, and neonatal death.

Disclosures: The authors do not report any potential conflicts of interest.

Human subjects: The CDC reviewed and approved the data request for this study.

Abstract:

1. The abstract is specific and representative of the article.

Introduction:

2. The problem is stated and the objectives are clear. The background is succinctly reviewed.

Methods:

3. Lines 152: This sentence is unclear.
4. Women who screen positive for hepatitis C are likely to remain seropositive in the absence of treatment. How were women who delivered more than once during the study period handled?

Results:

5. The data answer the question and relate to the main point. The sample is so large differences are likely to be statistically significant but this referred to in the discussion.

Discussion:

5. Highly relevant discussion with well articulated argument to support universal hepatitis C screening in pregnancy.

6. Are the authors in support of universal screening primarily only in those geographic areas with the highest rates of reported infections or in all states?

References:

7. The references seem pertinent.

TABLES and FIGURES:

8. Tables and figures are clearly labeled. The heat maps are much appreciated.

REVIEWER #2:

Manuscript Review

ONG-19-1571

Prevalence of Maternal Hepatitis C
Virus in the United States

The objective of this retrospective study was to evaluate the incidence of maternal Hepatitis C infection in the US between 2009-2017 with subgroup evaluation of maternal and neonatal demographic data and outcomes between 2014-2017.

Data was extracted from the National Center for Health Statistics birth records.

During the 9-year period the rate of maternal HCV increased from 1.8 to 4.7 cases per 1000 live births.

Multivariate analysis of the contemporaneous cohort was completed demonstrating increased risk for infection in white, non-Hispanic women, Medicaid insured, and smokers. Co infections were more frequent in HCV infected patients.

Most alarmingly, almost all adverse maternal and neonatal outcomes were more frequently found in HCV infected women after adjusting for confounders.

The authors recommend that on the basis of their study, all pregnant patients be screened for Hepatitis C infection rather than screening on the basis of maternally reported risk factors for acquisition.

Comments

In their discussion, the authors might consider referencing the financial cost of universal Hepatitis C screening. This should be considered in terms of a currently untreatable (in pregnancy) disease. Significant additional cost will be incurred beyond maternal antibody screening, as the next step would be to assess maternal viral titer. Antibody screening alone does not prove current infection. While knowledge of HCV status is important in avoidance of invasive procedures such as amniocentesis and fetal scalp electrode monitoring, will screening all new gravidas reduce maternal-fetal transmission rates significantly? This is unlikely given a declining incidence of amniocentesis and no reported increased incidence of neonatal HCV infection reported in cohorts of women receiving intra partum fetal scalp electrode monitoring.

The authors should also consider commenting on possible etiology(s) for the increased risk of numerous significant adverse maternal and fetal outcomes that are significantly increased in association with HCV infection in pregnancy.

REVIEWER #3:

This manuscript describes a retrospective cohort study of births in the United States between 2009-2017 in an effort to estimate maternal Hepatitis C prevalence and a more detailed subcohort analysis of 2014-2017 births to assess perinatal outcomes related to maternal HCV status. Hepatitis C is of particular interest given disparate recommendations from IDSA vs ACOG/SMFM regarding universal screening of pregnant women. The authors use the National Center for Health Statistics vital records data to produce their estimates for this very important topic.

Overall, the paper is interesting and touches on an important topic. In general, I would recommend a close eye to copy-

editing. The authors seem to have a tendency to craft very long sentences (these are numerous) and there are several misplaced commas. Addressing these issues would improve readability.

Otherwise, I have the following comments and clarifications:

1) Abstract:

- a. Objective is not stated as a simple, straight-forward objective
- b. The phrase "systematically reviewed" implies a chart review or other in-depth review of records. To this reviewer's understanding, this study is a straightforward epidemiologic study, and I would suggest a wording change here so as to avoid confusion for readers
- c. Line 71 extra comma after "period"
- d. Line 80, standard phraseology is "non-Hispanic white;" reversal of these terms (especially with a comma between) leads the reader to expect more than one race/ethnicity designation or other qualifier
- e. Lines 82-83 strike "either" and use the conjunction "or" prior to syphilis. The location of the confidence interval after hepatitis B is confusing to this reviewer - based on the full manuscript, I presume this is an aRR for any co-infection, not just Hep B and should therefore be moved to the end of the list of possible included co-infections.
- f. Conclusion is one very long sentence, consider breaking this up as it is difficult to follow.

2) Introduction

- a. Line 114: This reviewer prefers the adjective "geographic" rather than geographical but recognizes that this is stylistic rather than incorrect.
- b. Line 118-119: "demonstrating demographic similarities between young women with HCV and IVDU" seems a somewhat awkward way to indicate that, among young people, IVDU accounts for nearly all new HCV.
- c. Line 119-122: Sentence starting "It is estimated that..." is another example of a long sentence that should be addressed.
- d. Line 126: ribavirin is still contraindicated in pregnancy, would recommend changing "were" in this line to "is"

3) Methods & Materials

- a. The first two paragraphs are somewhat redundant and confusing in their structure and content:
 - i. The objective should conclude the introduction, rather than be placed at the end of the first methods paragraph.
 - ii. Lines 152 and 159 both discuss data abstraction from records to create the dataset and obtain variables of interest - is this repetition because of the cohort and subcohort studies? Is the subcohort study data different from the overall 2009-2017 data?
 - iii. Line 152 there is/are a word(s) missing after "including," it seems.
 - iv. Lines 151 and 153 - redundant description of the birth certificate version and form
- b. Presuming my interpretation is correct regarding the fact that the same data is utilized for both the cohort and subcohort studies, the authors may wish to consider a substructure to the methods with the following sections/paragraphs:
 - i. Data - describing the NCHS dataset, the way the data was collected for variables of interest. Of note, the current description is confusing as to whether the authors reviewed records (which they presumably did not) or whether record review/chart abstraction describes the way that data is collected at the time of filing the birth certificate.
 - ii. Variables - Primary exposure variable with description (e.g., one of five infectious variables...), outcome variables with definitions, and covariates with definitions
 - iii. Analysis - starting with inclusion/exclusion criteria and describing statistical methods
 - iv. There is no mention of the analysis by state or the geographic analyses used to create the heat maps discussed in the results. In addition, the results reference state reporting. Is this derived from NCHS or from another data source?

4) Results:

- a. The heat maps data are interesting but seem to come as a surprise since there is no mention of this in the Methods section. Maps are excellent for visualizing data trends, but maps, like other types of descriptive analyses, require some basic description of how they were constructed. These maps lack sufficient detail to understand what data they convey:
 - i. Based on shape and size of the divisions, I presume these heat maps are divided into counties, but this is not clear. Please provide the geographic unit of measurement (county, hospital district, etc.)
 - ii. Are the data in the heat maps derived from state reporting or NCHS data? If these data were derived from NCHS, were the birth certificate data geocoded from mother's residence at time of birth or was another geographic identifier used?
- b. State data are, I presume, also based on NCHS rates by state rather than on state reporting data, but this should be specified in methods.

5) Discussion:

- a. Lines 246-249: There are more recent data on estimated numbers of neonates and mothers infected with HCV based on testing than Jhaveri. See: Ly KN, Jiles RB, Teshale EH, et al. Hepatitis C Virus Infection Among Reproductive-Aged Women and Children in the United States, 2006 to 2014. *Ann Intern Med.* [Epub ahead of print 9 May 2017]166: 775-782. doi: 10.7326/M16-2350
- b. It would be both interesting and useful for the authors to situate their findings in light of those of Ly et al., which were cited by the IDSA in their guidelines recommending universal screening. Different methods were utilized, with somewhat different findings due to these methods, but it would be important to discuss that.
- c. Line 243 - it may be useful to cite some sources that show that risk-based screening (for Hep C specifically) is not effective and that many diagnoses are missed utilizing this method.

- d. Line 256: Citation 30 is typed incorrectly, with First Name/Last Name order, and therefore the author's first name is being cited in line on line 256. This should be Jhaveri et al., if I am reading the citation correctly.
- e. Again, there is a reference in the discussion to "states reporting" (line 265). The use of this language implies data from states on reportable infections. If another data source besides NCHS was utilized, this should be described. However, if the authors simply mean that when broken down at the state level, the NCHS data provide maternal HCV infection rates of greater than 0.07%, then this should be phrased differently.
- f. Lines 242 - 272 are written as a single paragraph, but there are several main ideas. I would recommend re-ordering some of this information in a more succinct way and making it into 2 paragraphs.
- g. The subcohort results receive almost no attention except in part of a sentence in the paragraph on limitations. Given that there are several morbidities associated with Hepatitis C, including cesarean delivery despite the lack of evidence that cesarean reduces transmission rates, it would be interesting for the authors to address these in a more systematic way.
- h. In general, this reviewer feels the discussion could be tightened to make a more powerful and succinct point about how these results can be utilized in the discussion of universal vs risk-based screening for maternal HCV. The authors make several points about the cost-effectiveness of screening and the availability of interventions and postpartum treatments, but these points are somewhat lost in the closing arguments of the discussion. I would recommend spending some time closing the discussion with a succinct statement about whether these results should sway us toward universal screening, and also whether any of the subcohort analyses raise important hypotheses for future testing. The final paragraph instead feels somewhat vague and less grounded in the work the authors have presented in this study.
- 6) References: There seem to be several mistakes in the references. Recommend a close eye to ensure all are formatted correctly, etc.

STATISTICAL EDITOR'S COMMENTS:

1. Tables 1 and 4, lines 273-274: As the Authors note, reporting of HCV is not mandatory, and during this time frame, the total of HCV and non-HCV represent about 1/2 of total live births in US. Therefore, unless this is a representative sample and maintains the representation during each of the years and regions studied, the time and geographic trends may be biased. Likewise, some of the subsets may be over or under represented, thus complicating comparisons. The representation that this study summarizes every live birth during this time period needs modification, since the study can only report data from those women who were tested for HCV.
2. Table 1: Should include a column of maternal non-HCV for each year, to demonstrate whether the proportion of women tested for HCV changed during 2009-2017.
3. Table 3: Should include a Table (could be on-line material), analyzing the proportion of women who had HCV testing by State for each of the years.
4. Tables 4, 5, 6: What were the maternal characteristics of all women whose HCV status was not known during this time period?

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:
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2. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.

3. In order for an administrative database study to be considered for publication in Obstetrics & Gynecology, the database used must be shown to be reliable and validated. In your response, please tell us who entered the data and how the accuracy of the database was validated. This same information should be included in the Materials and Methods section of the manuscript.
4. 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 reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), quality improvement in health care studies (ie, SQUIRE 2.0), 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, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

5. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric and gynecology data definitions at <https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize>. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

6. 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.

7. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

- * All financial support of the study must be acknowledged.
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- * 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).

8. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count.

9. 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.

10. 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.

11. 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%).

12. 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.

13. The American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG documents in your manuscript, be sure the reference you are citing is still current and available. If the reference you are citing has been updated (ie, replaced by a newer version), please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly (exceptions could include manuscripts that address items of historical interest). If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All ACOG documents (eg, Committee Opinions and Practice Bulletins) may be found via the Clinical Guidance & Publications page at <https://www.acog.org/Clinical-Guidance-and-Publications/Search-Clinical-Guidance>.

14. The Journal's Production Editor had the following to say about the figures in your manuscript:

"Figure 5: Please upload the original version (we are assuming this was created in an Office product). We would like to change a few elements to fit with journal style. "

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.

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- * 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 Oct 10, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2018 IMPACT FACTOR: 4.965

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

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