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Jin-Lei Wang, Director, Editorial Office
Baishideng Publishing Group Co., Limited

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 4034-revised.doc).

Title: LIVER DISEASES IN PREGNANCY: DISEASES NOT UNIQUE TO PREGNANCY

Author: Ashraf A. Almashhrawi, MD, MSc; Khulood T. Ahmed, MD; Rubayat N. Rahman, MD, MPH; Ghassan M. Hammoud, MD, MPH; and Jamal A. Ibdah, MD, PhD*

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 4034

The manuscript has been updated.

(1) Format has been updated as per revision policies for mini-reviews.

(2) Revisions have been made according to the suggestions of the reviewers as follows:

Reviewer 00013180:

1. *I appreciate the opportunity to review the review article "LIVER DISEASES IN PREGNANCY: DISEASES NOT UNIQUE TO PREGNANCY" by Almashhrawi and colleagues. The mini review is well written and succinct but at places is sketchy and has some limitations. General comments: The authors have tried to do justice to the number of conditions that can affect the pregnancy state.*

Authors' response: We thank the reviewer for his interest in our manuscript.

2. *The references are not up to date and some key references are left out and important messages are not clearly spelt out.*

Authors' response: We made the following changes in the revised manuscript:

The references were updated. 25 references were published within the last 3 years (2010 and above). 6 references were published in 2013 and 6 references were published in 2012. We have tried to mainly use original publications as references even if those were older.

3. *In addition the references are not in sequential order. For example after reference 15, reference 73 appears. And this is a recurring theme.*

Authors' response: The references were rearranged in the revised manuscript to follow a sequential and logical order.

4. *Hepatitis B: The risks of HBV transmission with high viral load needs elucidation as much work has been published lately on this topic.. You should mention about the percentage risk with each log increase in HBV DNA for enough data is now available. You cite reference no 73, for viral load and risk of transmission, which is incorrect. Some useful references are as follows: a) Wiseman et al. Perinatal transmission of hepatitis B virus. Med J Aust 2009 May 4;190(9):489-92 b) Zou H et al. A retrospective study….hepatitis. Hepatology 2010;52:235A*

Authors' response: We made the following changes, including adding the above reference:

"Those with higher viral load (serum HBV DNA >10^8 copies/ml) were at higher risk for vertical transmission in one study[15]. Wan-Hsin et al showed recently that the adjusted odds ratio of transmission for each log10 copy/ml increase, is 3.49 (p = 0.001), with predictive rates of infection at maternal viral load levels of 7, 8, and 9-log10 copies/ml of 6.6% (p = 0.033), 14.6% (p = 0.001), and 27.7% (p <0.001), respectively[16]."

5. Further, you make a passing mention about the lack of evidence between mode of delivery and risk of transmission. Again, this has to be discussed a bit more with proper references.

Authors' response: We made the following changes in the revised manuscript:

"Although cesarean section is proposed as a measure to lower the risk of transmission particularly in women with high viral loads towards term, there is a conflicting evidence regarding choosing cesarean section versus vaginal delivery to lower the risk of vertical transmission[20,21]"

6. *"Breast milk …. discouraged if the mother receiving antiviral therapy" (Needs reference). Does this hold true for women on Lamivudine?*

Authors' response: We made the following changes, and references were added.

"Breast-feeding should be encouraged for infants receiving Hepatitis B immunoglobulins (HBIG) and vaccination[22–25]. On the other hand, no adequate evidence of the safety of breast-feeding in mothers receiving antiviral therapy is available and women on antiviral therapy with Lamivudine, Telbivudine or Tenofovir should be discouraged from breast-feeding[26–28]."

7. *Hepatitis E: Of all the viruses affecting pregnancy, HEV is perhaps the most important. This has not been dealt adequately. For example you fail to mention an important article, which debunks the theory that HEV is particularly fatal in pregnancy alone. Bhatia and colleagues have shown convincingly that the fatality rate is the same in pregnancy and non-pregnancy state and the trimester of pregnancy has no impact on mortality. Bhatia V, Singhal A, Panda SK, Acharya SK. A 20-year single-center experience with acute liver failure during pregnancy: is the prognosis really worse? Hepatology. 2008 Nov;48(5):1577-85*

Authors' response: We made the following changes, and the above reference was added.

"A report suggested that such variance in severity between endemic and non-endemic areas might be related to different genotypes of HEV [47]. Other studies suggested that pregnancy per se is not a poor prognostic factor for those who developed acute liver failure[48]."

8. Your statement "A review from Bangladesh suggests it is responsible for 9.8% of pregnancy-related deaths (31.1): is incorrect for this appears to be a Sudanese study which again is wrongly referenced. Please check reference 31.1

Authors' response: We made the following changes, and the reference was corrected.

"A review from Bangladesh suggests it is responsible for 9.8% of pregnancy-related deaths [46]."

9. *Reference 79, and the statement alluding to this reference appear out of context with regard to pregnancy.*

Authors' response: This statement comes as part of giving a background about hepatitis E before presenting issues specific to pregnancy. Reference number was corrected in the revised manuscript.

10. *For details regarding hepatitis E vaccine please quote the original NEJM study instead of a review article. Shrestha MP et al. Safety and efficacy of a recombinant*

hepatitis E vaccine. N Engl J Med. 2007 Mar 1;356(9):895-903 Krawczynski K. Hepatitis E vaccine--ready for prime time? N Engl J Med. 2007 Mar 1;356(9):949-51

Authors' response: The above references were added as suggested by the reviewer.

11. *Hepatitis simplex virus: Please mention about the striking lack of rise in bilirubin associated with striking massive rise in transaminases as a signal of HSV which needs to be treated with Acyclovir even when the definitive test reports are pending.*

Authors' response: We made the following changes:

"Providers should have high index of suspicion in this patient group in the appropriate clinical setting; elevated liver transaminases usually 100 times upper level of normal with typically normal or mildly elevated bilirubin (anicteric hepatitis)[57–60]."

"Although no strong evidence to support starting Acyclovir in patients with indeterminate acute liver failure, clinicians should consider empirical therapy with acyclovir when HSV hepatitis is suspected[59]."

12. *WILSON DISEASE: You do not mention the importance of decreasing the dose of D-penicillamine to aid wound healing in the latter months of pregnancy and the importance of not dis-continuing D-penicillamine. The dose of D-penicillamine has to be adjusted upwards after delivery.*

Authors' response: We made the following changes in the revised manuscript:

"therapy should not be discontinued as this can result in severe hemolysis, worsening of liver function and even death."

"AASLD recommends lowering D-penicillamine and trientine to the minimum needed (usually 25-50% of the pre-pregnancy dose)[78], particularly towards term to aid in wound healing. Baseline dosages can be resumed postnatal."

13. *Figures: Fig 2 [Table 2] appears unnecessary with regard to pregnancy. Instead you should focus more on the lacunae pointed out earlier.*

Authors' response: Although we agree that interpretation of serological markers is not specific to pregnancy, correct interpretation of the different serological markers is as important in pregnant patients as those non-pregnant. Subsequently, we feel that Table 2 will be helpful to the readers.

14. *Figure 3, [Table 3] title gives a mistaken or erroneous impression of being pertinent and safe in pregnancy. Again it is unnecessary with regard to HBV in a state as specific as pregnancy*

Authors' response: The authors feel that it would be relevant to the clinicians to be aware of all medications available in the market to treat hepatitis B and clearly identify the three medications that can be used in pregnancy as detailed in other paragraphs in the review. We have clarified the footnote to Table 2 in the revised manuscript.

Reviewer 00054966:

The mini review entitled "Liver diseases in pregnancy: diseases not unique to pregnancy" is to be considered of relevant interest, updated and its presentation of fluent readability. The only observation is a typo mistake at page 12, "Hepatocellular adenoma in pregnancy" paragraph, 6th line, where "oral" should be changed with "or".

Authors' response: We thank the reviewer's interest in our manuscript.
The typo was corrected.

Reviewer 00069262:

The authors present the first mini-review, on liver diseases in pregnancy. They use a logical, easy to read, with updated bibliography. Interestingly I hope the following two mini-reviews in this series of three. Very interesting work describing the various types of hepatitis and other liver diseases and pregnancy. I suggest, if the authors can add a conclusion to this mini-review. thanks

Authors' response: We thank the reviewer's interest in our manuscript. A conclusion was added.

Reviewer 00005986:

This review critically summarized the evidence of the relationship between pregnancy and liver diseases. Being ambitious in nature, this paper did not reports all the data available on this topic. However, it is well written.

Authors' response: We thank the reviewer's interest in our manuscript. We agree that the purpose of this review is not to provide detailed and comprehensive review inclusive of all available data about all conditions discussed, but rather to provide the readers with a concise summary on liver diseases in pregnant women and how to reach the diagnoses. This review also broadly outlines the available therapy to manage such diseases.

(3) References and typesetting were corrected

We believe that the comments made by the reviewer have greatly improved this mini-review article. We have made all necessary changes as suggested.

Thank you again for publishing our mini-review in the World Journal of Gastroenterology.

Sincerely yours,

Jamal A. Ibdah, MD, PhD