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# Hepatitis C and pregnancy outcomes: a systematic review protocol

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## ABSTRACT

**Introduction** Many women living with hepatitis C (HCV) are of childbearing age. While the risk of vertical HCV transmission has been well established, the impact of HCV on pregnancy outcomes are equivocal, with some studies reporting risks of preterm birth, low gestational weight, gestational diabetes and hypertension, while other studies report no such risks. With the shift of the HCV treatment landscape to more effective, tolerable and shorter medications, understanding pregnancy outcomes of women living with HCV are an important consideration in order to provide a baseline from which to consider the usefulness and safety of HCV treatment for this population. The objective of this systematic review will be to investigate pregnancy outcomes associated with maternal HCV infection.

**Methods and analysis** This systematic review will incorporate articles relevant to pregnancy outcomes among women living with HCV (eg, gestational diabetes and caesarean delivery). Articles will be retrieved from academic databases including MEDLINE, EMBASE, CINAHL, clinicaltrial.gov and the Cochrane Library and hand searching of conference proceedings and reference lists. A database search will not be restricted by date, and conference abstract will be restricted to the past 2 years. The Newcastle-Ottawa Quality Assessment Scale will be used to assess the quality of the retrieved studies. Data will be extracted and scored independently by two authors. A narrative account will synthesise the findings to answer the objectives of this review.

**Ethics and dissemination** This systematic review will synthesise the literature on the pregnancy outcomes of women living with HCV. Results from this review will be disseminated to clinical audiences, community groups and policy-makers, and may support clinicians and decision-makers in developing guidelines to promote best outcomes for this population.

## Strengths and limitations of this study

- This study will systematically report on the literature on the impact of hepatitis C infection on pregnancy outcomes, an area with equivocal findings.
- The literature will be carefully assessed for quality using the Newcastle-Ottawa Quality Assessment Scale.
- A possible publication bias might limit the study and will search databases such as clinicaltrial.gov and PROSPERO in order to find unpublished studies and minimise this issue.

## INTRODUCTION

Globally, up to 71 million people are affected with chronic hepatitis C (HCV).[1] HCV-related mortality rate and disability-adjusted life years (DALY) continue to increase, with DALY increasing by 43% between 1990 and 2013[2]. Mortality due to viral hepatitis increased by 22% between 2000 and 2015, and at least 402 000 deaths were HCV-related worldwide in 2015.[3] Women can be particularly vulnerable to HCV infection,[4] and approximately 40% of women living with HCV are of childbearing age.[5] In the USA, between 2011 and 2014, detection of HCV among women of childbearing age increased by 22% nationally and by 213% in the state of Kentucky.[6] Moreover, due to similar transmission routes, women living with HCV can be co-infected with HIV.[7] Yet, it is known that women living with viral infections have fertility intentions.[8] HCV infection does not seem to affect the ability of women to become pregnant.[9] An estimated 0.1%–0.5% of pregnant women are HCV carriers in high-income settings, and the prevalence varies widely depending on jurisdiction.[5 10–12] In these settings, 15% of women of childbearing age and living with HCV will become pregnant.[5] This number is likely to be an underestimation, as routine HCV screening is currently not widely recommended during pregnancy.[13]

A large body of literature has indicated that maternal HCV infection can be vertically transmitted, particularly for women with high HCV viral load or HIV coinfection.[14] Worldwide, the risk of vertical transmission is 5.8% (95% CI 4.2% to 7.8%),[14] although it is likely lower in high-income settings. For example, a study conducted in British Columbia reported a vertical HCV transmission rate of 4.7% for HCV RNA-positive women.[15] Beyond transmission risks, other difficulties can arise for pregnant women living with HCV; however, available literature appears to be inconsistent with some studies suggesting that HCV has been linked with risks of preterm birth, low

gestational weight, gestational diabetes and hypertension, while others report no such risks.[15–23] In addition, little is known regarding women living with HCV's choices in regards to abortion. These discrepancies, along with the scale-up of access to effective, shorter and more tolerable HCV treatment regimens, highlight the need for a systematic evaluation of studies on the outcomes for pregnant women living with HCV. As such, the objective of this systematic review will be to investigate the pregnancy outcomes associated with HCV infection.

## METHODS AND ANALYSIS

This protocol conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) checklist (online supplementary additional file 1). We will conform to the PRISMA guidelines for the development of this systematic review.[24]

### Research question

The systematic review will aim to answer the following question: what are the pregnancy outcomes associated with hepatitis C?

### Patient and public involvement

No patients were involved in the design of the study. We will disseminate plain language summaries to relevant patient groups.

### Eligibility criteria

Quantitative articles investigating the association between HCV infection and pregnancy outcomes, including but not limited to hypertension, gestational diabetes and stillbirth, will be included. We will also examine pregnancy complications such as hospitalisation or caesarean section, and outcomes such as abortions. Since a meta-analysis was recently conducted on the association between HCV and preterm birth, we will not focus on this outcome for this review.[17] Review articles (including literature reviews) and opinion pieces, including commentaries, letters to editors and editorials, will be excluded. 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 monoinfection and HIV co-infection in the results, whenever available. If we are unable to distinguish between HCV monoinfected and HIV/HCV coinfected women, we will discuss the findings of HIV/HCV coinfected women in a separate section of the manuscript. Given the efficacy of new interferon-free direct-acting antiviral therapies, our search will also examine the impact of these medications on pregnancy outcomes. The search will be restricted to publications in English and French. Our search will not be restricted by publication date or setting in order to compare outcomes across time and geographical location, and the study period will be included in our analysis.

### Information sources and search strategy

A University of British Columbia medical reference librarian with expertise in systematic reviews and obstetrics and gynaecology at the University of British Columbia has been consulted to develop the following search methods (H Brown, personal communication, 22 September 2017). A search of academic databases including MEDLINE, EMBASE, CINAHL, clinicaltrial.gov, and the Cochrane Library will be performed by an author experienced in conducting systematic reviews. We will use a combination of search terms related to HCV and pregnancy outcomes (see the online supplementary additional file 2). We will also hand-search the reference lists of research and review articles, and look for additional potentially eligible articles on Google Scholar.

Additionally, we will hand-search relevant abstracts and full texts from HCV and obstetrics and gynaecology conferences (eg, American Association for the Study of Liver Diseases, European Association for the Study of the Liver, Conference on Retroviruses and Opportunistic Infections, International AIDS Society Conference, Infectious Diseases Society for Obstetrics and Gynecology) between 2016 and 2018. We have restricted an abstract search to 2 years in order to avoid duplication with older abstracts that may have already been published.

### Screening and data collection

The abstracts and full-text articles retrieved from the search strategy will be imported into Endnote X7 and duplicates will be removed. Two authors will independently examine: (1) titles and abstracts; and (2) full texts of relevant articles in two separate stages. Any study not meeting the inclusion criteria will be removed. Disagreements between the two authors will be resolved by discussion or by a third author.

### Quality assessment

The methodological quality of included quantitative research studies will be assessed using a modified version of the Newcastle-Ottawa Quality Assessment Scale (NOS).[25] This tool is reliable and valid to assess case–control and cohort studies, and we expect our retrieved studies to follow these two designs, as randomised controlled trials are unlikely to be included given the topic. Additionally, this tool has been used previously by a meta-analysis on a similar topic, and thus allows for comparison across studies.[17] Similar to this meta-analysis,[17] scores between 7 and the maximum score of 9 will be defined as high quality, scores between 4 and 6 will be defined as intermediate quality, and scores between 1 and 3 will be defined as low quality. Two authors will score each study independently, and disagreements in scoring will be resolved by discussion with a third author.

### Data extraction and synthesis

As per PRISMA guidelines, a flowchart indicating each stage of the selection process will be produced. A standardised form developed a priori will be used to capture

study characteristics (eg, design, setting and sample size), participant characteristics, main outcome measures (eg, low birth weight and gestational diabetes), main study findings and NOS scores. The results will be synthesised and qualitatively analysed.

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.

## ETHICS AND DISSEMINATION

To our knowledge, this systematic review will be the first to synthesise the available evidence on pregnancy outcomes among women living with HCV. These findings may provide evidence to support clinicians in monitoring women living with HCV throughout pregnancy and delivery. The results of this review will also inform policy-makers and leaders in developing appropriate guidelines for the understudied population of pregnant women living with HCV. Our results may highlight gaps in knowledge and guide future research concerned with improving outcomes for women living with HCV and their offspring.

While we have developed this systematic review protocol according to the highest standards for this type of research, including using validated tools such as the PRISMA guidelines and the NOS tool, some potential limitations are worth noting. First, studies on pregnant women living with HCV may be done in a variety of settings with widely differing healthcare systems. As such, our conclusions may only be applicable to specific settings, and it may be difficult to draw universal conclusions. Second, it is possible that we miss some relevant studies; we will try to minimise this issue by consulting a librarian to develop a broad search strategy. We will also consult research and clinical experts in the field of HCV and pregnancy to ensure we have not missed important studies. Lastly, as with all systematic literature reviews, a possible publication bias might limit the study. We will search databases such as clinicaltrial.gov and PROSPERO in order to minimise this issue.

On completion of the systematic review, a robust and comprehensive knowledge translation strategy will be developed. This strategy will include presenting findings to academic audiences at international conferences focused on infectious diseases and obstetrics and gynaecology. We will also publish the results in a peer-reviewed academic journal (eg, *Infectious Diseases in Obstetrics and Gynecology*) to reach clinical and academic experts interested in the topic. Plain language summaries and presentations to hospitals and other relevant clinical programmes will also be developed. Additionally, we will reach out to policy-makers via briefing notes or other avenues, as appropriate.

In conclusion, this systematic review will be the first to examine the full range of pregnancy outcomes in women living with HCV. Findings from this review may ascertain the current issues on the topic of HCV and pregnancy outcomes, and help experts and clinicians reach consensus and develop guidelines to minimise problems and optimise favourable outcomes for pregnant women living with HCV.

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**Contributors** SP designed the systematic review protocol, with support of a health librarian. SP prepared the first draft. LA, LT and KS reviewed and revised the first draft. All authors read and approved the final manuscript.

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