

July 7th, 2022

Re: Manuscript ID 77577

Dear Prof. Dong-Mei Wang and Prof. Yue Zhao,

Thank you for the opportunity of resubmitting our manuscript, which we have revised carefully based on your recommendations and the reviewers' comments. We provided the point-by-point responses to the reviewers' comments in this letter. The revision portions of the manuscript have been highlighted in red ink. We thank you and the reviewers for your time and efforts in reviewing the manuscript. We are glad that the related changes have significantly improved the manuscript. We believe you will now find the current version suitable for publication in your journal.

We look very much forward to receiving your positive reply soon

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Sincerely yours,

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Reviewer(s)' Comments to Author:

Reviewer: 1

The authors and his team did make a good job to fulfil the gap between HCV active infection influence on pregnancy and infant outcomes. The manuscript is recommended to be accepted with minor revision.

- 1) When considering risk factors associated with obstetric complications, more factors regarding obstetrics should be considered rather than simply age, parity, BMI, and HCV infection. Factors such as fetal weight, pelvic condition, and previous uterine surgery could have a direct influence on complications like cesarean section and nuchal cord.

Reply: Thank you for your positive comments and insightful suggestions. We have revised the main text and presented fetal weight (mean weight at birth), maternal pelvic condition, and previous uterine surgery in Table 1. In addition, multivariate analysis was performed and showed that these factors did not influence our previous findings (revised Tables 4 and 5)

- 2) Several writing mistakes exist with the manuscript in numbers and units

Reply: Sorry for the oversight and errors. The manuscript has been proofread carefully and revised for errors.

Reviewer: 2

The paper presented by Pan et al. is a study conducted with a cohort of HCV-infected and non-infected pregnant women. This study assessed the influences and risk of HCV infection on the occurrence of unfavorable gestational and neonatal factors. Furthermore, it was to provide

maternal-infant transmission rates in this population. The authors presented an article with an interesting goal and scope, as well as being well written and presented cohesively and understandably, with data highly relevant to the topic of HCV infection during pregnancy. However, some points require minor revision and attention to make them clearer. Here are a few suggestions that may help to improve this paper further:

- 1) On page 6, in paragraph 1 - in the part where the authors talk about: "which occurs in approximately 6% of infants born to women with HCV infection", Here it might be worth comment about that the higher the viral load of these pregnant women, the higher the likelihood of MTCT (Pott et al, 2018; Terrault et al, 2020).

Reply: Thank you very much for your constructive comments. We revised the manuscript as suggested with relevant citations.

- 2) In the methods section, in the three first lines, in the subsection "Study design, setting, and patient selections" more information about the study's location should be provided. Where exactly was this study conducted? In what part of China? Does this referral center receive pregnant women from all over China or only from one region?

Reply: Thank you for the suggestions. We have revised the manuscript with details on the study location and the referral patterns.

- 3) In the subsection "Patient data collection and outcome assessment", In the last paragraph, in the part where the authors talk about: "finding elevated serum aminotransferase levels in the HCV-Ab positive child", What was the threshold used to determine elevated aminotransferase

levels? It would be interesting to have the normal ranges available.

Reply: Thank you! We inserted the normal range for children as suggested.

- 4) Table 1 - The presented subtitle is unclear. "**All cases in the study were singleton" Table 4 - in the last line, in the parameter "Anemia", Isn't there something missing? Where can I find the data for this category, as well as the others? It is also necessary to include. In the discussion section, in the part where the authors talk about: the "(high prevalence of HCV genotype 1)", Was genotype 1 prevalent in this population? The genotype data was not included in the results section; it would be useful to include this information to support the proposed hypothesis.

Reply: We clarified those with the following statements:

- a) All mothers in the study had a singleton pregnancy**
- b) Data in Table 4 regarding the anemia has been populated in the revised table.**
- c) We did not have HCV genotype data in the current study because testing genotype was not required during pregnancy based on the standard of care. Other studies in China indicated that the majority of Chinese patients with HCV have genotype 1.**

Reviewer: 3

This was an informative report about HCV infection in pregnant women and neonates. Some queries should be clear. First, Table 1 showed the data at baseline in both HCV-infected mothers and healthy mothers.

- 1) To compare outcomes during pregnancy, more information should be

shown; for example, hemoglobin, platelet counts, and prothrombin time.
How about enrolment of pregnant women with advanced fibrosis?

Reply: Thank you for the constructive comments. We have added the variables in table 1 as suggested. We did not have any clinically cirrhotic patients in our cohort. However, there was no data to determine the advanced fibrosis stage as fibroscan or serum markers for fibrosis were not performed as standard of care.

- 2) Next, it is difficult to understand the results in Tables 4, and 5. What was Case/Exposed? In my thought: C-section; Age <35 59/169 (35%), Age ≥35 11/25 (44%). How about this? Authors should revise them.

Reply: We have revised that and clarified the Case/Exposed in Tables 4 and 5 with the detailed explanation in the footnote under each table. Thank you!

- 3) Next, was 33 cm of the neonate head circumference critical borderline for the development of intelligence? Authors should show the setting basis of neonate head circumference.

Reply: Thank you for your comments. The head circumference of <33 cm only indicated that the measurement was below the average. However, the data is not feasible to be used for assessing if smaller head circumference would eventually lead to the delay of mental development of low intelligence. This kind of investigation is needed in the future and data should be generated from the prospective study

or case-control study. We could not draw any conclusion from the current data set. Thank you!

4) Finally, the authors concluded that the negative outcome was associated with HCV viremia. However, chronic HCV infection induced several disorders in the liver. Which was directly associated with a negative outcome, HCV viremia or liver disorder? Some comments had better be added to the Discussion.

Reply: We fully agree that the advanced stage of liver disease might have an impact on the pregnancy outcomes on top of HCV infection. Again due to lacking data in fibrosis assessment, we could not rule out patients who have advanced fibrosis enrolled in our study. However, all patients in our study had no clinical indicator for liver decompensation. We have inserted these statements in the section of DISCUSSION.

5) Minor; Line 3, Page 3; 'Their HCV-ab' should be revised to 'Their HCV-Ab'. Table 4; There was no data about Anemia. Authors should add the data.

Reply: Thank you for pointing out the errors. We are sorry for the oversight and they are corrected as suggested.