PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (http://bmjopen.bmj.com/site/about/resources/checklist.pdf) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Hepatitis C and pregnancy outcomes: a systematic review protocol</th>
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<tr>
<td>AUTHORS</td>
<td>Parent, Stephanie; Salters, Kate; Awendila, Lindila; Ti, Lianping</td>
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VERSION 1 – REVIEW

| REVIEWER               | Laura E. Riley, MD  
Massachusetts General Hospital Boston, MA, USA |
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<tr>
<td>REVIEW RETURNED</td>
<td>02-Jul-2018</td>
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<td>GENERAL COMMENTS</td>
<td>It is not clear if the authors will entertain other poor pregnancy outcomes if found in the literature such as cholestasis or will they only report on preeclampsia, diabetes and stillbirth. I would argue that any other pregnancy outcomes would be informative for future HCV pregnancy guidelines.</td>
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| REVIEWER               | Erica Villa  
University of Modena and Reggio Emilia |
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<td>REVIEW RETURNED</td>
<td>21-Jul-2018</td>
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| GENERAL COMMENTS       | The Authors aim to investigate pregnancy outcomes associated with maternal HCV infection, retrieving data from academic databases and hand searching of conference proceedings and reference lists. They plan to evaluate the impact of HCV on the following pregnancy outcomes: risks of preterm birth, low gestational weight, gestational diabetes, and hypertension.  
The topic of the proposed review is certainly interesting. However, the main indicated outcomes (preterm birth, low gestational weight) have been quite extensively explored in the literature (even with meta-analysis) so far and affirming that “the impact of HCV on pregnancy outcome is equivocal” is an overstatement. Instead on of more recently identified risks, i.e. abortion, which deserve to be extensively explored, in only mentioned in the key words for the literature search but not explicitly indicated in the introduction.  
The Authors aim to include women HIV co-infection, hoping to be able to stratify results by HIV infection (“..whenever available”): studies in which this is not possible should not be considered as HIV coinfection can blur the results of mono-infected women. Last but not least, the Authors mention the possible relevance of antiviral therapy on pregnancy outcome. This would be the most interesting and novel issue to evaluate as, as said before, the others have been extensively explored. However, antiviral therapy is not even listed in the search terms. |
The authors propose to conduct a systematic review of pregnancy outcomes associated with maternal hepatitis C infection. This is an important undertaking given the conflicting literature, changing therapeutic landscape, and worsening epidemic in some regions. The manuscript would benefit from certain clarifications regarding methodology and rationale as discussed below.

The proposed population of study should be more clearly defined. Most, if not all, referenced studies are from high-income nations. Impact of hepatitis C on pregnancy outcomes may differ in low- or middle-income nations (eg PMID: 28956137, 25368456). Do the authors intend to study impact of HCV on pregnancy outcomes in just high-income settings or globally?

The search strategy uses generic terms for hepatitis C and pregnancy outcomes that will likely capture a wide swath of the relevant literature, but it also includes search terms for several specific outcomes of interest (eg gestational diabetes). It would be helpful if the authors better described how they decided which pregnancy outcomes to include as special search terms, as these search terms could impact (bias) their ultimate findings. For instance, “hemorrhage” is an association found in several studies from low- or middle-income nations not included in their search strategy.

Finally, the proposed protocol does not specifically address whether the authors are interested in the independent effects of hepatitis C on pregnancy outcomes, or simply describing the bivariate associations. A major challenge in high-income nations where hepatitis C is usually acquired by injection drug use is separating effects of drug use and other covariates that adversely affect pregnancy outcomes from the effects of maternal hepatitis C infection. Some studies attempt to control for these confounding variables. A discussion of this problem in the data analysis plan would be helpful, even if the authors do not propose a quantitative analysis of the effects of such variables.

The line numbers listed on the Prisma-P checklist do not match the protocol manuscript line numbers. Thus it is difficult to confirm that the manuscript meets some of the criteria. I would prefer to reserve my assessment of whether the protocol meets the Prisma-P checklist until after the line numbers are corrected.

References 1 and 3 may be duplicates.

**VERSION 1 – AUTHOR RESPONSE**

Response to the comments of Reviewer 1

5. We agree with you that other poor pregnancy outcomes should be included in order to provide a comprehensive evidence base to develop guidelines. Thus, we have added new text in the methods section (p.6):
Quantitative articles investigating the association between HCV infection and pregnancy outcomes, including but not limited to hypertension, gestational diabetes, and stillbirth, will be included.

Response to the comments of Reviewer 2

6. We appreciate your suggestion to talk more explicitly about recently identified risks such as abortion. We have added new text in the introduction and methods section, and included the term in our key word search:
(p.5) In addition, little is known regarding women living with HCV’s choices in regards to abortion.
(p.6) We will also examine pregnancy complications such as hospitalization or cesarean section, and outcomes such as abortions

7. Thank you for your suggestion regarding the need to tease apart mono-infection from co-infection. On page 6, we have clarified that:
HIV and HCV are closely tied together due to similar transmission route; thus, women living with HCV as well as those co-infected with HIV will be included in our study. However, we will stratify by HCV mono-infection and HIV co-infection in the results, whenever available. If we are unable to distinguish between HCV mono-infected and HIV/HCV co-infected women, we will discuss the findings of HIV/HCV co-infected women in a separate section of the manuscript."

8. Following your suggestion, we have now added direct-antiviral therapy in the search terms (supplemental file 2)

Response to the comments of Reviewer 3

9. Thank you for suggesting we clarify whether we will restrict our search strategy by setting. New text has been added in the Methods section as well as appropriate references as follows (p.7)
Our search will not be restricted by publication date or setting in order to compare outcomes across time and geographical location.

10. Thank you for the suggestion to better describe how we decided on our search terms. The search terms for specific outcomes of interests were decided with the help of a librarian with expertise in systematic reviews and obstetrics and gynecology (p.7):
A University of British Columbia medical reference librarian with expertise in systematic reviews and obstetrics and gynecology at the University of British Columbia has been consulted to develop the following search methods (H. Brown, personal communication, September 22 2017).

We have also kept the search strategy broad in order to capture a breadth of pregnancy outcomes. In addition, experts in the field will be consulted to ensure no relevant papers are missed (p.10). We will also consult research and clinical experts in the field of HCV and pregnancy to ensure we have not missed important studies.

11. Thank you for the suggestion to distinguish between bivariate and multivariable associations. We have added new text in the methods section on page 9:

Because our search will include studies across settings, other factors such as injection drug use (in high-income countries) or sub-standard prenatal care (in low-income countries) may confound the independent effect of HCV on pregnancy outcomes. To tease out the independent effect of HCV or pregnancy outcomes, we will distinguish and report between descriptive studies and those that adjust for independent effects.
12. The PRISMA-P checklist has been revised with the appropriate page number. Please see comment 1.

VERSION 2 – REVIEW

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<th>REVIEWER</th>
<th>Erica Villa</th>
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<td></td>
<td>University of Modena and Reggio Emilia, Italy</td>
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<td>REVIEW RETURNED</td>
<td>04-Oct-2018</td>
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| GENERAL COMMENTS | The Authors have satisfactorily addressed the comments. |